Australian Government
Cancer Australia

Risk factors for breast cancer: A review of the evidence

2018

Risk factors for breast cancer: A review of the evidence was prepared and produced by:

Cancer Australia
Locked Bag 3 Strawberry Hills NSW 2012 Australia
Tel: +61 2 9357 9400 Fax: +61 2 9357 9477
canceraustralia.gov.au

ISBN Print: 978–1–74127–336–6 ISBN Online: 978–1–74127–337–3

Recommended citation
Cancer Australia, 2018. Risk factors for breast cancer: A review of the evidence, Cancer Australia, Surry Hills, NSW.

Risk factors for breast cancer: A review of the evidence can be downloaded from the Cancer Australia website: canceraustralia.gov.au

Table of contents

Figures

Tables

1 Introduction

1.1 Context

In Australia, breast cancer is the most commonly diagnosed cancer, excluding common types of non–melanoma skin cancer. In 2018, an estimated 18,087 women and 148 men will be diagnosed with breast cancer in Australia.[1] The age–standardised incidence rate has increased from 81 women per 100,000 in 1982 to 123 women per 100,000 in 2013. The incidence rate in women increases with age up to 65–69 years, before decreasing.[1]

Breast cancer is the second most common cause of cancer death in women in Australia. It is estimated that 3,128 women will die from breast cancer in 2018[1] compared with 28 men.[1] The age–standardised mortality rate in Australia decreased from 30 women per 100,000 in 1968 to 20 women per 100,000 in 2014.[1]

Survival from breast cancer in Australia has increased over time. From 2010 to 2014, the five–year relative survival rate from breast cancer was 91% for women and 85% for men.[1] The risk of developing breast cancer increases with age. For Australian women, in 2017 the risk of developing breast cancer by age 85 years is approximately one in eight.[1]

There is a large community interest in recognising the risks for breast cancer and ways in which risk can be decreased. An evidence–based review of risks for breast cancer is also needed to address potential myths and misconceptions that perpetuate in the community.

This report is intended primarily for researchers and health professionals seeking a more in–depth understanding of the nature and extent of the evidence base supporting various factors as being associated or not associated with the risk of breast cancer among women. This information aims to improve understanding of the current state of the evidence relating to risk and protective factors for breast cancer in women.

1.2 What is a risk factor?

The World Health Organization (WHO) defines a risk factor as 'any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury'. Strictly speaking, risk factors for cancer are factors associated with an increased likelihood of developing cancer. Protective factors are the opposite: they are associated with decreased likelihood of developing cancer.[2] In this and many similar reports, the collective term 'risk factors' may incorporate protective factors when appropriate. Some risk factors may be regarded as causes of disease, while others may be correlates but not causal.[2]

Studies looking at large numbers of women have shown that there are some characteristics, or risk factors, that are more common among groups of women who have developed breast cancer, compared with groups of women who have not. These epidemiological studies have established a number of risk factors that are associated with an increased likelihood of a woman developing breast cancer.[3-5] Greater understanding of breast cancer risk factors may help to identify women who may benefit most from tailored surveillance.[4] Some risk factors for breast cancer cannot be modified or avoided, such as increasing age or

inheriting certain gene mutations, but other risk factors, such as alcohol consumption, can be modified.

There is a multiplicity of risk factors for breast cancer and they are often interrelated through complex pathways and mechanisms.[5] In general, risk factors do not occur in isolation and the chain of events leading to disease includes both proximal and distal factors.[6] Proximal risk factors act directly or almost directly to cause or precipitate the disease. Distal risk factors are further back in the causal chain and act more remotely or indirectly via intermediary causes.[6] The factors that lead to developing disease are likely to have their roots in a complex chain of events and exposures, with potentially complex interactions, such as an amplifying effect of distal risk factors on proximal risk factors.[6]

Web–like conceptual frameworks and models have been developed to indicate the interrelations between breast cancer risk factors and the multiple potential mechanisms involved.[4] The possible role of the timing of exposures across the lifespan has also been noted.[7] These models indicate the biological complexity of the pathways along which breast cancer risk factors may be acting. They highlight the difficulty of distinguishing truly causal effects from non–causal associations and the challenges of designing, conducting, and interpreting studies directed at determining risk factors for the various forms of this disease.[8]

1.3 Approach

This report outlines the evidence for factors associated with female breast cancer. While acknowledging the complexities and potential interrelations between risk factors, this report only considers risk factors individually. The risk estimates presented are for differences in single risk factors, with all other factors assumed to be equal.

This report provides an overview of current epidemiological knowledge about the evidence for the association of a broad range of exposures or factors and risk of breast cancer. It focuses on providing the best available, up–to–date evidence indicating whether factors of interest are or are not associated with risk of breast cancer. The evidence in this report relates to breast cancer in women only.

Input and advice from a multidisciplinary Expert Reference Group comprising epidemiological experts, health professionals, risk communication experts, and consumers, in consultation with Cancer Australia, has guided the underlying evidence review, this report and its translation into web material.

This review followed a systematic process to identify the evidence available for each factor. In doing so, higher levels of evidence from the most recent meta–analyses and large cohort studies were sourced. Lower quality evidence (for example, from individual case–control studies) was sourced when higher quality evidence was not available. This evidence is classified (rated or graded) so that communication about the strength of the evidence for each factor can be consistent.

A ‘best estimate’ of the magnitude of risk is reported for those factors for which there is sufficiently strong evidence—classified as either ‘convincing’ or ‘probable’—that they are associated with an increased or decreased risk of breast cancer. For other factors, the evidence is classified as either ‘suggestive’, ‘inconclusive’ or ‘evidence of no association’. Those that have been rated as ‘suggestive’ may be associated with risk of breast cancer,

whereas factors for which the evidence base is 'inconclusive' have a limited basis from which to determine likelihood of an association. Where there is 'evidence of no association', such factors are unlikely to be associated with risk of breast cancer.

Readers should note that strength of evidence does not reflect the effect size of a factor or the direction of effect, and these elements should be considered as separate entities. For example, a factor can be of a convincing strength of evidence yet be associated with only a small increased risk of breast cancer.

2 Methods

2.1 Overview

This review aimed to determine whether there is sufficient evidence to support an association between various exposures, or factors of interest, and the risk of breast cancer; and to identify the magnitude of breast cancer risk—increased or decreased—for each factor where there is sufficiently strong evidence of an association.

Various international agencies including the World Cancer Research Fund /American Institute for Cancer Research (WCRF/AICR) and the International Agency for Research on Cancer (IARC), provide reports and monographs indicating the strength of the evidence for various factors of interest and risk of cancers (Appendix C). This review builds on the existing high level evidence reviews conducted by these authoritative bodies, where available.

This review did not explicitly consider the quality of individual studies or meta–analyses, although studies were selected according to the established hierarchy of evidence for aetiology studies, such that study type was a proxy for study quality. Further, other elements of the evidence, including consistency across studies, were considered in determining the strength of the evidence.

An explicit process of classification of the evidence was undertaken to inform the reader about the likelihood of each factor of interest being either associated or not associated with risk of breast cancer.

2.2 Search strategy

Reviews of aetiology include 'population', 'exposure of interest' (independent variable), and 'outcome' (dependent variable).[9]

Population

- Healthy females of all ages independent of their exposure to any risk factors, for prospective cohort studies
- Women diagnosed with primary breast cancer of any age, and unaffected study participants, for retrospective cohort and case–control studies
- Women at risk of developing primary breast cancer, for randomised controlled trials
- Women generalisable to the Australian female population

Exposures

- A large range of exposures—behavioural factors, occupational factors, environmental factors, infectious agents, genetic predispositions, medical conditions and treatments, and reproductive and hormonal factors—were considered for evidence review. The factors were identified and selected through an initial scoping of the literature and relevant, prominent national and international websites. A selection of factors known to

be of particular interest to the community and media (for example, those about which Cancer Australia regularly receives queries) were included. This list is not exhaustive since the media features many factors for which there is very little or no good quality evidence. The Expert Reference Group made the final selection of factors for inclusion.

- Approximately 100 individual exposures or factors of interest were identified for review.

Outcome

- Primary invasive breast cancer
- Primary invasive premenopausal breast cancer
- Primary invasive postmenopausal breast cancer
- Breast cancer histological or molecular sub–types

Search dates

If the WCRF/AICR had included the factor of interest in its most recently published systematic literature review[10] and breast cancer report[11] as part of the WCRF/AICR Continuous Update Project (CUP) then, for this review, evidence was searched from the cut–off date (30 April 2015) of the CUP systematic literature review. If the WCRF/AICR hadn't reviewed the factor then, for this review, the IARC monographs were searched for any evidence and considerations relating to the human epidemiological evidence in breast cancer. Where evidence was identified, relevant information was extracted and evidence was only searched from IARC's most recent search date for that factor and breast cancer. For all other factors of interest, the search date of 1January 2008 onwards was used. This approximated the cut–off date in the previous Cancer Australia review of the evidence on breast cancer risk factors published in 2009.[12]

Earlier search dates were only used if there was a very limited amount of evidence (or no evidence) published since 2007 for a factor of interest. Occasionally, despite this review's emphasis on using the most recent data, pre–2007 studies were included as background or to provide a fuller picture of the body of evidence. This pertains particularly to the more established risk factors mediated through hormonal pathways—for example, findings from the Collaborative Group on Hormonal Factors for Breast Cancer (CGHFBC; https://www.ceu.ox.ac.uk/research/hormonal-factors-in-breast-cancer)—which has conducted multiple pooled analyses from large numbers of epidemiologic studies.

For this review, the search for primary studies focused only on the time since the last search date of the most recently published systematic review. For example, if a systematic review had searched primary studies until 30 September 2012 then primary studies published since 30 September 2012 were sourced.

Search terms

The PubMed database was initially searched to identify optimal search terms. Those used by the most recent WCRF CUP systematic literature review (CUP Breast SLR)[10] were used for the relevant factors.

Bibliographic searches were performed on the Cochrane Library, Medline, Embase, and PsycINFO for articles appearing between 1 January 2008 and 30 October 2017 using MeSH terms and free text words:

Breast Neoplasms [MeSH Terms] #2 Breast AND (cancer* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma*) #3 mammary AND (cancer* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma*)

and relevant exposure search terms.

Each factor of interest was searched again using the simple search string '[factor]' AND 'breast cancer' AND 'risk OR incidence', on both PubMed and the IARC website (http://monographs.iarc.fr).

Snowballing

In addition, a citation search of key studies was conducted to identify any more recent primary research studies or any other key studies that may have been missed in the PubMed search.

2.3 Study selection

Inclusion criteria

Studies were included in this review if they had:

- published quantitative risk estimates and 95% confidence intervals (or some other measure of variability) of the association between each factor of interest and breast cancer. Odds ratios, hazard ratios, standardised incidence ratios, and risk ratios were all interpreted as relative risk
- results from an epidemiologic study of one of the following types, in order of the generally accepted hierarchy of evidence for aetiologic studies:
    - meta–analysis
    - pooled analysis
    - randomised controlled trial (RCT)
    - prospective cohort study
    - nested case–control study
    - retrospective cohort study
    - population–based case–control study (preferably with more than 1,000 cases)
    - non–population–based case–control study (only if no higher level evidence identified)
- human subjects
- articles published in English
- a publication date from 2007 onwards (unless no recent studies were identified or an earlier study was considered a key study)
- relevance to the Australian population.

Exclusion criteria

Studies were excluded from this review if they:

- were cross–sectional studies
- reported only on breast cancer mortality
- reported only on breast cancer in men
- reported only on breast cancer clinical outcomes
- did not have full text available (with certain exceptions for conference abstracts where these were considered to substantially inform the body of evidence)
- were not conducted in humans
- were not on the topic of breast cancer
- were not published in the English language
- did not provide quantitative risk estimates or only provided unadjusted risk estimates.

In cases where this review retrieved many systematic reviews with meta–analyses addressing the same factor of interest, only the reviews that were most up–to–date, of the highest methodological quality, and included the largest number of primary studies (preferably RCTs or cohort studies) were selected. Additional meta–analyses were included if they presented further information about a specific epidemiological element, such as different sub–exposures or a dose–response analysis. If there was significant overlap in included studies, then these additional meta–analyses were excluded. Overlap in studies contained within the various meta–analyses was not systematically explored for all factors.

2.4 Data extraction and synthesis

After the search and study selection process, applicable full–text papers were retrieved for data extraction and analysis.

Risk estimates were retrieved from the original article, along with 95% confidence levels. Odds ratio (OR) is a good approximation of the relative risk when the outcome occurs relatively infrequently (<10%). OR, rate ratios, standardised incidence ratios (SIR), hazard ratios (HR) and risk ratios were all interpreted as relative risk (RR) given that all measures of relative risk are very similar when the risks are relatively small. Where explicit adjustments were made, the type of statistic used and the variables of adjustment were noted.

Often, factors such as age, menopausal status, breast cancer subtype (for example, receptor status, ductal versus lobular, in situ versus invasive, and so on), and racial/ethnic identity are reported as main factors of analysis, along with effects of particular exposures. This review reports significant main effects and interactions between exposures and these other variables are noted.

Within the data extraction table for each factor of interest, the studies are ordered according to the NHMRC hierarchy of study design and, within each design, in reverse chronological order.

2.4.1 Assessment of evidence base

In this report, the methods used for assessing the body of evidence for each factor align with those the WCRF/AICR uses. This system was selected because it uses explicit criteria that are straightforward to apply and it enables integration of the judgements by the WCRF/AICR.[13] The clearly defined classification criteria (Appendix C, Table C.2) provide a systematic way to judge the strength of evidence relating to association with breast cancer risk.

The WCRF/AICR criteria require a range of factors to be considered, including quality of the studies, for example, whether the possibility of confounding, measurement errors and selection bias has been minimised. They also include the number of different study types and cohorts, whether there is any unexplained heterogeneity between results from different studies or populations, whether there is a dose–response relationship, and whether there is evidence of plausible biological mechanisms at typical levels of exposure. This review considered these elements of the evidence.

The WCRF/AICR labels the various categories of evidence as:

- Strong—Convincing
- Strong—Probable
- Limited—Suggestive
- Limited—No conclusion
- Strong—Substantial effect on risk unlikely.

This review, guided by the Expert Reference Group (ERG), considered the WCRF/AICR nomenclature for describing the evidence, and changed 'No conclusion' to 'Inconclusive'. In addition, the WCRF/AICR uses the collective terms 'strong' and 'limited' to make evidence–based recommendations about lifestyle behaviours. Only evidence judged to be 'strong' is usually used as the basis for health recommendations. The collective terms 'strong' and 'limited' were considered to be less applicable and useful for the purposes of this review, since the term 'strong' could be misinterpreted as relating to the strength (magnitude) of the risk and 'limited' could be misinterpreted as a limited quantity of evidence. A factor with a 'limited' evidence base, according to the WCRF/AICR, could be due to a limited quantity of evidence but it could also be due to inconsistency in direction of effect, because of methodological flaws, the level or quality of the evidence; or any combination of these reasons. Thus, the terms 'strong' and 'limited' are not applied in this review.

Further, the WCRF/AICR[11] seldom classifies any factors into the 'Substantial effect on risk unlikely' category, but the evidence for several factors within this review is considered to meet the criteria for this classification, and this classification can be used to usefully communicate the likelihood that a factor is not associated with risk of breast cancer. The ERG recommended clarification of the term to reflect the focus of this review on the human epidemiological evidence. As such, the category 'Substantial effect on risk unlikely' was defined as 'Evidence of no association' for this review.

The categories of evidence used within this review are:

- Convincing
- Probable
- Suggestive

- Inconclusive
- Evidence of no association.

Table 1.1 shows the system used in this review to classify the strength of the evidence for an association of a factor with an increase or decrease in the risk of breast cancer, noting that the criteria align with those of the WCRF/AICR.[11]

Cancer Australia, in consultation with four epidemiological experts of the Expert Reference Group, used a consensus–gaining method to determine final evidence classifications.

Table 1.1 Criteria for classifying the strength of the evidence in terms of likelihood of association between an exposure (factor) and the risk of breast cancer

Classification	Generally required criteria
Convincing	*There is compelling and consistent evidence that the factor is associated with risk[i] of breast cancer. This classification includes factors that are causally associated with breast cancer as well as others that may be markers of underlying causes.* • Evidence from more than one study type and at least two independent cohort studies • No substantial unexplained heterogeneity within or between study types or in different populations regarding presence or absence of association, or direction of effect • Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias • Presence of a plausible biological gradient ('dose–response') in the association. (Gradient need not be linear or in same direction across different levels of exposure, so long as this can be explained plausibly.) • Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes
Probable	*The factor is likely to be associated with risk[i] of breast cancer but the evidence is not as strong as for Convincing.* • Evidence from at least two independent cohort studies/at least five case–control studies • No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect • Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias • Evidence for biological plausibility
Suggestive	*The evidence is suggestive of an association between the factor and risk[i] of breast cancer but there is not sufficiently strong evidence to be more certain.* • Evidence from at least two independent cohort studies/at least five case–control studies • Direction of effect is generally consistent, although some unexplained heterogeneity may be present • Evidence for biological plausibility

[i] Increase or decrease in risk

Inconclusive	*The evidence is too limited to determine the likelihood of an association with risk of breast cancer.* • This category represents an entry level, and is intended to allow any exposure for which there are sufficient concerns to warrant consideration, but where insufficient evidence exists to permit a grading. • The evidence might be limited in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders), or by any combination of these factors.
Evidence of no association	*There is consistent evidence from good quality studies to show that the factor neither increases nor decreases the risk of breast cancer.* • Evidence from more than one study type • Evidence from at least two independent cohort studies • Summary estimate close to 1.0 for comparison of high versus low exposure categories • No substantial unexplained heterogeneity within or between study types or in different populations • Good quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding, and selection bias • Absence of a demonstrable biological gradient ('dose–response') • Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes

2.4.2 Selection of best estimate of risk

A best estimate of risk was selected for all factors where the evidence for an association with breast cancer was classified as either 'convincing' or 'probable'. This estimate was selected as being representative of the data from the range of available studies, predominantly selected from a large pooled analysis or the most recent quality meta–analysis of a large number of (preferably) cohort studies. Consideration was given to the types of studies, the populations from which the estimates were derived, the precision of the estimates, and their relevance to exposure levels experienced among Australian women. Best estimates of risk were selected using a consensus–gaining method by Cancer Australia, in consultation with four epidemiological experts of the Expert Reference Group.

A comparative risk estimate, mostly relative risk, of appropriate exposures is provided in this report, together with the 95% confidence intervals. The source of the risk estimate is noted. The risk estimate may be presented for a continuous, binary or integer exposure, as relevant and as recorded in the published studies.

3 Breast cancer aetiology

3.1 Introduction

Breast cancer develops when cells grow and divide abnormally as a result of changes in the genes that control the way cells function, especially how they grow and divide.[14] It is likely that development of breast cancer is a multistep process involving several biological mechanisms that initiate then promote cancer.[8, 15] This process may occur spontaneously due to errors in normal processes (such as DNA replication), or through the effects of environmental exposures (such as environmental chemicals and radiation). It may also be potentiated and potentially sustained by physiologic conditions such as obesity.[8]

In cancer development, changes or aberrations in the genome may confer selective advantage on clones of cells, enabling them to outgrow and eventually dominate their local tissue environment.[15] Multistep tumour progression may be a succession of clonal expansions, each of which is triggered by the chance acquisition of an enabling genomic change.[15] In addition, the surrounding stroma, the immune system, and the hormonal and metabolic milieu play a role in dictating whether particular clones thrive or not. Functional capabilities acquired by cancer cells, which have been described as 'hallmarks of cancer', allow them to survive, proliferate and disseminate, enabling tumours to grow and metastasise.[15]

The aetiology of breast cancer and the biological mechanisms involved in the development of cancer are areas of ongoing and emerging research. Underlying biological mechanisms identified to date that are likely involved in the development of breast cancer include those that are further described below.

3.2 Underlying biological mechanisms in breast cancer development

3.2.1 Genomic changes

Changes or aberrations in the genome, such as DNA mutations, can contribute to the development of cancer. There are different genetic changes or 'drivers' of cancer, such as changes in oncogenes (cancer–causing genes), tumour suppressor genes (genes that usually protect cells from abnormal proliferation), or DNA repair genes. These changes can be inherited or can arise during a person's lifetime due to errors as cells divide or damage to DNA caused by certain environmental exposures.

Accumulated genomic mutations and expansion of rapidly proliferating abnormal cells can result in the progression of an increase in the number of normal looking cells (hyperplasia), to cells that look abnormal under the microscope but are not cancer (dysplasia), to an increase in cancer cells that have not spread (carcinoma in situ), and eventually to invasive cancer.[4]

Uncontrolled growth of cells can occur through cellular mechanisms such as overproduction of growth stimulating factors, reduced inhibitors of cell proliferation, loss of balance between

cell proliferation and programmed cell death (apoptosis), or defective DNA repair mechanisms.[5] The longer a person lives, the more mutations occur in cells and the more likely it is that cells may progress to carcinoma.

3.2.2 Epigenetic changes

Epigenetic changes involve changes in gene expression—what genes, and by how much genes are turned on in a cell to make RNA and proteins—that are due to mechanisms other than changes in the underlying DNA sequence. Epigenetic changes can be transmitted across cell generations or inherited.

Epigenetic alterations involve changes in DNA methylation (addition of methyl groups to DNA along the chromosome), modifications in histones (the proteins that bind to DNA that help give chromosomes their shape and regulate the activity of genes), and expression of small regulatory non–coding RNAs (microRNAs).[5, 7, 8] These epigenetic mechanisms may be associated with breast cancer by directly affecting the expression of genes and interaction to regulate gene expression.[5, 7]

Environmental chemicals may alter the regulation of genes involved in cell proliferation and cell death signalling pathways in the breast through epigenetic processes, including DNA methylation, histone modification, and expression of small regulatory microRNAs.[7]

3.2.3 Hormonal influences

Many of the established hormonal and reproductive factors associated with breast cancer risk suggest that lifetime exposures to endogenous oestrogen and progesterone play a role in the development of breast cancer.[4, 5] In normal cells, their growth–promoting effects are highly regulated, but in cancer cells they can be subverted to promote uncontrolled cell growth.[5]

Oestrogen, which is critical for normal breast development, appears to play a major role in breast carcinogenesis. Longer exposure to endogenous oestrogen and exposure to exogenous oestrogen can be associated with increased risk of breast cancer. The mitogenic actions of oestrogen cause increased cell proliferation which may increase susceptibility to breast cancer in several ways: by selectively promoting the growth of altered preneoplastic and neoplastic cells; by increasing the potential for DNA changes through shortening the cell cycle and decreasing the time available for DNA repair; and by increasing the target population of cells for transformation into cancer cells.[8]

There is limited understanding of the way endogenous progesterone acts in the normal human breast and in the development of breast cancer. Much of the evidence is from studies in mice and in vitro human cell line studies.[16] Progesterone appears to stimulate cyclic proliferation of the mature breast epithelium through local effects on nearby cells and also activates stem cells in the breast.[17] The repeated activation of progesterone signalling during the luteal phase of the menstrual cycle may be tumour promoting.[16] However, the effects of progesterone may be context–specific and depend on other factors, such as dose and duration, oestrogen levels and age, since not all progesterone signalling is tumour promoting; progesterone can also be anti-proliferative.[16, 18]

3.2.4 Metabolic changes

Development of cancer is linked to changes in the metabolism of cells. Changes in energy metabolism are needed in order to fuel cell growth and division. In cancer cells, energy metabolism may be reprogrammed to meet high energy and anabolic requirements. These metabolic changes may confer a selective advantage to the cells.[15] Effects on metabolism of some major oncogenes or tumour suppressor genes have been identified. This has suggested that metabolic dysregulation may be a key mechanism in development of cancer.[19]

3.2.5 The immune system

Inflammation can promote tumour proliferation and metastasis.[5] Cancer often originates in tissue that is chronically inflamed due to infections or other causes. Tumour–induced inflammation can also contribute to progression.[20]

Inflammation can contribute to cellular processes involved in cancer development by supplying factors that sustain proliferation and invasiveness.[15] Inflammatory cells may also release chemicals, such as reactive oxygen species, that are mutagenic for nearby cells and may accelerate their transformation into cancer cells.[15]

Immunosurveillance can have a tumour–antagonising effect by detecting and eliminating cancer cells by mechanisms of adaptive and innate immunity.[8, 15] Cells and tissues are monitored by the immune system and this immune surveillance can recognise and eliminate incipient cancer cells and thus very early tumours.[15] However, cancer cells may escape detection and elimination by the body's immune cells. The effectiveness of the immune system in detecting and eliminating cancer cells may be modulated by factors such as environmental exposures.[8]

3.2.6 Stem and progenitor cells

Stem cells have the capacity to self–renew and to differentiate into the different lineages required for a particular tissue.[21] In the breast, stem cells generate new differentiated epithelial cells that enable the breast to develop during puberty and pregnancy, as well as regenerate after changes during the menstrual cycle and involution after lactation. The breast maintains stem and progenitor cell populations to sustain multiple pregnancies.[5]

As stem and progenitor cells are long lived and resistant to cell death, they may accumulate larger numbers of mutations and be more likely to develop into cancerous cells or tumours over time. Therefore, it has been suggested that breast cancers may be fuelled by the stem cell subpopulation, with properties of self–renewal, tumourigenicity and the capacity to differentiate into many cell types.[5, 15]

3.2.7 The tumour microenvironment and interactions with stroma

The microenvironment, or close surroundings, of a tumour comprises several distinct cell types, including immune cells, together with supporting stroma.[15] There are interactions and bidirectional signalling between cancer and stromal cells. The microenvironment and

changes in the microenvironment can affect how cancer cells grow and spread and cancer cells, in turn, can affect their microenvironment.

Interactions with breast stroma may be involved in the development of breast cancer.[8] The stroma maintains the structural and functional integrity of breast tissue and accounts for the majority of the breast volume, although most breast cancers originate from the epithelium. Interactions between the cells in the epithelium and between epithelial and stromal cells, such as immune cells, fibroblasts and adipocytes, are critical for normal breast development.[22] Changes in the stromal and hormonal environments of the breast are part of the age– and event–related changes in the breast throughout a woman's lifetime.[8] Changes in interactions between neighbouring cells and their microenvironment may promote a malignant phenotype, and may be especially relevant to breast cancer.[7, 8]

3.3 Windows of susceptibility

The breast undergoes substantial changes throughout life, from gestation to puberty, pregnancy, lactation and menopause.[8] There is rapid growth in ducts and lobules during puberty, pregnancy and lactation, and a decrease in the number of ducts and lobules followed by involution after lactation and after menopause. Oestrogen and progesterone play a major role in the different stages of mammary gland development. Other hormones and growth factors are also involved.[5]

During periods of rapid cell proliferation or maturation—such as in the early stages of development in the prenatal, early childhood and adolescent periods—specific mechanisms that increase the likelihood of breast cancer developing may be more likely to come into play and breast cells may be more susceptible to the carcinogenic effects of hormones, chemicals and radiation during these critical windows.[7, 8]

The time from menarche to first pregnancy may be a particularly vulnerable window of susceptibility for breast tissue.[23] A window of susceptibility to oestrogen at a young age which increases later breast cancer risk has been suggested due to the association of young age at menarche with increased risk of breast cancer, and to the age–dependency of the reduction in breast cancer risk associated with full term pregnancy.[24] The susceptibility of young breast tissue may be due to rapid cell proliferation at puberty and the risk of accumulating deleterious mutations, with risk accumulating most rapidly until the terminal differentiation that accompanies first pregnancy.[23, 24]

Windows of susceptibility to risk factors may present windows of opportunity for breast cancer prevention by nutritional or lifestyle interventions for modifiable risk factors.[25] The important role of early life exposures on breast cancer risk suggests that breast cancer prevention through modifiable risk factors is best initiated then sustained from an early age.[23]

4 Breast cancer risk factors

4.1 General factors

4.1.1 Age

Evidence summary

Evidence classification: Convincing.

Other than gender (that is, being female) age is the most significant factor for developing breast cancer. The risk of breast cancer increases with age up to 75 years, although the rate of increase decreases in mid–life, around menopause, reflecting the hormonal influence on breast cancer.

Using incidence rates in Australia, women aged 50 years are at 10 times increased risk of breast cancer compared with women aged 30 years.[27]

If all women less than 65 years of age are compared with women aged 65 years or older, the relative risk of breast cancer associated with age has been estimated as 5.8, in the United States.[26]

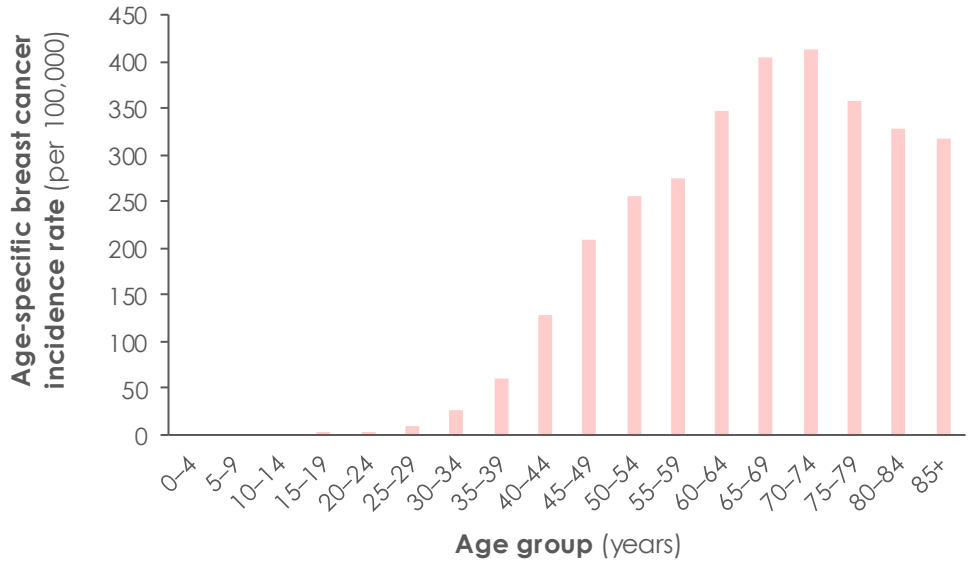
Incidence

In Australia, the breast cancer age–specific incidence rate increases steeply from age 30–34 (25.6 per 100,000 in 2014) to age 50–54 (255.9 per 100,000 in 2014), then increases more slowly to a peak around 70–74 years (412.4 per 100,000 in 2014), before decreasing (317.6 per 100,000 for 85+ years in 2014) (Figure 4.1; data taken from AIHW).[27] This equates to a risk of diagnosis before age 75 as 1 in 10 and before age 85 as 1 in 8. These results represent an increased incidence of breast cancer in Australia since 1984: from 1 in 16 before age 75 and 1 in 11 before age 85. This increased incidence is partly due to the ageing population.

Over 75% of all breast cancers in Australia are diagnosed in women when they are aged 50 years or over.[27] The average age of the first diagnosis of breast cancer in women is 61.[27]

Based on data from the United States, a 30–year–old woman has a 1 in 250 chance of being diagnosed with breast cancer in the next 10 years, whereas a 70–year–old woman has a 1 in 27 chance.[4] If all women less than 65 years of age are compared with women aged 65 years or older, the relative risk of breast cancer associated with age is 5.8.[26, 28]

Figure 4.1 Age–specific incidence of breast cancer in Australia, by age group, 2017



Source: Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality (ACIM) books 2017 [Available from: https://www.aihw.gov.au/reports/cancer/acim–books/contents/acim–books.] Last updated 11 Dec 2017.[27]

4.1.2 Geographic location and residence

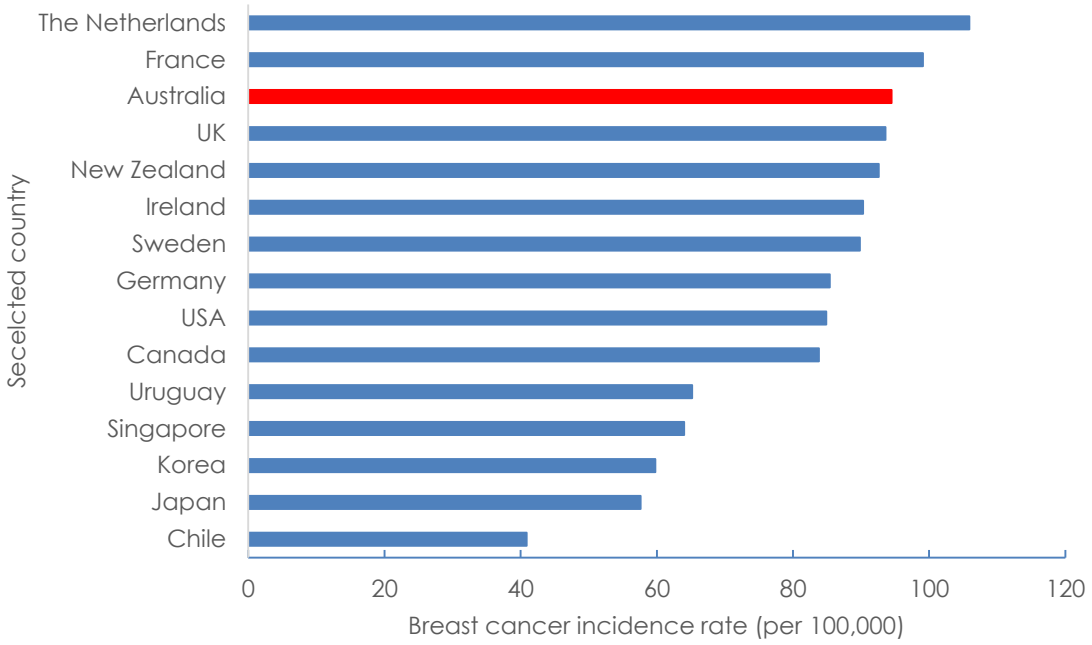
International geographic differences

Internationally, breast cancer incidence rates vary (Figure 4.2).[29] Rates need to be interpreted with care, as they are influenced by competing risks for death and depend on the presence and quality of local registries.[30]

The highest breast cancer incidence rates[30] reported are from countries in northern and western Europe such as the Netherlands: 105.9 per 100,000 and France: 99.1 per 100,000), Australia (94.5 per 100,000), UK (93.6 per 100,000), New Zealand (92.6 per 100,000), USA (84.9 per 100,000) and Canada (83.8 per 100,000).[29, 31] The lowest rates reported are from other countries including eastern Asia (such as Japan: 57.6 per 100,000) and South America (such as Chile: 40.9 per 100,000).[29] Breast cancer incidence rates are also increasing in developing countries.[31]

There are also differences between countries in the median age at diagnosis of breast cancer.[31] The peak age at breast cancer diagnosis reported in Asian countries is 40–50 years, in western countries is 60–70 years and in African countries (where data are available) is approximately 45 years.[31]

Figure 4.2 Age–standardised breast cancer incidence rates in selected countries



Source: Cancer Australia. National cancer control indicators. Cancer incidence 2018. [Available at: https://ncci.canceraustralia.gov.au/diagnosis/cancer–incidence/cancer–incidence].[29] Data sourced from International Agency for Research on Cancer GLOBOCAN 2018 database.

Higher incidence of breast cancer in some countries has been attributed to changing reproductive patterns, such as earlier age at menarche, later age at first childbirth, lower parity and shorter duration of breastfeeding, as well as lifestyle factors, such as overweight and obesity for postmenopausal breast cancer.[31] Younger age at diagnosis of breast cancer may be related to factors such as differences in patterns of risk factors and relative incidence of breast cancer subtypes and differences in population structure between low–, middle– and high–income countries.[31]

Within country differences

Differences in breast cancer incidence associated with a woman's country of birth have been reported in a New South Wales (NSW) study.[32] The highest rates of breast cancer in NSW were in women born in the Western world, typically English speaking areas.[32] The breast cancer incidence rates averaged for 2004–2008 were: women born in Australia (81.9 per 100,000), New Zealand (91.4 per 100,000) and western Europe (84.4 per 100,000), compared with women born in southeast Asia (62.7 per 100,000), East Asia (57.2 per 100,000), and high–income Asia Pacific countries (49.8 per 100,000).[32]

Breast cancer incidence differs between Indigenous and non–Indigenous women in Australia.[33] The age–standardised breast cancer incidence rate is lower for Aboriginal and Torres Strait Islander women at 94.2 per 100,000 (2010–2014) compared with 109.7 per 100,000 in 2010–2014 for non–Indigenous women.[29] Internationally, there are lower breast cancer incidence rates for Indigenous compared with non–Indigenous populations, except for Indigenous women in Alaska and New Zealand who have higher rates than their non–Indigenous counterparts.[33, 34]

There is evidence to suggest that lifestyle factors have contributed to an increase in breast cancer incidence among some population subgroups worldwide. For example, a study of the prevalence of modifiable cancer–related risk factors in the United States indicated that a larger proportion of breast cancer risk was attributable to the lifestyle–related risk factors examined in the study among African–American women (16%) compared with white women (8%).[35] Similarly, changes in lifestyle, including adoption of a western diet, less physical activity and more overweight and obesity associated with acculturation among Asian women is suggested to have contributed to the increased incidence of breast cancer observed in this population group, in the United States.[8]

Potential pathways for differences in Indigenous compared with non–Indigenous rates of breast cancer include differences in reproductive patterns, different age structure and lower screening participation.[33, 36] Indigenous women are more likely to have their first child at a younger age and have more children than non–Indigenous women. Overall breastfeeding duration may be longer due to multiparity.[36] Further, the Indigenous population has a younger age structure and most breast cancer is diagnosed in women above the age of 50 years.[36] Indigenous women in Australia have lower participation in breast screening; 37.3% of Indigenous women aged 50–74 years participated in BreastScreen Australia compared with 53.2% of non–Indigenous women (age–standardised) in 2014–15.[37]

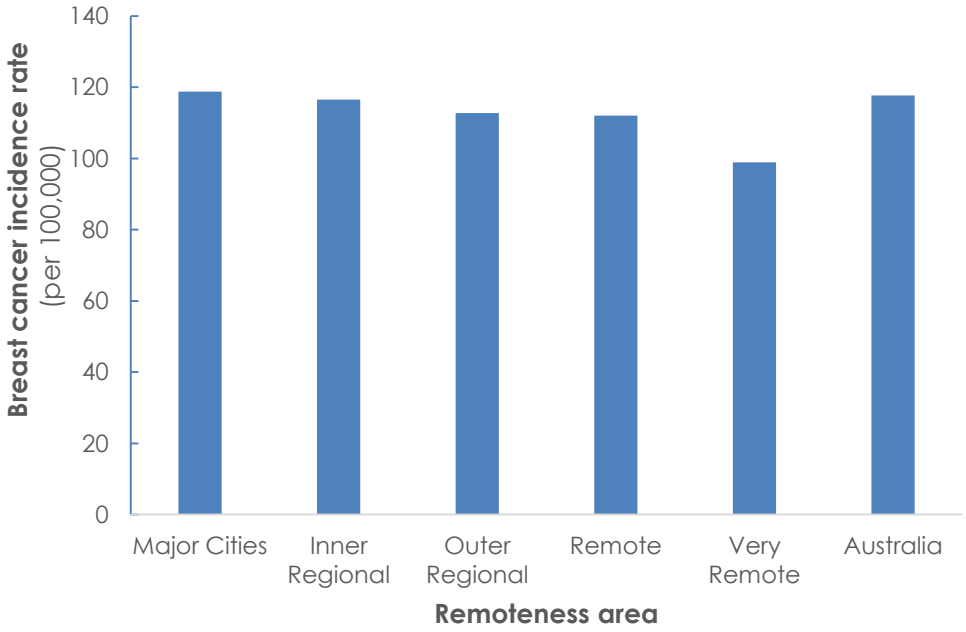
4.1.3 Remoteness and urbanisation

A systematic review and meta–analysis of studies, including studies conducted in the United States, Canada, the United Kingdom, Australia, Italy and Switzerland, indicated that residing in urban versus rural areas was associated with a 9% higher breast cancer incidence (pooled relative rate for urban versus rural 1.09, 95% CI 1.01–1.19).[38]

Additional Australian data show that breast cancer incidence is higher for women living in major cities (age–standardised rate 118.8 per 100,000 in 2008–2012) than for women living in very remote areas (age–standardised rate 98.9 per 100,000 in 2008–2012) (Figure 4.3).[29]

Potential pathways or mechanisms linking remoteness or urbanisation with breast cancer risk include availability of and access to screening and clinical services for early detection of disease, differences in reproductive factors (such as early menarche, lower parity and later age at first birth), and, possibly, differences in lifestyle factors.[38-41]

Figure 4.3 Age–standardised breast cancer incidence rates in Australia by remoteness of area, 2008–2012



Source: Cancer Australia. National cancer control indicators. Cancer incidence. 2018 [Available from: https://ncci.canceraustralia.gov.au/diagnosis/cancer–incidence/cancer–incidence.][29]

4.1.4 Socioeconomic status

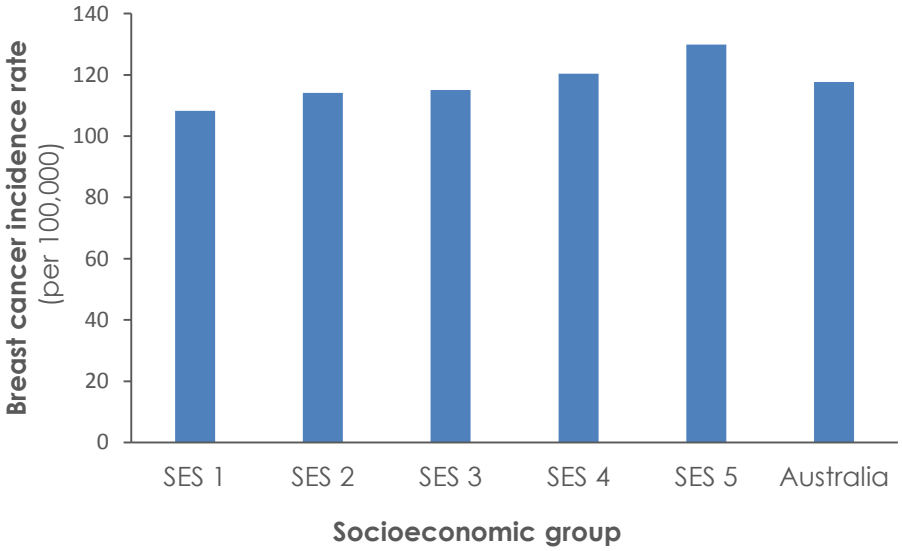
Evidence from national databases in Australia and from systematic reviews in Australia and in other westernised countries have shown that women who reside in areas of higher socioeconomic status (SES) have an increased risk of breast cancer compared with those that reside in more disadvantaged areas.[38, 39] This relationship appears to be independent of ethnicity.

In Australia, age–standardised breast cancer incidence was 108.3 per 100,000 for women in the most disadvantaged quintile (SES 1), compared with 129.9 per 100,000 in the least disadvantaged quintile (SES 5), in 2008–2012 (Figure 4.4).[29]

A systematic review and meta–analysis of studies conducted in the United States, Canada, the United Kingdom, Australia, Italy and Switzerland indicated that residing in higher socioeconomic areas, characterised by higher income, was associated with higher breast cancer incidence.[38] Higher income was associated with a 17% increase in breast cancer incidence, and higher composite SES was associated with a 25% increase in breast cancer incidence.[38]

In the United States, 1988–1992 SEER data showed that breast cancer incidence in the most advantaged quintile was 47% higher than the most disadvantaged quintile, independent of ethnicity.[40] There has also been a noted increase in breast cancer incidence among women residing in high SES areas compared with lower SES areas across all racial/ethnic groups.[41]

Figure 4.4 Age–standardised breast cancer incidence rates in Australia, by socioeconomic status, 2008–2012



Note: SES 1=most disadvantaged, SES 5=least disadvantaged.

Source: Cancer Australia. National cancer control indicators. Cancer incidence. 2018 [Available from: https://ncci.canceraustralia.gov.au/diagnosis/cancer–incidence/cancer–incidence.][29]

Similar pathways may be involved in the association between breast cancer risk and socioeconomic status as for remoteness and urbanisation. These pathways include the physical attributes of an area that may promote or hinder breast cancer risk factors, such as physical activity, and availability of resources relevant for screening and diagnosis, such as access to mammography and clinics.[38] In Australia, there are also inter–relationships between SES, remoteness and Indigenous status.[39]

4.2 Personal characteristics

4.2.1 Birthweight

Evidence summary

Evidence classification—premenopausal breast cancer: Probable.

Birthweight is probably associated with an increased risk of premenopausal breast cancer. This was the judgement by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR).[11] Findings from more recent large prospective studies generally support an association. The increased risk of premenopausal breast cancer has been estimated as 1.05 (95% CI 1.02–1.09) per 500 gram increase in birthweight.[10, 11]

Evidence classification—postmenopausal breast cancer: Inconclusive.

The evidence for an association between birthweight and risk of breast cancer is inconclusive. The WCRF/AICR[11] judged the evidence as 'Limited–no conclusion' for any association between birthweight and risk of postmenopausal breast cancer, due to inconsistent findings across cohort studies. Recent evidence from two large cohort studies did not find an association between birthweight and risk of postmenopausal breast cancer.

Background

Birthweight is determined by genetic and environmental influences. Potential biological pathways linking birthweight with breast cancer have been proposed, including the influence of oestrogens and other endocrine factors, such as insulin–like growth factor 1 (IGF1) *in utero* on foetal growth and very early mammary gland development, thought to play a role in the initiation and promotion of breast cancer.[11, 42] WCRF/AICR[11] indicated birthweight is a marker for prenatal growth, reflecting a combination of factors including foetal nutrition. Birthweight is also a predictor of later growth and maturation—for example, age at menarche—which are themselves determinants of breast cancer risk.

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project [11] considered there was 'Strong–probable' evidence that '*factors that lead to greater birthweight, or its consequences*' increase the risk of premenopausal breast cancer. The judgment was based on evidence from 25 studies, one of which was a large pooled analysis of individual level data from 13 studies (including eight cohort studies).[43] Sixteen studies contributed to a dose–response analysis for premenopausal breast and the summary estimate per 500 gram increase in birthweight was 1.05 (95% CI 1.02–1.09), with no evidence of significant heterogeneity.[10] Some of the studies contributing to the dose–response meta–analysis had not adjusted for age, alcohol intake, reproductive factors and/or adult body mass index.

The WCRF/AICR considered that the evidence for an association between birthweight and postmenopausal breast cancer was limited, and no conclusion was made—that is, the judgment was 'Limited–no conclusion'. Fourteen studies contributed to a dose–response

analysis for postmenopausal breast cancer and the summary estimate per 500 gram increase in birthweight was 1.00 (95% CI 0.98–1.02) with no evidence of significant heterogeneity.[10]

Recent evidence

Findings from the French Teachers Cohort of 67,634 women (497 premenopausal and 3,138 postmenopausal breast cancer cases) were consistent with the findings of the WCRF/AICR.[11] A significant positive association was observed between higher birthweight and premenopausal breast cancer but not postmenopausal breast cancer (RR for ≥4 kg compared with <2.5 kg 1.99, 95% CI 1.05–3.76; and 1.03, 95% CI 0.82–1.29, respectively).[44]

Xue et al.[45] reported on findings from 1,133,893 person–years of follow–up of participants in the Nurses' Health Study II. They reported a lower incidence of premenopausal breast cancer associated with lower birthweight (HR 0.74, 95% CI 0.58–0.94 for <2.5 kg versus ≥3.9 kg). This trend did not change appreciably after additional adjustment for body fatness later in life.

Conversely, a cohort study from Norway[46] did not find any association between birthweight and either premenopausal or postmenopausal breast cancer.

Table D.1 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.2.2 Height

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that adult-attained height is associated with an increased risk of breast cancer.

The increased risk of breast cancer has been estimated as 1.17 (95% CI 1.15–1.19) per 10 cm increase in height,[47] and 1.06 (95% CI 1.02–1.11) for premenopausal breast cancer and 1.09 (95% CI 1.07–1.11) for postmenopausal breast cancer, per 5 cm increase in height.[10, 11]

Background

Adult attained height is unlikely to directly influence breast cancer risk.[48] However, it is a marker of shared mechanisms that determine both height and cancer risk, such as growth processes that are determined by both genetic and environmental, including nutritional, components.[49]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project[11] considered the '*developmental factors leading to greater linear growth (marked by adult attained height)*' to be a convincing cause of

premenopausal and postmenopausal breast cancer—that is, the judgement was 'Strong–convincing'. The evaluation was based on evidence from 29 studies reporting on premenopausal and 41 studies reporting on postmenopausal breast cancer. Dose–response analyses provided summary estimates per 5 cm increase in attained adult height of 1.06 (95% CI 1.02–1.11; 26 studies, significant heterogeneity) for premenopausal breast cancer and 1.09 (95% CI 1.07–1.11; 33 studies, significant heterogeneity) for postmenopausal breast cancer.[10] The increased risk was similar across geographic regions and when restricted to studies that adjusted simultaneously for age, alcohol and reproductive factors.

Recent evidence

A systematic review and meta–analysis of a large number of prospective studies reported a summary estimate per 10 cm increase in adult attained height of 1.17 (95% CI 1.15–1.19) with evidence of significant heterogeneity.[47] The summary estimate was similar for premenopausal and postmenopausal breast cancer. It was similarly increased for oestrogen receptor positive (ER+) (RR 1.18, 95% CI 1.13–1.23), progesterone receptor positive (PR+) (RR 1.16, 95% CI 1.10–1.22), and progesterone receptor negative (PR–) (RR 1.11, 95% CI 1.02–1.20) but not oestrogen receptor negative (ER–) disease.

The California Teachers Study involving 109,862 women (3,844 breast cancer cases) in the United States[50] reported a significant association between taller height and risk of premenopausal and postmenopausal ER+ breast cancer. Among non–menopausal hormone therapy (MHT) users, the increased risk of postmenopausal breast cancer among women who had attained a height of 65–66 inches compared with those that attained a height of less than 65 inches was HR 1.20 (95% CI 1.06–1.35).

Conversely, a cohort study of 38,610 Japanese women did not find an association with risk of breast cancer for the highest versus lowest quartile of height, and the positive trend with increasing height was not statistically significant.[51]

Table D.2 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.2.3 Having been breastfed

Evidence summary

Evidence classification: Inconclusive.

The evidence of any association between having been breastfed as an infant and risk of breast cancer is inconclusive. Evidence from the highest–quality studies indicates no association between having been breastfed as an infant and risk of breast cancer.

Background

Being breastfed in infancy, which has established benefits for infant nutrition and health, is an early–life exposure that has been hypothesised to be associated with the risk of breast cancer as an adult. Potential mechanisms have been suggested for an increased and a decreased risk of breast cancer associated with having been breastfed as an infant. Having

been breastfed may increase breast cancer risk through the possible presence in breast milk of environmental toxicants such as organochlorines, the transmission of a tumour virus, or the consumption of growth factors in breast milk.[52] Potential mechanisms hypothesised for association of having been breastfed with decreased breast cancer risk include anti–apoptotic milk proteins, progesterone and gonadotropin–releasing hormones, or reduced cytochrome P4501A activity.[52]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project[11] judged the evidence for any association between having been breastfed ('being breastfed') and breast cancer risk as 'Limited–no conclusion'. The evidence had been previously considered too limited to draw conclusions in the 2007 WCRF/AICR Second Expert Report, and the evidence was not updated as part of the Continuous Update Projectfor the Third Expert Report, 2018.[11]

Recent evidence

A meta–analysis by Wise & Titus[52] included three cohort studies, 10 case–control studies, one cross–sectional study and one case series study. The meta–analysis indicated that having been breastfed compared with never having been breastfed had a weak association with decreased risk of breast cancer (RR 0.94, 95% CI 0.89–0.99). There was a decreased risk of premenopausal breast cancer (RR 0.88, 95% CI 0.78–0.98) and no association with postmenopausal breast cancer risk (RR 0.98, 95% CI 0.91–1.05).[52] The two largest cohort studies in the meta–analysis by Wise & Titus showed no association between having been breastfed and breast cancer risk,[53] among neither premenopausal or postmenopausal women.[54] The largest case–control study in the meta–analysis that included over 4,500 cases also indicated no association between ever being breastfed and breast cancer risk in either premenopausal or postmenopausal women.[55]

Table D.3 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.2.4 Mammographic breast density

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that higher mammographic breast density is associated with an increased risk of breast cancer. The evidence is consistent across meta-analyses. Breast density is indicated to be an independent risk factor and a biomarker of breast cancer.

The increased risk, expressed as odds ratio per standard deviation (SD) of normally transformed density, has been estimated in a large meta–analysis predominantly of nested case–control studies to be 1.53 (95% CI 1.44–1.64) for percent dense area.[56] Thus, women with moderately dense breasts on mammography (85th percentile) are 1.53 times more likely to develop breast cancer than women with average breast density. The opposite also

applies—women with moderately non-dense breasts on mammography (15th percentile) are 0.65 times less likely to develop breast cancer than women with average breast density.

Background

Mammographic breast density refers to the appearance of the breast on mammographic screening. It reflects the proportional amounts of fat (dark in appearance) and stromal and epithelial tissues ('glandular tissue'; white in appearance) in the breast.[57]

There is no gold standard for mammographic density measurement,[58] and current methods rely on semi–quantitative reviews by trained experts. The most commonly used tool is the Breast Imaging Reporting and Data System (BI–RADS), which classifies mammographic breast density into four categories:[59]

1. Almost entirely fat—less than 25% glandular tissue
2. Scattered fibroglandular densities—approximately 25–50% glandular tissue
3. Heterogeneously dense—approximately 51–75% glandular tissue
4. Extremely dense—greater than 75% glandular tissue.

The distribution of BI–RADS density categories for US women of all ages is reported to be approximately 10%, 40%, 40% and 10%, respectively.[60, 61] However, as women get older the proportion of women with dense breasts, in BI-RADS categories 3 and 4, decreases.[62] Further, Moshina et al.[61] reported the distribution among Norwegian women attending breast cancer screening and aged 50–69 years as 38%, 35%, 24% and 5% respectively, and this distribution was indicated to correspond well with other European data. Similarly, Wanders et al.[63] has indicated the distribution of mammographic density to be 21.6%:41.5:28.9% and 8%, respectively, among women aged 50–75 years. There are currently no data on the distribution of breast density of women in Australia. [64]

Breast density has a strong genetic component (heritability accounts for approximately 60% of the variation in breast density), but is also influenced by lifestyle factors.[65, 66] Mammographic density declines with increasing age, and is associated with several other independent risk factors for breast cancer. Mammographic density is lower in parous compared with nulliparous women,[67] and decreases with increasing body mass index (BMI).[68, 69] The findings from the meta–analysis by Pettersson et al.[56] showed clearly the importance of BMI as a confounder between breast density and breast cancer risk, especially among postmenopausal women. Use of combined menopausal hormonal therapy (MHT) is associated with increased mammographic density.[70] In assessing the evidence for an association, therefore, it is important to consider the potentially confounding influence of age, parity, BMI and MHT use.

The pathways linking breast density with breast cancer risk are not fully understood. Higher mammographic density reflects a higher proportion of glandular tissue in the breast (percent dense area (PDA)), and thus a larger number of stromal and epithelial cells at risk of carcinogenesis.[66] Absolute dense area (ADA) and, conversely, absolute non–dense area, have also been linked to risk of breast cancer.

Recent evidence

A collaborative analysis on the association between mammographic density and breast cancer risk included data from 13 case–control studies—12 of which were nested in large cohort studies—conducted between 1980 and 2011.[56] The pooled odds ratio (OR) for one standard deviation (SD) increase in normally transformed mammographic density was: 1.52 (95% CI 1.39–1.66) for PDA and 1.37 (95% CI 1.29–1.47) for ADA for premenopausal breast cancer; and 1.53 (95% CI 1.44–1.64) for PDA and 1.38 (95% CI 1.31–1.34) for ADA for postmenopausal breast cancer. Estimates were adjusted for age, BMI and parity, and in the analysis for postmenopausal breast cancer, the summary estimate did not change after additional adjustment for MHT use.

Therefore, for the odds ratio per SD of 1.53: women with moderately dense breasts (1 SD above the mean; 85th percentile of density) have 1.53 times increased risk of breast cancer and women with the most dense breasts (2 SD above the mean; 95th percentile of density) have 2.34 times increased risk of breast cancer compared with mean breast density. Conversely women with moderately non-dense breasts (1 SD below the mean; 15th percentile of density) have 0.65 times decreased risk and women with the least dense breasts (2 SD below the mean; 5th percentile of density) have 0.43 times decreased risk of breast cancer compared with median breast density.

An odds ratio per standard deviation of 1.53 for normally transformed PDA can also be interpreted as a relative risk for each BI-RADS category. Assuming a distribution of women in BI-RADS categories 1–4 of 10%:40%:40%:10%, respectively: women with extremely dense breasts (BI-RADS 4) are estimated to have 2.14 times increased risk of breast cancer and women with heterogeneously dense breasts (BI-RADS 3) are estimated to have 1.28 times increased risk of breast cancer compared with women with median breast density (personal communication; J.G. Dowty via email). Conversely women with scattered fibroglandular densities (BI-RADS 2) are estimated to have 0.80 times and women with fatty breasts (BI-RADS 1) are estimated to have 0.48 times decreased risk of breast cancer compared with women with median breast density.

A 2006 systematic review with meta–analysis examining the association between mammographic density and breast cancer risk included 42 studies conducted between 1978 and 2005. This review included 17 prospective studies, 17 case–control studies and nine studies in 'symptomatic populations'.[71] Risks were presented with women with the least dense breasts (<5% PDA) as the referent category giving higher estimates of risk compared to estimates in which women with average breast density are the referent category. Compared with PDA <5%, the summary RRs for risk of incident breast cancer associated with PDA of 5–24%, 25–49%, 50–74% and 75% or greater were 1.79 (95% CI 1.48–2.16), 2.11 (95% CI 1.70–2.63), 2.92 (95% CI 2.49–3.42)and 4.64 (95% CI 3.64–5.91), respectively. These pooled risk estimates were comparable to those from three studies reported using the BI–RADs classification system: Compared with level 1 (fatty parenchyma), the pooled risk estimates were 2.04 (95% CI 1.56–2.67), 2.81 (95% CI 2.13–3.71) and 4.08 (95% CI 2.96–5.63) for levels 2 (scattered), 3 (heterogeneous) and 4 (extremely dense tissue) respectively.[71]

A meta–analysis of studies conducted in Asian populations (one cohort and five case–control studies) reported a pooled estimate for risk of postmenopausal breast cancer associated with a 25% increase in PDA of 1.73 (95% CI 1.20–2.47).[72] Risk of premenopausal breast cancer was similarly significantly increased. No information on adjustment for potentially confounding factors was reported.

An analysis of data from a Swedish randomised controlled trial of mammographic screening provides additional prospective data on the association between mammographic breast density and breast cancer risk in women aged 45–59 years.[73] Compared with women with non–dense mammographic breast tissue, women with dense breast tissue had a higher risk of breast cancer (RR 1.57, 95% CI 1.23–2.01), consistent with the findings of Pettersson et al.[56] for PDA. The analyses were adjusted for age and BMI, and stratification by age group showed a stronger association among women aged 40–49 compared with women aged 50–59 years.

A recent retrospective study in Norway[61] reported an adjusted odds ratio of a screen–detected breast cancer as 1.37 (95% CI 1.19–1.59) for screening examinations of women with dense (≥7.5%) versus non–dense breasts (<7.5%). Compared with women with non–dense breasts, women with dense breasts had 2.93 times higher (95% CI 2.16–3.97) odds of an interval breast cancer. This study was limited in that women included in the non–dense group differed in some factors other than breast density from those in the dense group. Hence the differences may not have been solely due to mammographic density.

Table D.4 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.2.5 Breast size

Evidence summary

Evidence classification: Inconclusive.

The evidence on any association between breast size and risk of breast cancer is inconclusive. Findings across studies are inconsistent and the studies are limited in quality. There is some evidence that surgical breast reduction is associated with a decreased risk of breast cancer.[74]

Background

Investigation of breast size and breast cancer risk is difficult due to lack of consistency in the appropriate measure of breast size. The measures used have included self–reporting, cup size, mammographic assessment and three–dimensional imaging. Confounding variables, such as body mass index (BMI) and reproductive factors, must be controlled for in analyses.[74]

The potential mechanism for any association between breast size and breast cancer risk may relate to the larger number of epithelial cells from which cancer may develop in larger breasts. Larger breasts may also affect breast cancer risk via increased amounts of fat tissue, which contributes to higher local oestrogen levels and may act as a slow–releasing source of fat–soluble carcinogens.[74]

Recent evidence

A systematic review by Jansen et al.[74] included 16 studies (four cohort studies, 10 case–control and two other studies) examining any association between breast size and risk of breast cancer. The overall results were conflicting, and meta–analysis was not performed due to the high heterogeneity between studies. Studies were limited by their small sample

size, retrospective designs and unreliable size measures, which included measurement of breast size by self–reported bra cup size, at different stages of life, by calculation from mammograms, and from chest circumference.

A population–based case–control study by Chen et al.[75] investigated bra wearing, including bra cup size, and breast cancer risk in postmenopausal women. There was no association between bra cup size and breast cancer risk in analyses adjusted for age, reference year and country.

The systematic review by Jansen et al.[74] also reported indirect evidence of a relationship between breast size and breast cancer risk, from studies of surgical breast reduction. Breast reduction surgery, including cosmetic breast reduction, was associated with decreased risk of breast cancer in seven of eight studies (six cohort and two case–control studies); no meta–analysis was performed.

Table D.5 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3 Family history & genetics

4.3.1 Family history of breast cancer

Evidence summary

Evidence classification: Convincing.

There is covincing evidence that family history of breast cancer is associated with increased risk of breast cancer. The evidence is consistent across two large meta–analyses and four large cohort and case–control studies published since the meta–analyses. The increased breast cancer risk associated with one affected first–degree relative has been estimated as 1.80 (95% CI 1.70–1.91),[76] with two affected first–degree relatives as 2.93 (95% CI 2.37–3.63)[76] and with 3 or more affected first–degree relatives as 3.90 (95% CI 2.03–7.49),[76] compared to no family history of breast cancer. The increased risk associated with one or more affected second–degree relatives has been estimated as 1.5 (95% CI 1.4–1.6).[77]

The increased breast cancer risk associated with having a first–degree relative with breast cancer is likely higher for younger women and for women whose relative was diagnosed with breast cancer at a younger age.

Background

While most women who develop breast cancer do not have a family history of the disease, it has been shown that family history, either on the maternal or paternal side and in first– or second–degree relatives, can influence breast cancer risk.[77, 78] First–degree relatives are an individual's parents, siblings and children. Second–degree relatives are an individual's aunts, uncles, grandparents, grandchildren, nieces, nephews and half–siblings.

Inherited genetic factors contribute to the mechanism for the association between increased breast cancer risk and family history of breast cancer. These genetic factors may include mutations in the *BRCA1* and *BRCA2* genes and in other genes such *as PALB2, TP53, PTEN and STK11*.[79] Shared environmental factors may also contribute to the association between family history and breast cancer risk. These include common environmental exposures and backgrounds (such as for sisters, especially in early life) and common lifestyle and dietary factors in families.[77, 80]

Recent evidence

Relationship (first–degree or second–degree) and number of affected relatives

Women who have one affected first–degree relative have a higher risk of breast cancer than who have no affected relatives. The risk was estimated in two meta–analyses as 1.80 (95% CI 1.70–1.91; 6,810 cases and 6,998 controls),[76] and 2.1 (95% CI 2.0–2.2; 38 studies).[77]

Two large cohort and one case–control study published since these meta–analyses reported a similarly increased risk of breast cancer for women with one first–degree relative compared with women with no affected relatives: HR 1.8 (95% CI 1.8–1.9; 69, 248 breast cancer cases from Swedish database);[81] HR for postmenopausal women 1.42 (95% CI 1.30–1.55) (78,171 women from Women's Health Initiative, United States);[82] and RR 1.79 (no CI provided; 7,861 cases from Swedish database study).[78]

For women with two affected first–degree relatives, the increased risk of breast cancer compared with women who have no affected relatives has been estimated as: RR 2.93 (95% CI 2.37–3.63; meta–analysis of 603 cases and 404 controls);[76] RR 3.6 (95% CI 2.5–5.0; meta–analysis of five studies);[77] HR for postmenopausal women 1.66, (95% CI 1.32–2.08);[82] and RR 2.84 (no CI provided; 543 cases).[78] For women with 3 or more affected first–degree relatives, the increased risk of breast cancer compared with women who have no affected relatives has been estimated as RR 3.90 (95% CI 2.03–7.49).[76]

For women with one or more affected second–degree relatives, the increased risk of breast cancer compared with women who have no affected relatives has been estimated in a meta–analysis of 10 studies as 1.5 (95% CI 1.4–1.6).[77] In a large case–control study of 56,498 cases of breast cancer in Sweden, women with an affected maternal grandmother had an increased risk of breast cancer of 1.27 (95% CI 1.09–1.47; 198 cases) and the increased risk for having a paternal grandmother with breast cancer was 1.26, (95% CI 1.05–1.50; 134 cases).[78] For women with at least two affected female second–degree relatives, increased breast cancer risk was estimated as 1.60 (95% CI 1.24–2.07; 64 cases).

Age of a woman and family history of breast cancer

The estimated risk of breast cancer for a woman with a first–degree relative with breast cancer was reported to be larger at a younger age in the meta–analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC).[76] For women with one first–degree affected relative compared with women with no affected relatives, the relative risk for women aged <50 years was 2.14 (95% CI 1.92–2.38); and for women ≥50 years the risk was 1.65 (95% CI 1.53–1.78). Similarly, for women with two first–degree relatives, the relative risk for women aged <50 years was 3.84 (95% CI 2.37–6.22) compared with the risk for women aged ≥50 years of 2.61 (95% CI 2.03–3.34).[76]

The meta–analysis by Pharoah et al.[77] reported inconsistent findings among the 11 studies that estimated breast cancer risk according to the age of the subject with a family history of breast cancer.

In a cohort study, Kharazmi et al.[81] reported a higher increased risk for a woman aged <50 years with a mother or sister with breast cancer, compared with a woman aged 60–78 years and the risk to a women with no affected relatives as 2.13 (95% CI 2.06–2.21) at age <50 years and 1.6 (95% CI 1.5–1.7) at age 60–78 years.

Age of relative at diagnosis and family history of breast cancer

In the meta–analysis by CGHFBC,[76] for women of a given age, the increased risks associated with having a first–degree relative with breast cancer were higher the younger their relative was at breast cancer diagnosis:

- For women aged <40 years with one first–degree relative with breast cancer, the RR with a relative diagnosed at <40 years was 5.7 (95% CI 2.7–11.8), compared with RR with a relative aged ≥60 years of 1.4 (95% CI 0.9–2.1).
- For women aged 50–59 years with one first–degree relative with breast cancer, the RR with a relative diagnosed at <40 years was 2.0 (95% CI 1.2–3.4), compared with RR with a relative aged ≥60 years of 1.5 (95% CI 1.2–2.0).
- For women aged <50 years with two first–degree relatives with breast cancer, the RR with at least one relative diagnosed at <40 years was 13.5 (95% CI 3.4–53.9), compared with RR when both relatives diagnosed >40 years of 7.8 (95% CI 2.4–25.0).[76]

In the meta–analysis by Pharoah et al.,[77] the risk reported was higher if the relative was diagnosed at a younger age, with the greatest risk for women aged <50 years with a first–degree relative diagnosed at <50 years as RR 3.3 (95% CI 2.8–3.9) from five studies that reported on the relative's age at diagnosis.

In cohort studies published since the meta–analyses, the findings were:

- for women with one affected first–degree relative diagnosed before 40 years, HR 2.3 (95% CI 2.1–2.6), compared with if the relative was diagnosed at >80 years, HR 1.5 (95% CI 1.4–1.6)[81]
- breast cancer risk in women whose mother or sister was diagnosed with breast cancer aged <50 years compared with women with no family history, RR 1.70 (95% CI 1.48–1.95; 219 cases) [83]
- in those whose mother or sister was diagnosed aged ≥50 years, RR 1.30 (95% CI 1.27–1.54; 467 cases), with p 0.016 for <50 years versus ≥50 years (69,805 women from the Nurses' Health Study, United States).[83]

Table D.6 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.2 Family history of other cancers

Evidence summary

Evidence classification: Convincing.

There is convincing evidence from modelling studies, cohort studies and case-control studies that a family history of ovarian cancer and a family history of prostate cancer is associated with an increased risk of breast cancer. The association between a family history of pancreatic cancer and increased risk of breast cancer is observed from the population-level data used to inform the BOADICEA risk prediction model. Several studies have also shown an association between family history of colorectal cancer and increased risk of breast cancer.

Risks are higher as more relatives are affected by the various cancers, and if a woman also has relatives affected by breast cancer.

Background

Inherited mutations in genes associated with increased risk of female breast cancer (such as *BRCA1* and *BRCA2*) are also associated with increased risk of cancers other than breast. Hereditary Breast And Ovarian Cancer Syndrome (HBOC), caused by mutations in the *BRCA1* and *BRCA2* genes, is the most common. Mutations in *BRCA1* and, particularly, *BRCA2* are also associated with cancers other than ovarian cancer and female breast cancer, including male breast cancer, pancreatic cancer and prostate cancer.

Rarer hereditary genetic mutations associated with increased breast cancer risk include: *TP53* (associated with Li–Fraumeni Syndrome and childhood sarcomas), *CDH1* (associated with diffuse gastric cancer), *PTEN* (associated with Cowden Syndrome and thyroid and endometrial cancers) and *STK11* (associated with Peutz–Jeghers Syndrome and gastrointestinal, pancreatic and gynaecological cancers). Mutations in *PALB2* are associated with an increased risk of pancreatic cancer in women and men. The evidence on the risks of breast cancer associated with carriers of mutations in these specific genes is summarised in separate evidence summaries (sections 4.3.12, 4.3.6, 4.3.9 and 4.3.11, respectively).

The mechanisms for associations between family history of cancers other than breast cancer and breast cancer risk are likely via shared genetic factors and/or shared exposure to environmental factors in the families. Inherited mutations in genes such as *BRCA1, BRCA2, TP53, CDH1, PALB2, PTEN and STK11* may increase the risk of other cancers as well as breast cancer through similar biological mechanisms.[82] Families may have similar dietary patterns, reproductive habits, physical activity or body size that may influence risk of different cancers.[84]

A family history of many of these cancers is known to be associated with increased risk of carrying one or more of the genetic mutations associated with these cancers. However, few studies have estimated the associations between familial history of these cancers and risk of breast cancer among those women with unknown inheritance of the various gene mutations.

Recent evidence

Family history of ovarian cancer

Evans & Howell[85] indicated family history of ovarian cancer is included in the individual risk prediction models: BRCA probability (BRCAPRO), Cuzick–Tyrer, and BOADICEA (Breast and Ovarian Cancer Disease Incidence and Carrier Estimation Algorithm). The indicated relative risk at the extremes was reported as 1.5. Evans & Howell[85] noted that only these three models

(from five tested) accurately predicted risk in women with a family history of ovarian cancer. Only these models accounted for ovarian cancer in their risk assessment algorithm, which confirmed family history of ovarian cancer has a significant effect on breast cancer risk.

Sutcliffe et al.[86] indicated few published estimates of the risk of developing breast (or ovarian) cancer in women with a strong family history of ovarian cancer. Risks in women from families with 2 or more confirmed ovarian cancers in first-degree relatives were determined using data from the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Familial Ovarian Cancer Register. The number of cancers observed in more than 10,000 person–years of follow-up was compared with the number expected based on national-, age-, sex- and period-specific incidence rates. For breast cancer, the relative risk for women aged under 50 was 3.74 (95% CI 2.04–6.28) and 1.79 (95% CI 1.02–2.90) for women 50 years of age and older. The average risk was 2.36 (95% CI 1.59–3.37). These relative risks were indicated to correspond to absolute risks by age 70 of 15% for breast cancer. When the analyses were restricted to families that had been negative for mutations in *BRCA1* and *BRCA2*, the breast cancer risk was 3.32 (95% CI 1.52–6.31).[86]

In the population–based case–control study by Slattery & Kerber,[87] the association with increased risk of breast cancer among women with a first–degree or second–degree relative with ovarian cancer were not significant. This result reflected the small number of cases (OR 1.13, 95% CI 0.91–1.38; 50 cases and OR 1.10, 95% CI 0.93–1.31; 67 cases; respectively).

Claus et al.[88] was the first study to calculate the risk of breast cancer for women with a first–degree family history of ovarian cancer. Data were from the Cancer and Steroid Hormone Study, a large, population–based, case–control study conducted by the Centers for Disease Control. The lifetime risk of developing breast cancer for a woman with one or two first–degree relatives affected with ovarian cancer was estimated to be approximately 14% and 31%, respectively. A woman with one first–degree relative affected with ovarian cancer and one first–degree relative affected with breast cancer has an estimated risk of 40% of developing breast cancer by age 79 years if the relative with breast cancer was diagnosed in her thirties. This risk decreases with increasing age of onset of the relative affected with breast cancer. The authors indicated that these estimates were preliminary.

Family history of prostate cancer

A large cohort study from the Women's Health Initiative included 78,171 women (median follow–up of 11 years); 3,506 breast cancer cases were diagnosed during follow–up.[82] A family history of prostate cancer in a first–degree relative was associated with an increase in breast cancer risk after adjustments for confounders such as a family history of breast cancer (HR 1.14, 95% CI 1.02–1.26). A family history of both breast and prostate cancer in first–degree relatives was associated with an increased risk of breast cancer (HR 1.78, 95% CI 1.45–2.19).[82] A family history among first–degree relatives that included breast, prostate and colorectal cancer was associated with approximately 2–fold increased risk of breast cancer (HR 2.06, 95% CI 1.38–3.08).

A pooled analysis of a number of case–control studies from Italy and Switzerland examined associations between risk of cancer at different sites and family history in first–degree relatives. Increased risk of breast cancer was associated with family history in first–degree relatives of prostate cancer (OR 1.6, 95% CI 1.1–2.4, 59 cases).[80]

A consecutive series study of prostate cancer families in France indicated increased breast cancer risk was associated with family history of prostate cancer (risk estimates not provided)

Valeri et al.[89] Breast cancer risk was substantially higher with multiple relatives with prostate cancer, and if relatives were diagnosed with prostate cancer at <55 years compared with diagnosis at ≥75 years.

Family history of pancreatic cancer

Around 5% of patients with pancreatic cancer carry germline mutations in *BRCA2*. Mutations in *PALB2* are also associated with an increased risk of pancreatic cancer.[90] For this reason, the BOADICEA risk prediction model includes occurrence of pancreatic cancers in families.[91] However, no individual studies were sourced examining the increased relative risk of breast cancer in women with a family of pancreatic cancer.

Family history of colorectal cancer

The large cohort study found no association between a family history of colorectal cancer and risk of breast cancer, after adjustments for a family history of breast and prostate cancer (HR 1.08, 95% CI 0.99–1.19).[82] A family history of both breast and colorectal cancer in first–degree relatives was associated with an increased risk of breast cancer (HR 1.47, 95% CI 1.34–1.61). A family history among first–degree relatives that included breast, prostate and colorectal cancer was associated with an approximately 2–fold increased risk of breast cancer (HR 2.06, 95% CI 1.38–3.08).

A pooled analysis of case–control studies from Italy and Switzerland examined associations between risk of cancer at different sites and family history in first–degree relatives.[80] Increased risk of breast cancer was associated with family history in first–degree relatives of colorectal cancer (OR 1.5, 95% CI 1.1–1.9; 150 cases).

A US population–based case–control study indicated an association between a first–degree relative with colon cancer and increased breast cancer risk (OR 1.26, 95% CI 1.08–1.45; 201 cases).[87] This study also showed an association between a second–degree relative with colon cancer and increased risk of breast cancer (OR 1.21, 95% CI 1.07–1.36; 230 cases).

Family history of other cancers

Turati et al.[92] found significant associations between breast cancer and family history of haemolymphopoietic cancers (OR 1.7, 95% CI 1.2–2.4), after controlling for multiple testing. This study included a network of case–control studies from Italy and Switzerland, including more than 12,000 cases of 13 different cancers.

Table D.7 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.3 *ATM* gene mutation

Evidence summary

Evidence classification: Convincing.

The risk of breast cancer for a woman in the general population who has an ataxia–telangiectasia mutated (*ATM*) gene mutation is approximately 1.7 times the risk for a woman without an *ATM* mutation, according to a large case–control gene panel testing study that adjusted for family history of cancer (OR 1.74, 95% CI 1.46–2.07).[93] The breast cancer risk

associated with carrying a heterozygous *ATM* mutation is estimated to be higher (approximately 3) for those carriers who have relatives with ataxia–telangiectasia and is higher for younger women than for older women who are *ATM* mutation carriers.[94]

Background

The *ATM* gene codes for a protein kinase that has a key role in DNA repair. This protein kinase recognises double–stranded DNA breaks and activates cellular responses by phosphorylating other proteins in the DNA–damage response cascade.[95, 96] Mutations in the *ATM* gene can prevent cells from responding correctly to DNA damage, allowing breaks in DNA strands to accumulate, and potentially leading to formation of cancerous tumours.[96]

The *ATM* gene mutation is associated with ataxia–telangiectasia (A–T), a rare, inherited, childhood–onset disorder that affects the nervous system. A–T is autosomal recessive, meaning that a person needs to inherit two mutated copies of the gene to develop the disease. People with A–T are 'homozygous mutation carriers' and the disease occurs in about 1 in 40,000 to 100,000 people worldwide.[94, 96] A–T is associated with an increased risk of several cancers, including leukaemia and lymphoma.

About 1% of the general population are estimated to be heterozygous carriers of a mutated *ATM* gene, with one mutated copy and one normal copy of the *ATM* gene.[96]

Associations with breast cancer risk have been investigated for carriers of inherited *ATM* mutations which can be truncating (resulting in a shortened protein that may function improperly or not at all) or, less commonly, missense mutations (a change in one gene base pair that results in an amino acid change in the ATM protein).[94, 95, 97, 98]

Recent evidence

A large case–control gene panel testing study from Kurian et al.[93] estimated risks of breast cancer associated with germline mutations. The study used sequencing results of a 25–gene panel drawn from 95,561 women tested clinically for hereditary cancer risk in a retrospective cohort study. *ATM* mutations were detected in 640 women (0.67%), 244 of whom had invasive ductal breast cancer. *ATM* mutations were associated with increased breast cancer risk, with an odds ratio (OR) of 1.74 (95% CI 1.46–2.07)[ii] from multivariate logistic regression and an OR of 2.02 (95% CI 1.49–2.75) from a matched case–control analysis. The *ATM* mutations in this analysis were classified using the American College of Medical Genetics and Genomics Recommendations[99] and the analyses were adjusted for age, race/ethnicity and family cancer history.[93]

Familial studies have produced higher risk estimates for carriers of the *ATM* gene who have family members with A–T. A meta–analysis by van Os et al.[94] analysed the risk of breast cancer in four studies from four cohorts of parents and siblings of A–T patients. Breast cancer incidences for all relatives of A–T patients and for relatives who were heterozygote *ATM* mutation carriers were compared with expected incidence rates for the general population or non–carrier reference populations. There was an increased risk of breast cancer for all

[ii] Risk estimates for invasive breast cancer overall, i.e. ductal and lobular breast cancer, were identical to those for ductal breast cancer (personal communication; A. Kurian via email).

relatives of A–T patients of RR 1.7 (95% CI 1.4–2.1). For heterozygous *ATM* carriers, the increased risk was higher (RR 3.0, 95% CI 2.1–4.5). Among heterozygous *ATM* carriers the breast cancer risk was higher for younger women (aged under 45 to 55 years) (RR for heterozygotes 7.0, 95% CI 4.1–11.9) than for older women (RR for heterozygotes 2.1, 95% CI 1.2–3.6).[94]

Easton et al.[98] reported increased risk of breast cancer for truncating *ATM* mutations in a meta–analysis of three large cohort studies of relatives of A–T patients of RR 2.8 (95% CI 2.2–3.7). Easton et al.[98] also reported increased risk of breast cancer associated with some missense *ATM* mutations, including one missense mutation (*ATM* c.7271T > G) that was associated with a higher risk of breast cancer than truncating mutations (RR 8.0, 95% CI 2.3–27.4) in a case–control family study.[95]

A meta–analysis by Aloraifi et al.[100] included 15 case–control studies of breast cancer risk in high–risk groups (cases with family history of breast cancer, bilateral breast cancer and/or early onset of breast cancer). For protein truncating mutations in the *ATM* gene, the pooled odds ratio for breast cancer was 3.2 (95 CI 2.04–5.04).[100]

A case–control study by Couch et al.[101] estimated risk of breast cancer in women with breast cancer referred for hereditary cancer genetic testing, compared with controls in a public reference data set, using results of germline multigene panel tests. In women of European ancestry, *ATM* mutations were detected in 274 of 29,229 breast cancer cases and in 90 of 26,644 controls and were associated with increased risk of breast cancer (OR 2.78, 95% CI 2.22–3.62).[101] For all ethnicities, the increased risk associated with *ATM* mutations was OR 2.91 (95% CI 2.41–3.50) (41,154 breast cancer cases and 52,160 controls).[101]

A case–control study by Decker et al.[102] of 13,087 breast cancer cases and 5,488 controls from the United Kingdom showed an increased risk of breast cancer for truncating *ATM* mutations of OR 3.26 (95% CI 1.82–6.46).

Table D.8 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.4 *BRCA1* gene mutation

Evidence summary

Evidence classification: Convincing.

The increased risk of breast cancer among women with a *BRCA1* mutation compared to women without a *BRCA1* mutation has been estimated as 5.91 (95% CI 5.25–6.67), in a large case–control gene panel testing study that adjusted for family history of relevant cancers.[93]

Risk estimates are considerably higher from a prospective cohort study, predominantly of *BRCA1* mutation carriers with a family history of breast or ovarian cancer and/or early age at onset of breast or ovarian cancer in a family member. Relative risk varies widely by age, and is substantially higher among younger women with a *BRCA1* mutation, with peak incidence in the 41–50 years age group.[108]

The cumulative risk to age 80 years among *BRCA1* mutation carriers was estimated as 72% (95% CI 65%–79%).[108]

Background

The *BRCA1* gene codes for a protein involved in repairing damaged DNA. It is a tumour suppressor protein that helps prevent cells from growing and dividing too rapidly or in an uncontrolled way. The BRCA1 protein interacts with several other proteins to mend breaks in DNA. By helping repair DNA, it plays a critical role in maintaining the stability of a cell's genetic information. The BRCA1 protein is also involved in other functions, including regulation of other genes and of cell division.[103]

Researchers have identified more than 1,800 mutations in the *BRCA1* gene and many of these are associated with various cancers. The increased cancer risk associated with a *BRCA1* mutation is inherited in an autosomal dominant manner.[79] Many different mutations associated with increased risk of cancer have been identified in *BRCA1*, including truncating and some missense mutations.[98] The frequency of *BRCA1* or *BRCA2* mutations in the general population has been estimated at 1 in 400 to 1 in 800.[79]

The frequency of *BRCA1* and *BRCA2* (see section 4.3.5) mutations is higher among certain ethnic populations associated with inheritance of the mutation—a founder mutation—from early ancestors in a group that is or was geographically or culturally isolated. Founder mutations in *BRCA1* and *BRCA2* have been identified in the Ashkenazi Jewish (Jews whose origins can be traced back to Eastern Europe) population and in populations of Iceland, the Netherlands, Sweden, Hungary, Italy, South Africa and Pakistan.[104, 105]

As many as one in 40 individuals (men and women) of Ashkenazi Jewish descent has one of the three founder mutations in the breast/ovarian cancer susceptibility genes *BRCA1* and *BRCA2*. In Australia, the frequency of *BRCA1* and *BRCA2* mutations in the Ashkenazi Jewish population has been estimated at approximately 2.5% compared with less than 1% in the general population.[106, 107]

Recent evidence

A large case–control gene panel testing study from Kurian et al.[93] estimated risks of breast cancer associated with germline mutations using a 25–gene panel testing of 95,561 women tested clinically for hereditary cancer risk. A *BRCA1* mutation was detected in 1,468 women (1.54%), 739 of whom were diagnosed with ductal invasive breast cancer. The mutation was associated with increased odds of breast cancer of 5.91 (95% CI 5.25–6.67)[iii] from multivariate logistic regression analysis and 5.89 (95% CI 4.57–7.68; 19,056 breast cancer cases, 15,826 controls) from a matched case–control analysis. The *BRCA1* mutations were classified using the American College of Medical Genetics and Genomics Recommendations.[99] The analyses were adjusted for age, race/ethnicity and family history of relevant cancers.[93]

The three cohorts included in a prospective study by Kuchenbaeker et al.[108] included Australian families. *BRCA1* mutation carriers were ascertained through family clinics and

[iii] Risk estimates for invasive breast cancer overall, i.e. ductal and lobular breast cancer, were almost identical to those for ductal breast cancer (personal communication; A. Kurian via email).

were therefore mainly unaffected women with a cancer family history, early age at onset of cancer in a family member, or both. The breast cancer standardised incidence ratio (SIR) for *BRCA1* mutation carriers compared with the general population was 16.6 (95% CI 14.7–18.7; 2,276 women with pathogenic *BRCA1* mutations, of whom 269 were diagnosed with breast cancer).[108] SIRs decreased with increasing age from 73.7 (95% CI 42.9–126.8) at age 21–30 years, to 17.2 (95% CI 14.0–21.2) at age 41–50, and to 4.8 (95% CI 1.8–12.8) at 71–80 years.[108]

Breast cancer incidence for carriers increased rapidly with age in early adulthood then plateaued in the 41–50 years age group and remained relatively constant throughout the remaining lifetime. Cumulative risk of breast cancer for *BRCA1* carriers to age 80 years was estimated to be 72% (95% CI 65%–79%).[108] Family history of breast cancer was indicated to be a strong risk factor for mutation carriers. For *BRCA1* carriers with 2 or more first- or second-degree relatives diagnosed as having breast cancer compared with those with no family history of breast cancer, the HR for breast cancer was 1.99 (95% CI 1.41–2.82) (cumulative risk estimates to age 70 years: 73% [95% CI 65%–80%] vs 53% [95% CI 39%–69%]). Cancer risks also varied by mutation location.

The pooled analysis by Antoniou et al.[109] reported that relative risk of breast cancer in *BRCA1* mutation carriers, relative to general population rates, increased with age to 30–39 years (RR 33, 95% CI 23–49), then declined with age to RR 14 (95% CI 6.3–31) at ages 60–69 years.

The cumulative risk of breast cancer for *BRCA1* carriers to age 70 years has been variously estimated as:

- 57% (95% CI 47%–66%) in a meta–analysis by Chen & Parmigiani[110]
- approximately 60% for Australian women by Suthers,[111] based on the meta–analysis by Chen & Parmigiani[110]
- 65% (95% CI 44%–78%) from the pooled analysis by Antoniou et al.[109]
- 60% (95% CI 44%–75%) from the EMBRACE cohort study by Mavaddat et al.[112]
- 75% by Easton et al.[98]

Table D.9 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.5 *BRCA2* gene mutation

Evidence summary

Evidence classification: Convincing.

The increased risk of breast cancer among women with a *BRCA2* mutation compared to women without a *BRCA2* mutation has been estimated as 3.31 (95% CI 2.95–3.71), in a large case–control gene panel testing study that adjusted for family history of relevant cancers.[93]

Risk estimates are considerably higher from a prospective cohort study among carriers of a *BRCA2* mutation, predominantly of women with a family history of breast or ovarian cancer and/or early age at onset of breast or ovarian cancer in a family member.[108] Relative risk varies widely by age, and is substantially higher among younger women with a *BRCA2* mutation, with peak incidence in the 51–60 years age group.[108]

The cumulative risk to age 80 years among *BRCA2* mutation carriers was estimated as 69% (95% CI 61%–77%), similar to that among *BRCA1* mutation carriers in this study.[108]

Background

The *BRCA2* gene codes for a protein involved in repairing damaged DNA. It is a tumour suppressor protein that helps prevent cells from growing and dividing too rapidly or in an uncontrolled way. The BRCA2 protein interacts with several other proteins to mend breaks in DNA. By helping repair DNA, it plays a critical role in maintaining the stability of a cell's genetic information. The BRCA2 protein is also involved in other functions including regulation of other genes and of cell division.[113]

The *BRCA2* gene was originally identified as a breast cancer susceptibility gene and has been associated with increased risk of ovarian, contralateral breast cancer and other cancers, including male breast cancer, prostate and pancreatic cancer.[79, 108, 114] The increased cancer risk associated with a *BRCA2* mutation is inherited in an autosomal dominant manner.[79] Many different mutations associated with increased risk of cancer have been identified in *BRCA2*, including truncating and some missense mutations.[98]

The frequency of *BRCA1* or *BRCA2* mutations in the general population has been estimated at 1 in 400 to 1 in 800.[79]

Recent evidence

A large case–control gene panel testing study from Kurian et al.[93] estimated risks of breast cancer associated with germline mutations using a 25–gene panel testing of 95,561 women tested clinically for hereditary cancer risk. A *BRCA2* mutation was detected in 1,539 women (1.61%), 703 of whom were diagnosed with invasive ductal breast cancer and was associated with increased breast cancer risk OR 3.31 (95% CI 2.95–3.71)[iv] from multivariate logistic regression analysis and OR 3.12 (95% CI 2.56–3.83; 19,056 breast cancer cases, 15,826 controls) from a matched case–control analysis. The *BRCA2* mutations were classified using the American College of Medical Genetics and Genomics Recommendations.[99] The analyses were adjusted for age, race/ethnicity and family history of relevant cancers.[93]

The three cohorts included in a prospective study by Kuchenbaeker et al.[108] included Australian families. *BRCA2* mutation carriers were ascertained through family clinics and were therefore mainly unaffected women with a cancer family history, early age at onset of cancer in a family member, or both. The breast cancer standardised incidence ratio (SIR) for *BRCA2* mutation carriers compared with the general population was 12.9 (95% CI 11.1–15.1; 1,610 women with pathogenic *BRCA2* mutations, of whom 157 were diagnosed with breast cancer).[108] SIRs decreased with increasing age from 60.8 (95% CI 25.5–144.9) at age 21–30 years, to 16.4 (95% CI 12.9–20.9) at 41–50 years, and to 6.6 (95% CI 3.0–14.7) at 71–80 years.[108]

Breast cancer incidence for carriers increased rapidly with age in early adulthood then plateaued in the 51–60 years age group (5–10 years later than for BRCA1 mutation carriers) and remained relatively constant throughout the remaining lifetime. Cumulative risk of

[iv] Risk estimates for invasive breast cancer overall, i.e. ductal and lobular breast cancer, were almost identical to those for ductal breast cancer (personal communication; A. Kurian via email).

breast cancer for *BRCA2* carriers to age 80 years was estimated to be 69% (95% CI 61%–77%).[108] Family history of breast cancer was indicated to be a strong risk factor for mutation carriers. For *BRCA2* carriers with 2 or more first- or second-degree relatives diagnosed as having breast cancer compared with those with no family history of breast cancer, the HR for breast cancer was 1.91 (95% CI 1.08–3.37) (cumulative risks to age 70 years: 65% [95% CI 56%–74%] vs 39% [95% CI 25%–56%]). Cancer risks also varied by mutation location.

The cumulative risk of breast cancer for *BRCA2* mutation carriers to age 70 years has been variously estimated as:

- 49% (95% CI 40%–57%) in a meta–analysis by Chen & Parmigiani[110]
- approximately 50% for Australian women by Suthers,[111] based on the meta–analysis by Chen & Parmigiani[110]
- 45% (95% CI 31%–56%) from pooled analysis by Antoniou et al.[109]
- 55% (95% CI 41%–70%) from the EMBRACE cohort study by Mavaddat et al.[112]

These estimates are approximately 10% lower than those from the same studies for *BRCA1* mutation carriers (section 4.3.4).

Table D.10 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.6 *CDH1* gene mutation

Evidence summary

Evidence classification—breast cancer: Inconclusive.

Evidence classification—lobular breast cancer: Convincing.

A large case–control gene panel testing study did not find an association between women with *CDH1* mutations and risk of ductal breast cancer after adjusting for family history of cancer.[93] All other studies were among women at high risk for breast cancer due to a personal or family history of breast cancer or hereditary diffuse gastric cancer (HDGC) and risk estimates are higher among these populations.

The same study reported an increased risk of lobular breast cancer of 17.7 (95% CI 7.68–40.11) for women with a *CDH1* mutation compared with women without a *CDH1* mutation, after adjusting for family history of cancer.[93]

Background

Inherited, or germline, mutations in the *CDH1* gene are associated with the autosomal dominant cancer susceptibility syndrome, HDGC. Mutations in *CDH1* include small deletions and insertions, splicing mutations, nonsense, missense and large deletions.[115, 116]

The vast majority of families with truncating *CDH1* germline mutations have a history of HDGC. However, mutations have been found in at least one family with only a family history of lobular breast cancer.[117]

The *CDH1* gene codes for the protein epithelial cadherin (E–cadherin), which is found in the membrane that surrounds epithelial cells (that line the surfaces and cavities of the body). E–cadherin helps neighbouring cells stick together to form organised tissues and plays a major role in epithelial architecture, cell adhesion and cell invasion. It acts as a tumour suppressor protein, which means it prevents cells from growing and dividing too rapidly or in an uncontrolled way.[118]

Recent evidence

A large case–control gene panel testing study from Kurian et al.[93] estimated risks of (invasive ductal) breast cancer associated with germline mutations, using sequencing results of a 25–gene panel from 95,561 women tested clinically for hereditary cancer risk. *CDH1* mutations were detected in 42 women (0.04%), 13 of whom had invasive ductal breast cancer. Mutations in the *CDH1* gene were not associated with invasive ductal breast cancer risk (OR 1.34, 95 %CI 0.66–2.68 from multivariate logistic regression analysis; OR 4.00, 95%CI 0.80–38.7 from a matched case–control analysis of 19,056 breast cancer cases, 15,826 controls). An exploratory analysis using a multivariable model showed a strong association of *CDH1* mutations with invasive lobular breast cancer risk (OR 17.7, 95% CI 7.68–40.1).[93] The *CDH1* mutations in this analysis were classified using the American College of Medical Genetics and Genomics Recommendations.[99] The analyses were adjusted for age, race/ethnicity and family cancer history.

A case–control study by Couch et al.[101] estimated risk of breast cancer in women with breast cancer referred for hereditary cancer genetic testing compared with controls, using results of germline multigene panel tests. *CDH1* mutations were detected in 23 of 37,277 breast cancer cases and in three of 25,961 controls, and were associated with increased risk of breast cancer (OR 5.34, 95% CI 1.60–20.94). Breast cancer cases qualifying for clinical genetic testing were enriched for a clinical history of early–onset, bilateral, and triple–negative breast disease and a family history of breast cancer. None of the 23 breast cancer patients with *CDH1* mutations reported a personal history of gastric cancer, but familial HDGC was not ascertained.[101]

In a cross–sectional study by Lowstuter et al.[116] of patients undergoing multigene panel testing, *CDH1* mutations were detected in 0.06% (16 of 26,936) patients. Breast cancer was diagnosed in 14 patients with a *CDH1* mutation, but the study provided no estimate for breast cancer risk associated with *CDH1* mutations. Breast cancer was lobular in eight of the 14 patients with breast cancer and a *CDH1* mutation.[116]

A large case–series analysis by Hansford et al.[115] estimated cancer risk from 75 *CDH1* mutation positive HDGC families. This study included 17 families and 58 additional families, some of who were reported earlier by Pharaoh et al.[119] and Kaurah et al.[120] (see below). The 3,858 probands included 89 breast cancer cases. *CDH1* germline mutations were associated with increased risk of breast cancer, with RR (age 10–49 years) 7.7 and RR (age ≥50 years) 7.4 (no CIs provided). The cumulative risk of breast cancer to age 80 years for women with *CDH1* mutations was 42% (95% CI 23%–68%).[115]

Two additional studies, by Kaurah et al.[120] and Pharoah et al.[119] were based on small numbers of patients with *CDH1* mutations. A case–series study by Kaurah et al.[120] estimated the cumulative risk of breast cancer to age 75 years for women with *CDH1* mutations as 52% (95% CI 29%–94%). This estimate was based on four HDGC families, each with the same *CDH1*

mutation; these four families included 16 cases of breast cancer. There were 'concentrations of lobular breast cancer cases' in branches of these families, but the number or percentage of lobular cases was not specified.[120]

A segregation analysis by Pharaoh et al.[119] included 235 women from HDGC families recruited internationally, where the family had at least three cases of diffuse gastric cancer and at least one affected family member with an identified *CDH1* mutation. There were seven cases of breast cancer diagnosed and of the four cases with histopathology available, two were lobular adenocarcinoma. *CDH1* mutations were associated with increased risk of breast cancer overall (RR 6.6, Standard error SE 0.67), and cumulative risk to age 80 years was 39% (95% CI 12%–84%).[119]

Table D.11 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.7 *CHEK2* gene mutation

Evidence summary

Evidence classification: Convincing.

The increased risk of breast cancer among women with a *CHEK2* mutation compared to women without a *CHEK2* mutation has been estimated as 1.99 (95% CI 1.70–2.33), from a large case–control gene panel testing study that adjusted for family history of relevant cancers.[93] The magnitude of risk varies depending on the specific *CHEK2* mutation. The CHEK 1100delC mutation has been studied most and has been estimated to be associated with an increased breast cancer risk of 2–3 times compared with women without this mutation.[98, 101, 121-123]

Background

The *CHEK2* gene codes for the checkpoint kinase 2 (CHK2) protein. Initially, mutations were identified in *CHEK2* that are associated with familial breast cancer. More mutations and polymorphisms have since been identified in *CHEK2* and investigated for any association with breast cancer risk. Many *CHEK2* mutations are protein truncating mutations (resulting in a shortened protein that may function improperly or not at all). However, splice junction, deletion and missense mutations have also been associated with breast cancer risk.[98, 122]

The *CHEK2 1100delC* mutation that results in a dysfunctional truncated CHK2 protein has been studied extensively. This mutation is present primarily in individuals of Northern and Eastern European descent and has a frequency of approximately 1% in these populations.[124]

Inherited *CHEK2* mutations have also been identified in some families with cancers characteristic of Li–Fraumeni syndrome and Li–Fraumeni–like syndrome that do not have *TP53* mutations commonly associated with this syndrome.[125]

The CHK2 protein, encoded by the *CHEK2* gene, is a kinase that is activated when DNA becomes damaged or when DNA strands break. The CHK2 protein interacts with several other proteins, including tumour protein 53 (encoded by the *TP53* gene). These proteins halt cell division and determine whether the DNA is repaired or the cell will undergo programmed

cell death (apoptosis). This process stops cells with mutated or damaged DNA from dividing, which helps prevent tumours developing. CHK2 acts as a tumour suppressor, which means it regulates cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way.[126]

Recent evidence

A large case–control gene panel testing study from Kurian et al.[93] estimated risks of breast cancer associated with germline mutations, using sequencing results of a 25–gene panel from 95,561 women tested clinically for hereditary cancer risk. *CHEK2* mutations were detected in 771 women (0.81%) including 319 women with invasive ductal breast cancer, and were associated with increased breast cancer risk of 1.99 (95% CI 1.70–2.33)[v] in multivariate logistic regression analysis, and 2.12 (95% CI 1.63–2.77;19,056 breast cancer cases and 15,826 controls) from a matched case–control analysis.[93] The *CHEK2* mutations in this analysis were classified using the American College of Medical Genetics and Genomics Recommendations.[99] The analyses were also adjusted for age, race/ethnicity and family cancer history.

A case–control study by Couch et al.[101] estimated risk of breast cancer in women with breast cancer referred for hereditary cancer genetic testing compared with controls, using results of germline multigene panel tests. In women of European ancestry, pathogenic mutations in *CHEK2* were detected in 424 of 29,090 breast cancer cases and in 163 of 25,215 controls. Further, these mutations were associated with increased risk of breast cancer (OR 2.26, 95% CI 1.89–2.72). Including two common *CHEK2* missense variants (*sp.Ile157Thr* and *p.Ser428Phe*) in the estimate increased the odds of breast cancer for women of European ancestry (OR 1.48, 95%CI 1.31–1.67).[101]

A meta–analysis by Aloraifi et al.[100] included nine case–control studies of breast cancer risk in high risk groups (cases with family history of breast cancer, bilateral breast cancer and/or early onset of breast cancer). CHEK2 protein truncating variants were associated with increased breast cancer risk, with aggregated OR 3.25 (95% CI 2.55–4.13; 7,263 cases and 13,785 controls).[100]

CHEK 1100delC mutation

Four meta–analyses[98, 121-123] and a large case–control study[101] indicated the *CHEK 1100delC* mutation is associated with increased breast cancer risk:

- RR 3.02, 90% CI 2.6–3.; pooled analysis of two large case–control studies[98]
- OR 2.75, 95% CI 2.25–3.36; 25 studies with 29,154 cases and 37,064 controls[121]
- OR 3.10, 95% CI 2.59–3.71; 47 studies with 41,791 cases and 50,910 controls[122]
- OR 2.4 (95%CI 1.8–3.2; unselected breast cancer in 12 studies) and OR 4.6 (95% CI 3.1–6.8; familial breast cancer)[123]
- OR 2.31 (95% CI 1.88–2.85; case–control study with 29,090 cases and 25,215 controls).[101]

A UK population–based case–control study by Decker et al.[102] indicated an association between truncating *CHEK2* gene mutations and increased breast cancer risk: OR 3.11

[v] Risk estimates for invasive breast cancer overall, i.e. ductal and lobular breast cancer, were almost identical to those for ductal breast cancer (personal communication; A. Kurian via email).

(95% CI 2.15–4.69; 13,087 breast cancer cases and 5,488 controls). Truncating mutations in *CHEK2* were more strongly associated with the risk of oestrogen receptor positive (ER+) breast cancer (OR 3.42, 95% CI 2.33–5.21) than for oestrogen receptor negative (ER–) breast cancer (OR 1.59, 95% CI 0.80–3.00).[102]

A meta–analysis by Liu et al.[127] indicated *CHEK2* I157T was associated with increased risk of unselected breast cancer (OR 1.48, 95% CI 1.31–1.66; 13 studies with 17,073 cases and 26,501 controls).

A meta–analysis by Zhang et al.[122] investigated breast cancer risk for candidate genes or loci that each had a minimum of three data sources available. The study included four CHEK2 variants (three mutations and one single nucleotide polymorphism that were associated with increased breast cancer risk:

- *CHEK2 IVS2+IG>A*—OR 3.07 (95% CI 2.03–4.63; five studies with 9,970 cases, 7,526 controls)
- 5.5 kb deletion (exons 9 and 10 of *CHEK2*)–OR 2.53(95% CI 1.61–3.97; five studies with 10,543 cases and 8,447 controls)
- *CHEK2 rs17879961*—OR 1.52 (95 % CI 1.31–1.77; eight studies with 13,311 cases and 10,817 controls).

Southey et al.[128] genotyped rare mutations in *CHEK2* in white European women from the Breast Cancer Association Consortium (BCAC) (42,671 cases and 42,164 controls). Three *CHEK2* mutations were associated with increased risk of breast cancer:

- *CHEK2 c.349A>G* (*p.Arg117Gly*)—OR 2.26 (95% CI 1.29–3.95)
- *CHEK2 c.1036C>T* (*p.Arg346Cys*)—OR 5.06 (95% CI 1.09–23.5)
- *CHEK2 c.538C>T* (*p.Arg180Cys*)—OR 1.33 (95% CI 1.05–1.67).

The mutation *CHEK2 c.715G>A* (*p.Glu239Lys*) was not associated with breast cancer risk.[128]

Table D.12 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.8 *PALB2* gene mutation

Evidence summary

Evidence classification: Convincing.

The increased risk of breast cancer among women with a *PALB2* mutation compared to women without a *PALB2* mutation has been estimated as 3.39 (95% CI 2.79–4.12), in a large case–control gene panel testing study that adjusted for family history of cancer.[93] Risk estimates are moderately higher among *PALB2* carriers with a family history of relevant cancers and younger women with a *PALB2* mutation.

Background

The *PALB2* gene codes for the partner and localier of BRCA2 (PALB2) protein, which was identified originally as a protein that interacts with BRCA2. *PALB2* is one of the genes associated with the recessive childhood illness Fanconi's anaemia; pathogenic *PALB2* mutations that are biallelic (mutations in both copies of the gene) have been identified in

some Fanconi's anaemia families. Loss of function *PALB2* mutations that are heterozygous, or monoalllelic (mutations in only one allele), have been associated with increased risk of pancreatic cancer and association with breast cancer risk has also been investigated.[129, 130] Breast cancers reported in women with a *PALB2* mutation are frequently triple negative.[129]

Mutations in *PALB2* that have been identified include the founder mutations *PALB2 c.1592delT* in Finland, and *PALB2 c.2323C→T (p.Glu775X)* in French Canadian women. Mutations in *PALB2* that result in loss of function are frequently truncating mutations (resulting in a shortened protein that may function improperly or not at all). They have now been observed in persons from many countries and are found in 0.6–3.9% of families with a history of breast cancer, depending on the population.[129, 130] Cybulski et al.[131] estimated the frequency of *PALB2* mutations in the general population to be 0.2%.

The PALB2 protein interacts with both BRCA1 and BRCA2 to form a BRCA1–PALB2–BRCA2 complex that has a key role in DNA repair. The PALB2 protein is involved in localising this complex to sites of DNA damage in the nucleus of the cell. *PALB2* mutations that result in reduced or defective PALB2 protein disrupt the BRCA1/ BRCA2–dependent DNA repair pathway, which is part of the body's defence against developing cancer.[129, 132, 133]

Recent evidence

A large case–control gene panel testing study from Kurian et al.[93] estimated risks of breast cancer associated with germline mutations, using sequencing results of a 25–gene panel from 95,561 women tested clinically for hereditary cancer risk. *PALB2* mutations were detected in 484 women (0.51%) including 257 women with invasive ductal breast cancer, and were associated with increased breast cancer risk of 3.39 (95% CI 2.79–4.12)[vi] from multivariate logistic regression analysis, and 4.13 (95% CI 2.88–6.05; 19,056 breast cancer cases and 15,826 controls) from a matched case–control analysis. The *PALB2* mutations in this analysis were classified using the American College of Medical Genetics and Genomics Recommendations[99]. The analyses were also adjusted for age, race/ethnicity and family cancer history.[93]

A population–based case–control study by Decker et al.[102] of 13,087 breast cancer cases and 5,488 controls from the United Kingdom indicated an association between truncating *PALB2* gene mutations and increased breast cancer risk (OR 4.69, 95% CI 2.27–9.68).

A case–control study by Couch et al.[101] estimated risk of breast cancer in women with breast cancer referred for hereditary cancer genetic testing compared with controls, using results of germline multigene panel tests. In women of European ancestry, pathogenic mutations in *PALB2* were detected in 241 of 30,025 breast cancer cases and in 29 of 26,869 controls. Further, these mutations were associated with increased risk of breast cancer (OR 7.46, 95% CI 5.12–11.19). In analysis of women of all ethnicities, the estimated OR was 6.25 (95% CI 4.82–8.14).[101]

A meta–analysis by Easton et al.[98] estimated the increased breast cancer risk associated with *PALB2* mutations as RR 5.3 (90% CI 3.0–9.4). The meta–analysis included the study by Antoniou

[vi] Risk estimates for invasive breast cancer overall, i.e. ductal and lobular breast cancer, were almost identical to those for ductal breast cancer (personal communication; A. Kurian via email).

et al.[130] summarised separately below, plus two studies based on the Finnish founder variant, c.1592delT, which provided lower risk estimates.

A meta–analysis by Aloraifi et al.[100] included 13 case–control studies of breast cancer risk in high risk groups (cases with family history of breast cancer, bilateral breast cancer and/or early onset of breast cancer). PALB2 protein truncating variants were associated with increased breast cancer risk (aggregated OR 21.40, 95% CI 10.10–45.32; 5,862 cases and 17,453 controls). The authors noted this high OR may be due to potential selection bias of high–risk cases.[100]

Southey et al.[128] genotyped rare mutations in *PALB2* in white European women (34,488 cases and 34,059 controls) from the Breast Cancer Association Consortium (BCAC). Two *PALB2* mutations were associated with increased risk of breast cancer: the OR for *PALB2 c.1592delT (p.Leu531Cysfs)* was 3.44 (95% CI 1.39–8.52) and the OR for *PALB2 c.3113G>A (p.Trp1038*)* was 4.21 (95% CI 1.84–9.60). There was no association with breast cancer risk for the missense mutation *PALB2 c.2816T>G (p.Leu939Trp)*.[128]

A case–control study in Poland by Cybulski et al.[131] reported increased risk of breast cancer associated with two mutations in *PALB2 (509_510delGA* and *172_175delTTGT*). The OR was 4.39 (95% CI 2.30–8.37; 12,529 cases unselected for family history and 4,702 controls).

A large family–based case–control study by Antoniou et al.[130] included 362 members of 154 families that had at least one family member diagnosed with breast cancer and had a germline loss–of–function *PALB2* mutation. The families were recruited internationally, including from Australia, and among the 154 families there were 48 different *PALB2* mutations. *PALB2* mutations were associated with an increased risk of breast cancer (RR 9.47, 95% CI 7.16–12.57), compared with the UK general population using a single gene model. All analyses were corrected for the method of ascertainment. For a woman with a *PALB2* mutation, the risk of breast cancer was larger at a younger age, compared with the general population. Estimated relative risks in comparison with age–specific breast cancer incidence in the United Kingdom from 1993–97 were: RR 8–9 for < 40 years, RR 6–8 for 40–60 years, and RR 5 for > 60 years. Breast cancer risk was also influenced by family history. By 70 years, the absolute breast cancer risk for women with a *PALB2* mutation ranged from 33% (95% CI 25%–44%) for those with no family history of breast cancer to 58% (95% CI 50%–66%) for those with ≥ 2 first–degree relatives with breast cancer diagnosed at 50 years of age.[130]

Table D.13 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.9 *PTEN* gene mutation

Evidence summary

Evidence classification: Convincing.

The increased risk of breast cancer for women with a *PTEN* mutation compared to women without a *PTEN* mutation has been estimated as 5.83 (95% CI 2.43–14.0) in a large case–control gene panel testing study that adjusted for family history of relevant cancers.[93] The risk estimate is uncertain due to the large confidence intervals resulting from the very low frequency of *PTEN* mutations in the general population.[93, 101] Risk estimates among women

carriers of PTEN mutation with *PTEN* Hamartoma Tumour Syndrome (PHTS) or familial PTEN–associated syndromes are substantially higher.

Background

The *PTEN* gene codes for a protein involved in regulating a cell survival signalling pathway—'phosphotase and tensin homolog'. *PTEN* acts a tumour suppressor gene, which helps regulate cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way. The PTEN protein is a phosphatase that removes phosphate groups from other proteins. It is involved in several functions that may be involved in development of cancer, including DNA repair, cellular senescence, cell migration and maintaining the stability of the cell's genetic information.[134, 135]

Inherited, or germline, mutations in the *PTEN* gene are associated with the *PTEN* Hamartoma Tumour Syndrome (PHTS) that encompasses several heritable disorders including Cowden Syndrome and Bannayan–Riley–Ruvalcaba Syndrome.[136] Cowden Syndrome is an autosomal dominant inherited disorder that affects many organs and is characterised by increased risk of several cancers, including breast, thyroid and endometrial cancer. Individuals affected by PHTS usually have macrocephaly and specific skin lesions (trichilemmomas).[137]

PTEN mutations associated with PHTS include frame–shift, deletions, missense, nonsense and splice site mutations.[136, 138, 139] PHTS is a rare condition and the prevalence of *PTEN* mutations in the general population is very low. Pathogenic mutations in *PTEN* are estimated to occur in approximately one in 200,000 individuals.[136]

Recent evidence

A large case–control gene panel testing study from Kurian et al.[93] estimated risks of breast cancer associated with germline mutations, using sequencing results of a 25–gene panel from 95,561 women tested clinically for hereditary cancer risk. *PTEN* mutations were detected in only 24 women (0.03%), including 15 women with invasive ductal breast cancer, and were associated with increased odds of breast cancer of 5.83 (95% CI 2.43–14.0)[vii] from multivariate logistic regression analysis adjusted for age, race/ethnicity and family cancer history. There were too few mutation carriers to conduct a matched case–control analysis.[93] The *PTEN* mutations in this analysis were classified using the American College of Medical Genetics and Genomics Recommendations.[99]

A case–control study by Couch et al.[101] estimated risk of breast cancer in women with breast cancer referred for hereditary cancer genetic testing compared to controls, using results of germline multigene panel tests. *PTEN* mutations were detected in 20 of 38,179 breast cancer cases and in one of 24,166 controls. *PTEN* mutations were associated with increased risk of breast cancer, OR 12.66 (95% CI 2.01–258.89).[101]

A pooled analysis by Easton et al.[98] assessing the association between mutations in a number of genes and breast cancer risk did not report an estimate for *PTEN* mutations. The authors noted the estimates reported in two studies available were based on selected families with

[vii] Risk estimates for invasive breast cancer overall, i.e. ductal and lobular breast cancer, were almost identical to those for ductal breast cancer (personal communication; A. Kurian via email).

Cowden or related syndromes and thus were subject to ascertainment bias. These two case studies are summarised below.[138, 139]

Nieuwenhuis et al.[134] estimated breast cancer risk in 99 women (24 of whom had breast cancer) with *PTEN* mutations, from Western Europe, Australia and the United States. Cumulative risk estimates for breast cancer from 30 years to 60 years were estimated, with lifetime risk estimated as 67% (by 60 years) compared to the general population at 12% (one in eight women).[134]

Bubien et al.[139] estimated breast cancer risk in a study of 70 women (23 of whom had breast cancer) with PHTS and an identified *PTEN* gene mutation, from Europe and North Africa. The cumulative breast cancer risk at 70 years was estimated to be 77% (95% CI 59–91). The standarised incidence ratio (SIR) for women with a *PTEN* mutation compared with expected incidence in the French population, was estimated as 39.1 (95% CI 24.8–58.6).[139]

Tan et al.[138] estimated breast cancer risk in 205 women (67 of whom had breast cancer) with PHTS and an identified *PTEN* gene mutation, from North America, Europe and Asia. Estimates for life time risk of breast cancer was estimated as 85% and the SIR for women with a *PTEN* mutation compared with expected US incidence using the Surveillance, Epidemiology, and End Results (SEER) database, was estimated as 25.4 (95% CI 19.8–32.0).[138]

Table D.14 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.10 Single nucleotide polymorphisms

Evidence summary

Evidence classification: Convincing.

A large number of single nucleotide polymorphisms (SNPs) have been identified that are associated with increased risk of breast cancer. Common susceptibility variants identified through genome–wide association studies (GWAs), including 65 newly identified susceptibility loci, explain an estimated 18% of familial relative risk of breast cancer.[140] In general, the predictive power of the SNPs increases with the number of SNPs.

Based on 77–SNPs, for women in the lowest 1% of the polygenic risk score (PRS) distribution compared to women in the middle quintile the OR was estimated to be 0.31 (95% CI 0.24–0.39). For women in the highest 1% of PRS distribution compared to women in the middle quintile the OR was 3.36 (95% CI 2.95–3.83).[141]

Background

SNPs are alterations in a single nucleotide (adenine, thymine, cytosine, or guanine) in the genome sequence, and are a common type of genetic variation that occur between different people. There are estimated to be approximately 10 million SNPs in the human genome. They occur normally throughout a person's DNA and most SNPs have no effect on health or development.[79, 142] SNPs can act as biological markers that can help to identify genes or positions (loci, or 'susceptibility loci') in the genome that may be associated with a disease such as breast cancer.[142]

The investigation of SNPs for any association with breast cancer risk, identification of breast cancer susceptibility loci using SNPs and development of polygenic risk scores, are areas of rapidly emerging research.

Genome–wide association studies (GWAS) analyse SNPs across the genome to identify SNPs that occur more frequently in people with a particular disease—such as breast cancer—than in people without the disease. These studies often look at hundreds or thousands of SNPs at the same time. By comparing SNPs between large numbers of cases and controls, these studies can identify SNPs associated with increased breast cancer risk and breast cancer susceptibility loci. Replication studies in other sets of subjects are then often used to validate any associations. Individual SNPs have a small effect size and PRSs for breast cancer risk have been developed based on combined scores for large numbers of SNPs.[141, 143] Transcriptome–wide association studies (TWAS) are another emerging methodology to identify novel risk loci and inform functional investigations of known breast cancer SNPs.[144]

Recent evidence

GWAS studies have been undertaken by several large consortium groups that have combined subjects from many studies to investigate breast cancer risk.[140, 143, 145] Combinations of SNPs or PRSs have been developed and the associations between the scores and breast cancer risk investigated.[141, 146] PRSs have also been developed for breast cancer subtypes or specific populations, such as *BRCA1/BRCA2* mutation carriers[147] and in women at high risk of breast cancer.[148] PRSs have been evaluated for independence with other risk factors such as breast density and for refining breast cancer risk estimates in combination with other risk prediction models.[149-151]

Single nucleotide polymorphisms and susceptibility loci studies

A large GWAS and meta–analysis undertaken by Michailidou et al.[140] included 122,977 cases and 105,974 controls of European ancestry, and 14,068 cases and 13,104 controls of East Asian ancestry, from 68 studies in the Breast Cancer Association Consortium (BCAC) and the Discovery, Biology and Risk of Inherited Variants in Breast Cancer Consortium (DRIVE). An array of over 500,000 SNPs was used for genotyping. The study identified 65 new loci through GWAs which explain 18% of familial relative risk of breast cancer.[140]

An earlier meta–analysis was undertaken by Michailidou et al.[145] of 11 GWASs comprising 15,748 breast cancer cases and 18,084 controls, and 46,785 cases and 42,892 controls from 41 studies genotyped on a custom array of more than 200,000 SNPs. All participants were of European ancestry. The meta–analysis confirmed 71 of the 79 previously published breast cancer susceptibility loci and an additional 15 new breast cancer susceptibility loci were identified.[145]

A large GWAS by Milne et al.[143] of 21,468 oestrogen receptor negative (ER–) breast cases, 18,908 *BRCA1* mutation carriers and 100,594 controls of European origin, identified ten new SNPs for ER– breast cancer. Ten of 11 SNPs previously identified by GWAS as associated with ER– or *BRCA1* mutation carriers were confirmed. A further 105 SNPs previously identified as associated with breast cancer risk overall were associated with ER– breast cancer risk. It was estimated these 125 variants explain approximately 14% of the familial risk of ER– breast cancer.[143]

Polygenic risk score studies

A large collaborative case–control study by Mavaddat et al.[141] developed a PRS based on 77 SNPs, in 33,673 cases and 33,381 controls of European origin from the large BCAC consortium. The risk of breast cancer was increased for women in the highest 1% of the PRS compared with women in the middle quintile, with odds ratio (OR) 3.36 (95% CI 2.95–3.83). In contrast, for women in the lowest 1% of the PRS distribution, the estimated OR compared with women in the middle quintile was 0.31 (95% CI 0.24–0.39). For oestrogen receptor positive (ER+) and ER– breast cancer risk, the ORs were 3.73 (95% CI 3.24 to 4.30) and 2.80 (95% CI 2.26 to 3.46) respectively. For women in the highest quintiles of the PRS, lifetime risks of breast cancer were 16.6% for women without family history and 24.4% for women with a first–degree family history of breast cancer (compared to 5.2% for women without and 8.6% for women with family history in the lowest PRS quintile).[141]

A PRS was derived by Li et al.[146] based on analysis of 24 SNPs in 4,365 women from two familial cohorts, the Breast Cancer Family Registry (BCFR) cohort (United States, Australia and Canada) and the Kathleen Cuningham Consortium Foundation for Research into Familial Breast Cancer (kConFab) (Australia and New Zealand). The study included women from breast cancer families not known to have a *BRCA1/BRCA2* mutation and those women unaffected (no breast cancer diagnosis) at baseline were followed up for an average of 7.4 years. The PRS was associated with increased breast cancer risk, with a HR for upper versus lower quintile PRS 3.18 (95% CI 1.84–5.23), and HR for continuous PRS (per SD) 1.38 (95% CI 1.22–1.56).[146]

In a study by Dite et al.,[149] the 77–SNP PRS developed by Mavaddat et al.[141] was combined with risk predictions from the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), BRCA PRObability (BRCAPRO), Breast Cancer Risk Assessment Tool (BCRAT) and International Breast Intervention Study (IBIS) models using 750 cases and 405 controls from the Australian Breast Cancer Family Registry. The study included Caucasian women who were not *BRCA1/BRCA2* mutation carriers and were less than 50 years of age at diagnosis or recruitment. Combining the PRS increased the ORs for the risk prediction models and was estimated to improve breast cancer prediction in women younger than 50 years by more than 20%.[149]

A nested case–control study by Shieh et al.[150] investigated the association between a PRS based on 83 SNPs and breast cancer risk in 486 cases and 495 controls (80% Caucasian and 20% non–Caucasian descent) from a screening cohort. There was association with increased breast cancer risk for increasing quartiles of the PRS, OR for highest versus lowest quartile 2.51 (95% CI 1.63–3.86). The PRS, family history, and breast density remained strong risk factors in a multivariable model. Incorporation of the PRS into the Breast Cancer Surveillance Consortium risk model improved the discrimination of the risk model. A specific PRS based on East Asian populations discriminated breast cancer risk better for Asian women than the overall PRS.[150]

Using 94 SNPs, Kuchenbaeker et al.[147] developed three different PRSs for risk of overall breast cancer, for ER+ breast cancer and for ER– breast cancer, and evaluated their associations for *BRCA1* and *BRCA2* mutation carriers. The study used data from 15,252 female *BRCA1* and 8,211 *BRCA2* carriers, from the Consortium of Investigators of Modifiers of *BRCA1/BRCA2* (CIMBA), recruited from 26 countries. In *BRCA1* mutation carriers, the PRS for ER– breast cancer had the strongest association with breast cancer risk (HR 1.27, 95% CI 1.23–1.31). In *BRCA2* carriers, the PRS for overall breast cancer had the strongest association with breast cancer risk (HR 1.22, 95% CI 1.16–1.27).[147]

A study by Vachon et al.[151] examined a 76–SNP PRS and breast density using the Breast Imaging Reporting and Data System (BI–RADS) in data from three case–control studies from the United States with 1,643 cases and 2,397 controls. The 76–SNP PRS was associated with breast cancer risk within and across the three studies, and was a risk factor independent of BI–RADS density. The estimated OR was 1.48 (95% CI 1.38–1.58) based on a model with PRS and BI–RADS density compared with a model with BI–RADS alone.[151]

Table D.15 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.11 *STK11* gene mutation

Evidence summary

Evidence classification—women with *STK11* mutation but no clinical symptoms of Peutz–Jeghers Syndrome: Inconclusive.

Evidence classification—women with Peutz–Jeghers Syndrome: Convincing.

Due to the very low prevalence of *STK11* mutations in the general population, only a few *STK11* mutations were identified in a large case–control gene panel testing study, and there was no association with breast cancer risk.[93] If an *STK11* mutation is detected in a woman with breast cancer but no other features of PJS, the relevance of the mutation is uncertain.[137]

There is consistent evidence that women with the rare inherited disorder Peutz–Jeghers Syndrome (PJS) have an increased risk of breast cancer. The majority of women with PJS possess a mutation in the *STK11* gene. The risk of breast cancer for women with PJS has been variously estimated to be six to 15 times that of women in the general population.[152-154]

Background

The *STK11* gene, also known as the *LKB1* gene, codes for a protein called serine threonine kinase 11. Inherited, or germline, mutations in the *STK11* gene cause PJS, a rare condition inherited in an autosomal dominant manner. PJS is characterised by the development of noncancerous growths called hamartomatous polyps in the gastrointestinal tract and mucocutaneous pigmentation.[155] Colorectal cancer is the most common malignancy associated with PJS,[156] but PJS is also characterised by increased risk of developing several other types of cancer, including gastrointestinal, breast, pancreatic and gynaecological cancers. PJS mostly presents early in life with anaemia, rectal bleeding, abdominal pain, obstruction and/or intussusception.[137]

The majority of people (up to 90%) that meet the clinical diagnostic criteria for PJS have a causative mutation in the *STK11* gene, which is located at 19p13.3. [157, 158] The probability of a heritable mutation being detected in a person who has a first or second–degree relative with documented pathogenic mutation is 25–50%.[157]

Many different mutations in *STK11* associated with PJS have been identified, including truncating mutations (that result in a shortened non–functional protein), deletions and missense mutations.[153, 154, 159] PJS is a rare condition, with estimated incidence between 1 in

8,300 and 1 in 200,000 births.[156] Somatic mutations of the *STK11* gene are rare in sporadic forms of common cancer types associated with PJS.[160]

The serine threonine kinase 11 protein encoded by the *STK11* gene is an enzyme involved in cell programmed cell death (apoptosis), and in other roles such as cell polarisation and control of cell growth. It is a tumour suppressor, which means that it helps keep cells from growing and dividing too fast or in an uncontrolled way. *STK11* mutations may contribute to development of cancer through mechanisms including induction of angiogenesis, suppression of growth arrest, apoptosis and loss of cell polarity.[159]

Recent evidence

A large case–control gene panel testing study from Kurian et al.[93] estimated risks of breast cancer associated with germline mutations, using sequencing results of a 25–gene panel from 95,561 women tested clinically for hereditary cancer risk. There were very small numbers of *STK11* mutations detected: five mutations in all women (0.01%), and two mutations in women with invasive ductal breast cancer. There was no association with breast cancer risk with OR 4.41 (95% CI 0.66–29.6) from multivariate logistic regression analysis. The *STK11* mutations in this analysis were classified using the American College of Medical Genetics and Genomics Recommendations.[99] The analyses were adjusted for age, race/ethnicity and family cancer history, and the estimates represent the breast cancer risk among mutations carriers who survive to adulthood. In a complementary matched case–control analysis, there were too few mutation carriers to estimate an OR for *STK11*.[93]

A systematic review by van Lier et al.[156] on cancer risk in PJS patients, reported increased breast cancer risk associated with PJS, with cumulative risks for breast cancer ranging from 5–8% at age 40, increasing to 45% at 70 years. These risk estimates for breast cancer were based on three studies, including the study by Hearle et al.[153] summarised separately below.

A meta–analysis by Giardiello et al.[152] included 104 women with PJS. Confirmation of an identified germline *STK11* mutation in these patients was not specified. For women with PJS, there was increased risk of breast cancer (RR 15.2, 95% CI 7.6–27.0) compared with the breast cancer risk in the general population.[152] A retrospective cohort study conducted in Italy by Resta et al.[154] included 119 patients with PJS, of whom 99 had an identified *STK11* mutation. In the 68 women in the study, six breast cancer cases were diagnosed. For women with PJS, there was increased risk of breast cancer (RR 12.5, 95% CI 5.1–26.0) compared with the breast cancer risk in the general Italian populational.[154]

A case series by Hearle et al.[153] included 419 patients with a diagnosis of PJS from Europe, Australia and the United States. A germline mutation in *STK11* was identified in 297 (70%) of the 419 PJS patients. Sixteen women and one man developed breast cancer. There was no significant difference in risk for female breast cancer in women with and without germline mutations detected. The cumulative risks for developing breast cancer in women with PJS were: 40 years: 8% (95% CI 4–17%); 50 years: 13% (95% CI 7–24%); 60 years: 31% (95% CI 18–50%) and 70 years: 45% (95% CI 27–68). This suggested an approximate six–fold increased risk for breast cancer in PJS (based on 7% risk of breast cancer in the general population by 70 years).[153]

Table D.16 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.3.12 *TP53* gene mutation

Evidence summary

Evidence classification: Convincing.

The increased risk of breast cancer associated with a *TP53* mutation among women in the general population has been estimated as 5.37 (95% CI 2.78–10.4) in a large case–control gene panel testing study that adjusted for family history of cancer.[93] Higher breast cancer risks have been estimated from studies among women in families with Li–Fraumeni syndrome.

The risk of breast cancer associated with a *TP53* mutation is higher for a women at a younger age (<40 years), than at an older age.[101]

Background

TP53 is a tumour suppressor gene that has been referred to as 'the guardian of the genome'. The *TP53* gene codes for tumour protein p53 that has a critical role in the cell following DNA damage. It can either activate repair of the damaged DNA, or stop the cell dividing and initiate cell death (apoptosis). The p53 protein helps prevent development of cancer by stopping cells with mutated or damaged DNA from dividing.[161, 162]

Inherited, or germline, mutations in the tumour suppressor *TP53* gene are associated with Li–Fraumeni syndrome (LFS) and Li–Fraumeni–like syndrome. LFS is an autosomal dominant inherited disorder which is characterised by a high lifetime risk of malignancy. The commonest cancers are soft tissue sarcomas, particularly in children and young adults, and early–onset breast cancer in women.[161] Various sets of diagnostic criteria have been developed for LFS. The majority of pathogenic *TP53* mutations are missense mutations that result in an altered TP53 protein, with reduced or no function.[162]

LFS is a rare condition and the frequency of *TP53* mutations in the general population is uncertain, with estimates varying from 1 in 5,000 to 1 in 20,000.[161] Germline *TP53* mutations can occur *de novo* and germline mutations in *TP53* have been identified in approximately 4–8% of women with early–onset breast cancer without a family history of LFS.[163, 164]

Recent evidence

A large case–control gene panel testing study from Kurian et al.[93] estimated risks of breast cancer associated with germline mutations, using sequencing results of a 25–gene panel from 95,561 women tested clinically for hereditary cancer risk. Forty–two *TP53* mutations were detected in all women tested (0.04%), including 25 mutations in women with invasive ductal breast cancer. *TP53* mutations were associated with increased breast cancer risk, with OR 5.37 (95% CI 2.78–10.4)[viii] from multivariate logistic regression analysis and OR 5.00 (95% CI 1.07–46.9; 19,056 cases with 15,826 controls) from a matched case–control analysis. The *TP53* mutations in this analysis were classified using the American College of Medical Genetics

[viii] Risk estimates for invasive breast cancer overall, i.e. ductal and lobular breast cancer, were almost identical to those for ductal breast cancer (personal communication; A. Kurian via email).

and Genomics Recommendations.[99] The analyses were adjusted for age, race/ethnicity and family cancer history. For *TP53* mutations that are associated with childhood mortality, the estimates represent the breast cancer risk among mutation carriers who survive to adulthood.[93]

A case–control study by Couch et al.[101] estimated risk of breast cancer in women with breast cancer referred for hereditary cancer genetic testing compared to controls, using results of germline multigene panel tests. *TP53* mutations were detected in 48 of 38,305 breast cancer cases and in 13 of 26,789 controls, and were associated with increased risk of breast cancer, OR 2.58 (95% CI 1.39–4.90). For women with *TP53* mutations who were diagnosed with breast cancer aged ≤40 years, the OR was 8.25 (95% CI 4.27–15.84).[101]

A pooled analysis by Easton et al.[98] estimated the increased breast cancer risk associated with *TP53* mutations as RR 105 (90% CI: 62–165). The authors indicated estimates for *TP53* mutations in most published studies were subject to ascertainment bias. One study based on *TP53* carriers identified through probands with childhood sarcoma also reported high breast cancer risk, SIR 105.1 (95% CI 55.9–179.8; 13 cases of breast cancer out of 56 carriers).[165]

A prospective cohort study by Mai et al.[166] examined risks of first and subsequent cancers among germline *TP53* mutation carriers in the National Cancer Institute LFS Cohort. In the 186 women with a *TP53* mutation, breast cancer was the first cancer diagnosed in 76 women (68 of whom were diagnosed at <45 years), and was the second cancer diagnosed in 42 women. The annual hazard for breast cancer started to increase in the late teens and peaked at approximately 40 years. The cumulative incidence of breast cancer for women with a *TP53* mutation was approximately 85% by age 60 years.[166]

A case series by Bougeard et al.[167] of 257 French women with a history suggestive of LFS who had an identified germline *TP53* mutation. In adults, breast cancer was observed in 79% of the women with a *TP53* mutation, and 31% of these women also developed a contralateral breast cancer.[167]

Table D.17 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.4 Breast pathology

4.4.1 Previous benign breast disease

Evidence summary

Evidence classification—history of proliferative benign breast disease: Convincing.

Evidence classification—history of non–proliferative benign breast disease: Evidence of no association.

There is convincing evidence that a history of proliferative benign breast difsease (atypical hyperplasia or proliferative disease without atypia) is associated with an increased risk of breast cancer. The evidence is consistent across one meta–analysis and various studies reporting on one large prospective cohort. The increased breast cancer risk associated with atypical hyperplasia has been estimated as 3.93 (95% CI 3.24–4.76) and with proliferative disease without atypia as 1.76 (95% CI 1.58–1.95);[168] however these risk estimates should be interpreted cautiously as the reference population in most of the studies was not the general population.

No association between non–proliferative benign breast disease and risk of breast cancer was found in a meta–analysis of eight studies with high heterogeneity.[168]

Background

Benign breast disease (BBD) is a broad group of conditions with benign (non–cancerous) changes in breast tissue. These changes can appear as abnormalities on imaging, such as mammography or ultrasound, or as palpable lesions found on physical examination. Different types of benign breast disease include those caused by an increase in the number of cells (proliferation) or by the growth of abnormal cells in the breast ducts or lobes (atypia). BBD is classified according to the degree of proliferation and/or atypia as: non–proliferative (NP), proliferative disease without atypia (PDWA), and atypical hyperplasia (AH). BBD can also be classified according to histology as: adenosis, atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), fibroadenoma, papilloma, and cysts not otherwise specified.[168, 169]

The mechanism for any association between BBD and breast cancer risk may involve genetic components[170] and may be influenced by exogenous hormone use. Postmenopausal women who use combined menopausal hormone therapy have an increased risk of BBD,[171] while women prescribed the anti–oestrogen tamoxifen have a decreased BBD risk.[172] BBD is generally regarded as a marker for breast cancer susceptibility, although it has been suggested that precursor cells may exist in BBD that may progress into breast cancer.[168, 173] Shared risk factors, including genetic susceptibility, may contribute to any association between BBD and breast cancer.

Recent evidence

A meta–analysis by Dyrstad et al.[168] included 32 studies and estimated summary relative risks for breast cancer for BBD overall, for proliferative (PDWA and AH) disease, and NP disease compared with designated reference populations, or with a general or non–proliferative BBD

population, rather than the general population. Breast cancer risk has also been estimated in several studies from the prospective Mayo Clinic BBD cohort of approximately 13,400 women in the United States who underwent benign breast biopsy between 1967 and 2001.[174-177]

The meta–analysis by Dyrstad et al.[168] estimated an increased breast cancer risk for BBD (not otherwise specified) with relative risk, RR 2.07 (95% CI 1.64–2.61; 10 studies with high heterogeneity). For NP disease, the meta–analysis indicated no association with breast cancer risk, RR 1.17 (95% CI 0.94–1.47; eight studies with high heterogeneity).[168]

For AH, the meta–analysis by Dyrstad et al.[168] estimated the increased breast cancer risk as RR 3.93 (95% CI 3.24–4.76, 13 studies with low heterogeneity). Studies from the Mayo BBD cohort reported similar estimates for increased breast cancer risk for AH: HR compared with NP BBD at initial biopsy, 4.60 (95% CI 2.41–8.79);[174] HR compared with NP BBD in women with multiple biopsies, 5.49 (95% CI 2.56–11.81);[175] HR compared with NP BBD in women with excisional breast biopsies, 3.80, (95% CI 3.04–4.74);[176] and standardised incidence ratio (SIR) for women with AH on breast biopsy compared with the general population 4.34 (95% CI 3.66–5.12).[177]

Breast cancer risk varies with the degree of atypia, with increased number of atypical foci in the breast associated with increased breast cancer risk.[177, 178]

For ductal compared with lobular AH, inconsistent differences in the associated breast cancer risk have been reported from two meta–analyses[168, 169] and from the Mayo Clinic BBD cohort study.[177, 178]

For PDWA, the meta–analysis by Dyrstad et al.[168] estimated the increased breast cancer risk as RR 1.76 (95% CI 1.58–1.95; 15 studies with low heterogeneity). Studies from the Mayo Clinic BBD cohort have reported similar estimates for increased breast cancer risk for PDWA: HR compared with NP BBD at initial biopsy 1.79 (95% CI 1.20–2.66);[174] HR compared with NP BBD in women with excisional breast biopsies 1.61 (95% CI 1.40–1.85);[176] and HR compared with NP BBD in women with multiple biopsies 2.10 (95% CI 1.31–3.35).[175]

Table D.18 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.4.2 LCIS

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that a diagnosis of lobular carcinoma in situ (LCIS) is associated with increased risk of breast cancer. The evidence of effect is consistent, however large differences in methods, including sample size, study populations, inclusion of different treatment regimes, follow-up periods (including time since LCIS diagnosis) and statistical methods, combined with a low incidence of LCIS, have resulted in substantially different risk estimates across studies. Nevertheless, several studies have showed that there are no differences in the risk of subsequent breast cancer following a diagnosis of LCIS compared to DCIS. Moreover, the confidence intervals for the risk estimates for breast cancer after a diagnosis of LCIS are much wider than those for DICS, hence nearly all higher risk estimates

for LCIS compared to DCIS are unlikely to differ significantly from those for DCIS across studies. Finally, a validation study of an individual risk prediction model using Australian data has shown that actual incidence of breast cancer following an LCIS diagnosis is substantially lower than that predicted by a risk prediction model (IBIS-RET), for an LCIS diagnosis among women older than 50 years.

In conclusion, the body of evidence suggests that the risk of breast cancer after a diagnosis of LCIS may not be as high as reported in earlier studies; although a best estimate of risk remains unclear.

Background

LCIS is a non–invasive abnormality of the breast, characterised by abnormal changes in cells within the lobules and terminal ducts of the breast. It is usually found incidentally in breast biopsies performed for another reason, such as a suspicious mammogram.[179] The detection of LCIS has increased since the introduction of breast screening.[180, 181]

Any association between LCIS and subsequent breast cancer risk may be due to common risk factors that may predispose to both LCIS and invasive breast cancer. LCIS can be considered a breast cancer marker. More recently, it has been suggested that LCIS can also be a precursor lesion that may progress to invasive breast cancer, based on associations with the laterality of the subsequent breast cancer and whether it is lobular or ductal[182, 183]. Molecular similarities related to cancer development found between the LCIS and subsequent invasive cancer may also suggest progression of the LCIS to invasive cancer.[180, 184]

Recent evidence

Substantial differences in risk estimates are observed across studies. For this particular exposure, data are cited from studies published several decades ago as these risk estimates are still frequently cited in the literature.

Differences in risk estimates may be due to inclusion of women with a spectrum of lobular neoplasia, i.e. the inclusion of women with atypical lobular hyperplasia (ALH). Histopathological diagnostic thresholds for ALF and LCIS have changed over time[185]. The risk of subsequent breast cancer following LCIS also varies depending on the treatment for LCIS[180, 186]. For example, studies which include women who underwent either unilateral or bilateral mastectomy will underestimate the risk compared with conservative or no treatment beyond the excisional biopsy. As treatments have varied over time then period of the study will affect risk estimates. Further, depending on the study type, risk estimates might be inflated as LCIS patients undergo more intensive screening regimes than the general population.

Subsequent breast cancer after a diagnosis of LCIS is more likely to be lobular than ductal[181, 184, 187]. Mao et al.[186] reported a comparatively higher risk of subsequent invasive breast cancer for women with hormone receptor negative LCIS compared with hormone receptor positive LCIS (HR 0.356, 95% CI 0.14–0.90).

Chuba et al.[181] found that breast cancer subsequent to LCIS was equally likely in either breast. An earlier study by Rosen et al.[188] also found that breast cancers occurred equally in

the ipsilateral and contralateral breasts among 99 women with LCIS. However, the risk of subsequent invasive breast cancer was reported in a large cohort study by King et al.[180] to be higher in the breast on the same side (ipsilateral) compared with the breast on the opposite side (contralateral). Rawal et al.[189] also observed higher breast cancer incidence in the ipsilateral breast.

There are inconsistent findings regarding the effect of age at LCIS diagnosis on risk of subsequent breast cancer.[181, 186, 187, 190, 191]

Studies comparing LCIS and DCIS

The risk of breast cancer was lower after a diagnosis of LCIS than after a diagnosis of DCIS in a study of 1276 CIS patients (95% cases were DCIS) diagnosed in 1972-2002 and followed-up for less than 10 years, in The Netherlands (SIR = 2.5 vs. 3.4, respectively)[192]; although the risk estimate for LCIS did not exclude 1.0 and as the confidence intervals were not presented it is likely that the difference was not significant. Overall increased risk was estimated as SIR 3.4 (95%: CI 2.6–4.3). Robinson et al.[193] has indicated that it was not clear if Soergomataram et al.[192] allowed for mastectomies, but noted that they did apply overall incidence rates from the general population to each group, rather than half-rates, thus leading to expected numbers that were twice, and SIRs which were half, true values. Nevertheless, in the study by Robinson et al.[193] of 12 836 cases of CIS diagnosed in England between 1971 and 2003, the overall increased risk of breast cancer after a diagnosis of CIS was comparable to that observed by Soerjomataram et al.[192] (SIR 1.96; 95% CI 1.96-2.14). In this study the increased risk of breast cancer was not different for DCIS and LCIS (specific results were not shown).[193]

Rawal et al.[189] reported the increased invasive breast cancer risk associated with LCIS as RR 4.74 (95% CI 2.46–9.11) for ipsilateral invasive breast cancer and RR 3.16 (95% CI 1.42–7.03) for contralateral invasive breast cancer, from a cohort of 3,802 women in Sweden diagnosed between 1993 and 2003 with *in situ* disease. Comparative risks for DCIS were RR 3.80 (95% CI 2.98–4.84) and RR 1.96 (95% CI 1.40–2.74), respectively. This study included invasive cancers diagnosed at least one month after diagnosis of the *in situ* disease.[189]

In a cohort study of 3455 women with CIS in Sweden, Warnberg et al.[191] reported similar risks of subsequent breast cancer among women with a diagnosis of LCIS and DCIS (SIR 4.0, 95% CI 2.1–7.5 and SIR 4.5, 95% CI 3.7–5.5), respectively. Follow-up was only for around 5 years hence these data should be interpreted cautiously. Further, Franceschi et al.[194] observed that SIRs for subsequent breast cancer were higher for DCIS (8.6) than LCIS (4.2) among 249 primary cases of CIS in Switzerland (SIR 7.2; 95% CI 4.6–10.6). Using data from the same area in Switzerland, Levi et al.[187] showed that the incidence of subsequent breast cancer was similar among 579 cases of LCIS and DCIS (SIR 4.2 and 4.6, respectively; for CIS overall SIR 4.5, 95% CI 2.4-5.8).

LCIS only—relative risk

Chuba et al.[181] using the SEER (Surveillance, Epidemiology and End Results program) database of women diagnosed with LCIS from 1973 to 1998 (4,853 women), estimated the SIR for invasive breast cancer within 10 years of diagnosis for women with LCIS compared with the general population as 2.4 (95% CI 2.1–2.6). Subsequent cancer was equally likely to occur in either breast after partial mastectomy. This study included invasive cancers diagnosed at least 1 year after LCIS diagnosis but also included patients who had unilateral

mastectomy at LCIS diagnosis. King et al.[180] indicated that the Chuba study was limited by a lack of central pathology review and treatment information.

Rawal et al.[189] reported the increased invasive breast cancer risk associated with LCIS as RR 4.74 (95% CI 2.46–9.11) for ipsilateral invasive breast cancer and RR 3.16 (95% CI 1.42–7.03) for contralateral invasive breast cancer, from a cohort of 3,802 women in Sweden diagnosed between 1993 and 2003 with in situ disease. This study included invasive cancers diagnosed at least one month after diagnosis of the *in situ* disease and did not account for mastectomies.

Many earlier studies have reported much higher risks in the range of 5.4 to 12 in studies including much smaller sample sizes conducted in the 1970s and 1990s, and these are frequently reported in the literature. For example, a relative risk of 'about 9' was reported among 39 women diagnosed with LCIS from the United States after an average follow-up of 18 years[195]; increased risk 15 years after LCIS diagnosis was estimated to be 10.8 (95% CI: 4.3–27.0). Rosen et al.[188] followed up 99 patients with LCIS not treated by mastectomy for an average of 24 years and reported a 9 times higher incidence of subsequent invasive breast cancer (28 cases) compared to the general population. Andersen[196] reported an 'about 12 times' higher incidence of breast cancer among 52 women with LCIS, 44 of whom had been treated by biopsy alone. Estimated risk of breast cancer was slightly lower in the study by Bodian et al.[190] among 236 patients with lobular neoplasia (LCIS), in which the observed long-term risk was 5.4 (95% CI 4.2-7.0; median follow-up 18 years).

LCIS only—cumulative risk

In a validation of the IBIS-RET (International Breast Cancer Intervention Study Risk Evaluation Tool) Lo et al.[185] showed that the mean observed 10-year risk of invasive breast cancer was 14.1% (95% CI 11.3%-17.5%) among 732 Australian women (Victorian Cancer Registry) with a mean-follow-up of 9.8 years. The mean assigned IBIS-RET 10-year risk was 20.9%. The authors noted that the lack of information regarding bilateral mastectomy or risk-reducing medication after LCIS diagnosis should not have affected findings as these interventions are rarely used in Australia.

Wong et al.[197] used data from the Surveillance, Epidemiology & End Results (SEER) database to identify 19,462 women with an LCIS diagnosis (mean age 53.7 years) between 1983 and 2014. Subsequent breast cancer incidence was 11.3% (95% CI 10.7-11.9) and 19.8% (95% CI 18.8-20.9) after 10 and 20 years, respectively. Mastectomy was performed in 11.1% of LCIS cases.

Cumulative risks vary across studies and follow-up period:

- Minimum of 7.1% for 10 years[181]
- 11.3% (95% CI 10.7-11.9) for 10 years[197]
- 14.1% (95% CI 11.3-17.5) for 10 years[185]
- 17% for 15 years[195]
- 26% for 15 years[180]
- 19.8% (95% CI 18.8-20.9) for 20 years[197]
- 21.3% for 20 years[198]
- 26% for 20 years[187].

Table D.19 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.4.3 DCIS

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that a diagnosis of ductal carcinoma in situ (DCIS) is associated with increased risk of breast cancer. This evidence is consistent across cohort studies from several countries.

The increased breast cancer risk associated with DCIS (all grades) in Australia has been estimated as 3.9 (95% CI 3.6–4.2).[199] Risks are higher among women diagnosed at younger ages.

Background

DCIS is a heterogeneous, non–invasive abnormality of the breast, characterised by changes in the cells in the milk ducts. The abnormal cells are contained entirely within the milk ducts and have not spread into surrounding tissue. DCIS can be graded as high, intermediate or low. DCIS diagnoses were uncommon before mammography screening. The detection of DCIS in Australia has increased substantially since the introduction of breast screening.[199]

Risk factors that are common to DCIS and invasive breast cancer, such as breast density, family history, history of benign breast disease and genetic factors, may play a part in any association of DCIS with increased risk of invasive breast cancer.[200, 201] DCIS may be associated with increased risk for invasive cancer of the other breast or for cancers arising independently of the DCIS in the same breast, due to these common risk factors. Alternatively, it is possible that DCIS may progress to invasive breast cancer, although the probability of this occurring likely varies with characteristics of the DCIS, including its size and grade. Some DCIS tumours have been shown to have molecular features related to cancer development that are similar to those in subsequent invasive breast cancers, which may suggest progression of the DCIS to invasive breast cancer.[200]. Research aiming to clarify the malignant potential of DCIS lesions and factors that predict which lesions will become invasive is ongoing.

Recent evidence

In an Australian cohort study of 13,749 women diagnosed with DCIS between 1995 and 2005, the relative risk of invasive breast cancer compared with all Australian women was RR 3.9 (95% CI 3.6–4.2).[199] A similar increased risk of breast cancer was estimated for screen–detected DCIS in South Australian women (HR 4.0, 95% CI 3.4–4.8).[202]

Rawal et al.[189] reported the increased invasive breast cancer risk associated with DCIS as RR 3.80 (95% CI 2.98–4.84) for ipsilateral invasive breast cancer and RR 1.96 (95% CI 1.40–2.74) for contralateral invasive breast cancer, from a cohort of 3,802 women in Sweden diagnosed between 1993 and 2003 with *in situ* disease. This study included invasive cancers diagnosed at least one month after diagnosis of the *in situ* disease.[189]

Cohort studies from other countries estimated increased breast cancer risk associated with DCIS as follows:

- SIR for breast cancer compared with the general population 4.8 (95% CI 4.1–5.5; 3,046 Norwegian women diagnosed with DCIS 1993–2007)[203]
- SIR 1.4 (95% CI 1.2–1.5) for invasive breast cancer that is contralateral (cancer in the opposite breast) and SIR 1.7 (95% CI 1.4–2.1) for invasive breast cancer that is ipsilateral (cancer in the same breast) (23,547 Californian women diagnosed with DCIS 1988–1999)[204]
- SIR 4.6 (95% CI 3.4–6.2; 482 Swiss women diagnosed with DCIS 1977–2002).[187]

Other estimates for increased risk of breast cancer following a diagnosis of DCIS, compared to following a diagnosis of LCIS, are indicated in section 4.4.2.

The relative risk of invasive breast cancer was higher for those younger at DCIS diagnosis in Australian women: RR for <40 years at DCIS diagnosis 19.8 (95% CI 14.2–25.4), RR for 40–49 years at DCIS diagnosis 5.6 (95% CI 4.7–6.5), RR for ≥ 50 years at DCIS diagnosis 3.0–4.2.[199] Cohort studies from other countries also reported higher risk of invasive breast cancer for women who were younger at diagnosis of DCIS than for those older at DCIS diagnosis.[189, 203-206]

The relative risk of invasive breast cancer in the period up to five years from DCIS diagnosis in Australian women was RR 3.6 (95% CI 3.3–3.9), which was lower than for the subsequent period of 5–11 years from DCIS diagnosis (RR 5.3, 95% CI 4.5–6.0).[199]

A meta–analysis by Zhang et al.[207] that examined the effect of detection method (screening versus non–screening) and tumour characteristics, such as margins, grade and hormone receptors, reported a higher risk of invasive breast cancer for positive versus negative margins and for non–screening versus screening–detected cancers.

Cohort studies have reported differences in risk of invasive breast cancer for different treatment regimens for DCIS.[202-206, 208, 209]

Table D.20 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.4.4 Previous primary invasive breast cancer

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that having had a primary invasive breast cancer is associated with an increased risk of a second primary breast cancer. There is consistent evidence from a large number of cohort studies. The increased risk of a second primary breast cancer associated with a primary breast cancer has been estimated as 1.55 (95% CI 1.45–1.66) in an Australian study[210] and has ranged from 1.15 to 3.5 in European cohort studies.[211-217]

Background

A second primary breast cancer refers to a new primary breast cancer, which is different from a recurrence of the initial breast cancer. A second primary breast cancer occurs more commonly in the opposite (contralateral) breast, but can occur in the same (ipsilateral)

breast if treatment for the first primary cancer was breast–conserving surgery. Contralateral breast cancer has been commonly used as the outcome measure of a second primary breast cancer, with any ipsilateral cancers recorded as recurrent being excluded.[210, 212, 216]

Any association between risk of second primary breast cancer with first primary breast cancer may be due to common risk factors predisposing to both primary cancers, such as genetic, hormonal, environmental or lifestyle–related risk factors. Late effects of treatment, such as radiotherapy to the breast, may also potentially contribute to development of a second primary breast cancer.[210, 212]

Recent evidence

Many studies investigating an association between primary breast cancer and risk of second primary breast cancer used metachronous contralateral breast (which develops at a consequent time to the first primary breast cancer) as the outcome measure of the second primary breast cancer. Synchronous cancers (defined usually as those diagnosed within six months of the first primary) have been specifically excluded in some studies, because they are more likely to be diagnosed as a result of detection bias.[210, 213, 218]

In an Australian cohort study[210] of 26,725 women with primary breast cancer diagnosed from 1982– 2001 in Queensland, the SIR relative to the general population for a second invasive breast cancer was 1.55 (95% CI 1.45–1.66) (personal communication; D. Youlden via email). Cohort studies from other countries estimated increased risk of second primary contralateral breast cancer associated with a primary breast cancer:

- SIR 2.96 (95% CI 2.82–3.12; 17,745 women with non–metastatic breast cancer from France, 1981–2000)[211]
- SIR 1.15 (95% CI 1.02–1.29; European Prospective Investigation into Cancer and Nutrition (EPIC) cohort)[212]
- SIR 1.2 (95% CI 1.1–1.3; 49,804 women with primary breast cancer from German cancer registries)[213]
- SIR 2.46 (95% CI 2.40–2.52; 4,927 women diagnosed with invasive breast cancer, 1992–2004, from SEER database)[215]
- SIR 1.74 (95% CI 1.41–2.12; 5,663 women with primary breast cancer in France, 1989–1997)[214]
- SIR 1.9 (95% CI 1.8–2.1; 45,229 breast cancer patients diagnosed in the Netherlands, 1989–2002)[216]
- SIR 3.5 (95% CI 3.2–3.8 (9,919 women diagnosed with breast cancer in the Netherlands, 1972–2000).[217]

One cohort study (4,152 women diagnosed with breast cancer in Switzerland, 1995–2007) reported a higher risk of second primary breast cancer only among women with oestrogen receptor negative (ER–) rather than oestrogen receptor positive (ER+) primary breast cancers (SIR 1.98; 95% CI 1.19–3.09).[219]

The risk of second primary breast cancer associated with a primary breast cancer reported varies with the treatment regimen for the first primary breast cancer. Endocrine treatment for the first primary breast cancer was associated with a lower risk of second primary breast cancer compared with no endocrine treatment (HR 0.58; 95% CI 0.48–0.69) in the cohort study by Schaapveld et al.[216] Three other studies also reported a decreased risk of breast cancer for endocrine treatment versus no endocrine treatment.[211, 218, 219]. Schaapveld et al.[216]

reported chemotherapy for first primary breast cancer was associated with a lower risk of contralateral breast cancer compared with no chemotherapy (HR 0.73; 95% CI 0.60–0.90), but there was no association for radiotherapy treatment.

Table D.21 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.5 Endogenous hormones

4.5.1 Age at menarche

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that a younger versus an older age at menarche is associated with an increased risk of breast cancer. A large pooled analysis of 117 international studies estimated a 5% increased risk of breast cancer for each year younger at menarche (RR 1.05, 95% CI 1.044–1.057 per year).[220]

Background

Breast cancer risk has been related to several reproductive risk factors. This finding is consistent with the hypothesis that breast cancer risk is related to the total extent of breast mitotic activity, driven by oestrogen and progesterone exposure during the luteal phase of the menstrual cycle, which will determine the probability of tumorigenic somatic events. Early age at menarche therefore increases the period during which the breast is mitotically active, particularly the period before first full term pregnancy during which breast cells undergo differentiation.[221] Women who have an early age of menarche therefore have a higher lifetime exposure to oestrogen and progesterone and breast tissue is responsive to steroid hormones produced by the ovaries during the reproductive years.[222]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)[11] stated '*early menarche [before the age of 12] increases lifetime exposure to oestrogen and progesterone and the risk of breast cancer*', listing early menarche as an established cause of breast cancer. The WCRF/AICR 2018 Breast Report also noted the reverse applies: '*late menarche reduces the risk of breast cancer*'.

Recent evidence

A large pooled analysis conducted by the Collaborative Group on Hormonal Factors included 118,964 women with invasive breast cancer and 306,091 without the disease from 117 international studies conducted between 1970 and 1999.[220] Risk of breast cancer increased by a factor of 1.05 (95% CI 1.044–1.057) for each year younger at menarche. There was no evidence of significant heterogeneity across studies either overall, or according to study design. The association was stronger for lobular than ductal tumours, but there were no significant differences by oestrogen receptor status. Mean age of menarche was 13.1 years in the combined dataset. Compared with women aged 13 years at menarche, the RR for women aged 12, 11 and <11 years was 1.07 (95% CI 1.05–1.09), 1.09 (95% CI 1.06–1.12) and 1.19 (95% CI 1.13–1.25), respectively; and women aged 14, 15 and ≥16 years 0.98 (95% CI 0.96–1.00), 0.92 (95% CI 0.89–0.95) and 0.82 (95% CI 0.79–0.85), respectively.

Data from two more recent cohort studies generally support these findings. Findings from the French Teacher Cohort[44] (67,634 women) were presented stratified by menopausal status. Women who experienced menarche at age 12–14 years compared with ≥14 years were 36% more likely to develop premenopausal breast cancer (HR 1.36, 95% CI 1.09–1.70), although increased risks for younger ages at menarche were not significant. Among postmenopausal women, the increased risk of breast cancer associated with a later age at menarche was higher for women who experienced menarche at aged 10–12 years (HR 1.19, 95% CI 1.07–1.32) or 13–14 years (HR 1.13, 95% CI 1.04–1.23), compared with ≥14 years. There was a non–significant increased risk among those who experienced menarche at age less than 10 years (1.58, 95% CI 0.91–2.74).

The prospective Breakthrough Generations Study in the United Kingdom included 104,931 women. A significant inverse trend with increasing age at menarche was reported (HR for a one–year increase in age at menarche 0.89, 95% CI 0.81–0.99).[223] However, the analyses were not adjusted for known confounders of breast cancer risk including alcohol consumption and body mass index, and follow–up was only for four years.

Table D.22 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.5.2 Parity

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that parity is associated with a decreased risk of breast cancer and that nulliparity is associated with an increased risk of breast cancer.

In a dose–response analysis, the decreased breast cancer risk associated with parity compared to nulliparity was estimated to be 0.93 (95 % CI 0.95–0.91) per birth.[224] In a meta-analysis, the increased breast cancer risk associated with nulliparity was estimated to be 1.16 (95% CI 1.04–1.26) compared with parous women.[226]

Background

Parity can be defined as the number of times a female has been pregnant and carried the pregnancies to a viable gestational age. Nulliparity refers to never having completed a pregnancy to a viable gestational age. Parity may reduce breast cancer risk through changes that occur in breast epithelial cells in preparation for lactation; the more highly differentiated cells are thought to be less vulnerable to DNA–damage.[12, 225]

WCRF/AICR

The World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR)[11] stated that '*not bearing children increases lifetime exposure to oestrogen and progesterone and the risk of breast cancer*', listing 'not bearing children' as an established cause of breast cancer. The WCRF/AICR 2018 Breast Report also noted the reverse applies; '*bearing children reduces the risk of breast cancer*'.

Recent evidence

A pooled analysis of individual data from 47 epidemiologic studies in 30 countries reported that women with breast cancer had, on average, fewer births than did controls (2.2 versus 2.6).[224] The relative risk of breast cancer decreased by 0.93 (95 % CI 0.91–0.95) for each birth.

A meta–analysis by Nelson et al.[226] included 17 studies: 3 cohort, 13 case–control and one nested case–control study (with significant heterogeneity across the studies). Nulliparous women had an increased risk of breast cancer (OR 1.16, 95% CI 1.04–1.26) compared with parous women. Women with three or more births were at lower risk of breast cancer (summary OR 0.73, 95% CI 0.61–0.87), compared with nulliparous women.

The mostly recently published meta–analysis included 14 studies published between 2007 and 2014 reporting on the association according to tumour subtype (4 cohort and 10 case–control studies). This study found a significant protective effect of parity compared with nulliparity for luminal breast cancer (summary OR 0.75, 95% CI 0.70–0.81; with evidence of significant heterogeneity) but not human epidermal growth factor receptor positive (HER2+) or triple negative breast cancer (TNBC).[227]

The two recent meta–analyses by Nelson et al.[226] and Lambertini et al.[227] did not include data from the E3N & European Prospective Investigation in Cancer and Nutrition (EPIC) cohorts. Dartois et al.[44] reported an increased risk of postmenopausal breast cancer associated with nulliparity in the E3N cohort data (HR 1.28, 95% CI 1.13–1.45), when compared with women having more than one child with the first birth before age 30 years. In the EPIC cohort, ever having a full–term birth was associated with a decreased risk of ER+PR+ breast cancer (HR 0.87, 95% CI 0.78–0.96; with evidence of dose–response); however parity was not associated with risk of ER–PR– breast cancer.[228]

Table D.23 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.5.3 Age at first birth

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that women who give birth to their first child at later ages are at increased risk of breast cancer compared with women who have their first child at younger ages. The evidence is consistent across studies and there is also evidence of a dose–response association. Data from the Nurses Health Studies showed the increased risk to be 3% per one year increase in age at first birth (RR 1.03; 95% CI 1.02–1.03).[229] The association may only be for oestrogen–receptor positive (ER+) breast cancer sub–types.

Background

Prior to first pregnancy, the breast has a high proportion of undifferentiated ducts and alveolar buds.[228] An early age at first full term pregnancy may protect against breast cancer through the earlier induction of terminal differentiation of breast cells at risk.[230] Terminally

differentiated cells have lower proliferation rates and longer DNA repair phases, and thus are less likely to undergo malignant transformation.[228] The shorter the interval between menarche and first birth, the less time undifferentiated breast epithelial cells are at risk of carcinogenesis.[228] Full term pregnancies also cause long term reductions in levels of circulating sex hormones,[228] which may account for any association between age at first birth and risk of breast cancer.

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCR/AICR)[11] stated that '*a first pregnancy/birth over the age of 30 increases lifetime exposure to oestrogen and progesterone and the risk of breast cancer*', listing it as an established cause of breast cancer. WCRF/AICR 2018 Breast Report also noted the reverse applies, '*pregnancy before the age of 30 reduces the risk of breast cancer*'.

Recent evidence

Two recently published systematic reviews with meta–analysis[226, 227] and two large cohort studies not included in either review[228, 229] have examined the association between age at first birth and breast cancer risk.

The meta–analysis by Nelson et al.[226] included five studies and compared breast cancer incidence in women aged 30 years or older with women aged 25–29 years at first birth. This study reported a pooled RR of 1.20 (95% CI 1.02–1.42; with no evidence of significant heterogeneity).

The systematic review and meta–analysis by Lambertini et al.[227] included 12 studies (three cohort and nine case–control studies) and compared risk of breast cancer among women aged >24 years versus those aged ≤24 years at first birth for different breast cancer molecular subtypes. No estimate was provided for breast cancer overall. An increased risk of developing breast cancer of the luminal subtypes was observed (pooled OR for >24 years versus ≤24 years 1.15, 95% CI 1.00–1.32; with evidence of significant heterogeneity), but no association of age at first birth with human epidermal growth factor receptor 2 (HER2) or triple negative breast cancer subtypes was observed.

Ritte et al.[228] reported on data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (311,097 women; 9,456 breast cancer cases). No estimate was provided for breast cancer overall, only according to hormone receptor status. A later age at first birth (≥35 years versus ≤19 years) was associated with an increased risk of oestrogen receptor positive/progesterone receptor positive (ER+PR+) tumours (HR 1.47, 95% CI 1.15–1.88) but not with risk of oestrogen receptor negative/progesterone receptor negative (ER–PR–) tumours.

Data from the Nurses' Health Studies (NHS I and II; 121,700 and 116,430 women, respectively) indicated a positive association between older age at first birth and risk of developing breast cancer in a dose–response analysis (RR per one year increase in age at first birth 1.03, 95% CI 1.02–1.03).[229] Analysis according to luminal subtypes showed an association between age at first birth and risk of luminal–A breast cancer (RR per one year increase in age at first birth 1.03, 95% CI 1.02–1.05), but not HER2 breast cancer.

Table D.24 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.5.4 Breastfeeding

Evidence summary

Evidence classification: Probable.

Breastfeeding (or lactation) is probably associated with a small decreased risk of breast cancer in the mother.[11] There is evidence of a dose–response relationship, that is, the longer the duration of breastfeeding, the larger the protective effect. The risk of breast cancer associated with breastfeeding has been determined by the WCRF[10] from a pooled analysis of 13 prospective cohort studies as 0.98 (95% CI 0.97–0.99) per 5–month increase in breastfeeding duration.

Background

Breastfeeding is defined as feeding a child human breast milk.[231] Lactation is defined as the physiological process of milk production.

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) have indicated that there is robust evidence for mechanisms operating in humans.[11] Several potential mechanisms through which breastfeeding might influence breast cancer risk have been proposed. The most plausible mechanism is through the hormonal effects of amenorrhoea and the consequent reduction in lifetime exposure to steroid hormones, including oestrogen.[11] Lactation may also induce epigenetic changes that exert a lasting impact on the risk of carcinogenesis. Epithelial exfoliation of breast tissue during lactation and the process of epithelial apoptosis at the end of breastfeeding may also influence breast cancer risk by eliminating cells with DNA damage.[11, 232]

WCRF/AICR

The World Cancer Research Fund/American Institute of Cancer Research[11] considered that "*lactation probably protects against breast cancer (unspecified)*"—that is, the judgement was 'Strong–probable'. A dose–response of 13 prospective studies showed a small but significant protective effect per 5–month duration of breastfeeding and overall breast cancer risk (RR 0.98, 95% CI 0.97–0.99).[10] The evidence was insufficient to specify the association separately for premenopausal and postmenopausal breast cancer.

Recent evidence

Three meta–analyses reporting on the association between breastfeeding and breast cancer were published in 2015 and 2016.[227, 233, 234] There was substantial overlap between studies included in each of these meta–analyses and also with the Continuous Update Project systematic literature review.[10]

The meta–analysis by Zhou et al.[233] included three cohort studies and 23 case–control studies. The three cohort studies included were also included in the Continuous Update Project systematic review.[10] A significant protective effect of 'ever' breastfeeding compared with 'never' breastfeeding was observed (RR 0.61, 95% CI 0.44–0.85) and of longest versus shortest duration of breastfeeding (RR 0.47, 95% CI 0.37–0.60). Across all studies involving all exposures, findings were significant among 23 case–control studies (summary OR 0.44, 95% CI 0.36–0.55) but not among the more reliable cohort studies (summary RR 1.00, 95% CI 0.91–1.08).

Two recent meta–analyses and a pooled analysis examined the relationship for 'ever' versus 'never' breastfeeding—and longer duration of breastfeeding in the pooled analysis—and risk of breast cancer according to breast cancer subtype and not breast cancer overall. The majority of studies contributing to the summary estimates are case–control studies, some of which were not population based,[227] indicating the preliminary nature of the findings according to breast cancer subtype. Lambertini et al.[227] reported a significant protective effect of 'ever' versus 'never' breastfeeding for Luminal and triple negative disease but not for human epidermal growth factor receptor 2 (HER2) breast cancer. The pooled analysis of three case–control studies by Ma et al.[235] reported a significant inverse association between longer duration of breastfeeding and triple negative breast cancer and Luminal A–like breast cancer but not Luminal B–like nor HER2–enriched breast cancer. The meta–analysis by Islami et al.[234] included eight cohort studies (all of which were included in the Continuous Update Project systematic review).[10] For cohort studies, the association was significant only for oestrogen receptor negative (ER–)/progesterone receptor negative (PR–) breast cancer (summary RR 0.84, 95% CI 0.72–0.97) and triple negative subtypes (summary RR 0.73, 95% CI 0.62–0.87).

Table D.25 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.5.5 Age at menopause

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that older age at menopause is associated with an increased risk of postmenopausal breast cancer. Evidence from a large pooled analysis of a substantial number of studies indicates a dose–response relationship, with risk increasing by about 3% for each year older at menopause (RR 1.029, 95% CI 1.025–1.032).[220] The increased risk of breast cancer with later menopausal age is one of several findings showing that any factor that increases exposure to endogenous oestrogen increases the risk of breast cancer.

Background

Menopause is signalled by 12 months since last menstruation. The median age of menopause in Australian women is 51 years.[236] During natural menopause, the body's production of oestrogen and progesterone decreases. The later a woman goes through menopause, the longer her breast tissue is exposed to oestrogens released by the ovaries during her menstrual periods and the greater her lifetime exposure to oestrogen.

Recent evidence

The most reliable study providing evidence of an association between age at menopause and breast cancer risk is a large pooled analysis conducted by the Collaborative Group on Hormonal Factors in 2012.[220] This study included 118,964 women with invasive breast cancer and 306,091 without the disease from 117 international studies conducted between 1980 and 2011 (38% of the cases were from cohort studies, 42% from population–based case–control studies and the remaining 20% from case–control studies with hospital controls). Among 35 cohort studies, risk of postmenopausal breast cancer was approximately 3% higher (RR 1.029; 95% CI 1.025–1.032) for every 1–year increase in age at natural menopause and there was no evidence of significant heterogeneity either across studies overall or according to study design. Relative to women who experienced menopause at age 50–54 years, women with age at menopause of 55 years or older had a 12% higher risk of breast cancer (RR 1.12, 95% CI 1.07–1.17) and women experiencing menopause at age 45–49 years had 14% lower risk (RR 0.86, 95% CI 0.84–0.89), compared with women aged 50 years or older at menopause. The association was stronger for oestrogen receptor–positive (ER+) disease than for oestrogen receptor–negative (ER–) disease and for lobular than for ductal tumours. The magnitude of the association did not differ significantly between women with a natural menopause and women whose menopause was induced (for example, bilateral oophorectomy), although the association was attenuated in women who were overweight or obese.

There have been two other large studies examining age at menopause and risk of breast cancer published since the Collaborative pooled analysis. One was a meta–analysis of six case–control studies among Chinese and Japanese women that is not generalisable to the Australian population.[237] Another was a prospective cohort study—the European Prospective Investigation into Cancer and Nutrition (EPIC) study—of 311,097 European women,[228] focusing on hormone receptor status and which showed no association with ER+PR+ or ER–PR– subtypes.

Table D.26 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.5.6 Circulating hormones—steroids

Evidence summary

Evidence classification—Convincing: oestrogen (postmenopausal), testosterone, insulin–like growth factor [IGF1].

Evidence classification—Inconclusive: oestrogen (premenopausal), sex hormone binding globulin [SHGB], luteal phase progesterone, prolactin.

There is convincing evidence from large pooled analyses that higher circulating levels of oestrogen, testosterone, and IGF–1 are associated with an increased risk of postmenopausal breast cancer (OR 2.15, 95% CI 1.87–2.46;[238] OR 2.04, 95% CI 1.76–2.37;[238] and OR 1.28, 95% CI 1.14–1.44;[239] for highest versus lowest levels, respectively).

The evidence for an association between circulating levels of oestrogen and risk of premenopausal breast cancer, luteal progesterone and sex hormone binding globulin

(SHBG) and risk of breast cancer is inconclusive. The findings across studies are inconsistent. For prolactin the evidence is limited in amount.

There is some evidence that SHBG is not associated with risk of premenopausal breast cancer risk, and for postmenopausal breast cancer there is evidence of an inverse association.

Background

Endogenous sex or steroid hormones such as oestrogens, progesterone and androgens—such as testosterone—are hormones naturally produced by the body as part of normal healthy functioning. As a woman approaches and goes through menopause, levels of these hormones decline.

Oestrogen, produced by the ovaries, has multiple functions, including stimulating puberty including breast growth, laying down fatty deposits, causing the vagina to secrete mucous. It also affects skin and bones and can protect against heart disease. It regulates the menstrual cycle. Progesterone is produced by the ovaries and adrenal glands and is essential for fertility and for sustaining a pregnancy. Its most important function is to encourage the endometrium to secrete proteins in the second half of the menstrual cycle, in preparation for the fertilised egg. Testosterone is the most abundant biologically active female hormone, essential for physical and mental health in women.

Potential biological mechanisms suggested for the association between oestrogens and breast cancer risk include their actions to increase the mitotic rate and proliferation of breast epithelial cells, leading to increased risk of mutations and stimulation of the growth of early tumours.[240] There is limited understanding of the way endogenous progesterone acts in the development of breast cancer. Not all progesterone signalling is tumour-promoting and progesterone may have anti-proliferative actions in breast cells. (See also section 3.2.3.)

Androgens have more complex actions, with both inhibitory and proliferative effects on breast cells in pre–clinical studies.[241] Testosterone can act directly on breast cells via the androgen receptor, which may inhibit proliferation. Androgens may also act indirectly through conversion by the aromatase enzyme in breast tissue to oestrogen, which has a proliferative effect via the ER.[241]

SHBG is a protein that binds oestrogen and testosterone, transports them in the bloodstream and influences their bioavailability to cells. Levels of sex SHBG are inversely correlated with BMI. Any association between higher levels of SHBG and decreased breast cancer risk may involve reduced body fat and less aromatisation of hormones from androgens to oestrogens in fat tissue.[5]

Evidence

The evidence regarding any association between levels of oestrogen and risk of premenopausal breast cancer are inconclusive. Two pooled analyses have shown differing results.

The Endogenous Hormones and Breast Cancer Collaborative Group (EHBCCG)[240] conducted a pooled analysis of individual participant data from seven prospective studies, including data from the Nurses' Health Study II, the Hormones and Diet in the Aetiology of Breast Cancer Risk (ORDET) cohort, and the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort studies. Among 767 premenopausal women with breast cancer and

1,699 controls, increased odds of breast cancer were found for doubling of levels of circulating oestradiol (OR 1.19, 95% CI 1.06–1.35), calculated free oestradiol (OR 1.17, 95% CI 1.03–1.33), oestrone (OR 1.27, 95% CI 1.05–1.54), androstenedione (OR 1.30, 95% CI 1.10–1.55), dehydroepiandrosterone sulphate (DHEAS) (OR 1.17, 95% CI 1.04–1.32), and testosterone (OR 1.18, 95% CI 1.03–1.35). Breast cancer risk was not associated with luteal phase progesterone or SHBG. An earlier pooled analysis of many of the same studies did not find an association between circulating levels of oestradiol and risk of premenopausal breast cancer (OR 1.10, 95% CI 0.96–1.27).

No associations were found between circulating oestrogens and progesterone and premenopausal breast cancer risk in some of the individual studies, including the Nurses' Health Study II,[241] ORDET,[242] and the EPIC cohort.[243] However, in the Nurses' Health Study II, premenopausal luteal oestrogen levels were positively associated with ER+PR+ (oestrogen receptor positive/progesterone receptor positive) breast cancers.[241] For circulating testosterone, positive associations with breast cancer risk in premenopausal women were demonstrated in each of the Nurses' Health Study II,[241] ORDET cohort,[242] and the EPIC cohort.[243]

A pooled analysis of data by the EHBCCG from 18 prospective studies indicated a positive association between levels of circulating steroid hormones and risk of postmenopausal breast cancer—OR for highest versus lowest levels included oestradiol OR 2.15 (95% CI 1.87–2.46), oestrone OR 1.81 (95% CI 1.56–2.10) and testosterone OR 2.04 (95% CI 1.76–2.37).[238]

This analysis also showed a positive association between each of these endogenous steroid hormones and BMI in postmenopausal women. In an earlier analysis of these pooled data, from nine prospective studies, levels of oestrogens and androgens were positively associated with postmenopausal breast cancer risk.[244] SHBG was associated with a decreased risk of postmenopausal breast cancer.[244] Significant dose–responses were observed for all hormones. Levels of progesterone were not examined in this study.

For breast cancer subtypes, varying associations between circulating oestrogens and androgens and postmenopausal breast cancer risk have been reported. Associations with endogenous oestrogens and androgens are strongest for ER+ breast cancers. However, some associations have been also reported with ER– breast cancers—for example, in a nested case–control study[245] and the ORDET cohort[246]—including association between higher levels of testosterone with a lower risk of ER– breast cancer in postmenopausal women.[247]

Insulin–like growth factor 1

Background

IGF1 is a growth promoting peptide or hormone naturally produced by the body, which stimulates cell proliferation and inhibits programmed cell death (apoptosis) directly. There is also evidence from preclinical studies for crosstalk between the signaling pathways for oestrogen and IGF1. This may result in stimulation of cell growth and suppression of apoptosis, or programmed cell death. Therefore, higher circulating levels of IGF1, especially in combination with signaling via the ER, may facilitate cancer development in breast tissue.[248]

Evidence

Associations between circulating IFG1 level and increased breast cancer risk have been reported by EHBCCG.[239] The pooled analysis of individual data from 17 prospective studies

showed that plasma IGF1 concentrations were associated with increased breast cancer risk for women in the highest versus the lowest quintile of IGF1 concentration (OR 1.28, 95% CI 1.14–1.44). The association was not substantially modified by menopausal status or by adjustment for breast cancer risk factors. For ER+ breast cancer, the association was significant (OR 1.38, 95% CI 1.14–1.68); however, there was no significant association for ER– breast cancer (OR 0.80, 95% CI 0.57–1.13).[239] More recent data from the EPIC study showed an association only among ER+ breast cancer (OR 1.41, 95% CI 1.01–1.98) and among ER+ postmenopausal but not premenopausal breast cancer.[248]

Prolactin

Background

Prolactin is an endogenous hormone produced in the pituitary gland. It has a major role in milk production during lactation.[249] Prolactin also has other physiological actions, including reproductive, metabolic and behavioural. It regulates fluids and the immune system and may also be produced locally in several other tissues.[250]

Potential mechanisms for the association of prolactin with breast cancer risk include its effects on increasing cell proliferation and reducing apoptosis, and synergistic effects with oestrogen and progesterone in the breast.[251, 252]

Evidence

Analysis from the Nurses' Health Study has indicated an increased breast cancer risk for higher prolactin measured within 10 years of breast cancer diagnosis (RR 1.20, 95% CI 1.03–1.40 for highest versus lowest quartiles).[251] The association was stronger for ER+ breast cancer (RR 1.28, 95% CI 1.07–1.54) and for postmenopausal women (RR 1.37, 95% CI 1.11–1.69). Analysis from the EPIC cohort also indicated a positive association between prolactin levels and risk of postmenopausal breast cancer (OR 1.29, 95% CI 1.05–1.58 for highest versus lowest quartile).[252] This risk was only significant in women who used postmenopausal hormone therapy (MHT) at time of testing. A non–significant inverse association between prolactin and premenopausal breast cancer risk was observed.

4.5.7 PCOS

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between polycystic ovarian syndrome (PCOS) and risk of breast cancer is inconclusive. The limited moderate and low quality evidence available indicates no association between PCOS and risk of breast cancer.

Background

PCOS is an endocrine disorder that affects around 8–13% of women of reproductive age and is characterised by features such as irregular or absent menstrual periods, skin and hair changes related to high levels of androgens such as hirsutism, and cysts on the ovaries[253].

High blood pressure and obesity, and metabolic abnormalities such as insulin resistance, diabetes and high cholesterol levels, can be associated with PCOS.[254]

PCOS is associated with factors that increase risk of breast cancer (such as later age at first pregnancy), as well as factors that reduce risk of breast cancer (later age at menarche, anovulatory cycles).[255] Obesity may also be a mediator or confounder of any association of PCOS with breast cancer risk.[254] Potential mechanisms for any association of PCOS with breast cancer risk include prolonged anovulation with consequent exposure to oestrogen unopposed by progesterone, and increased androgen levels.[254]

Recent evidence

Methodological limitations in the evidence base include variable adjustment for confounding variables such as body mass index (BMI) and other established breast cancer risk factors, the use of patient recall for PCOS diagnosis, and differences in the diagnostic criteria used for PCOS.[254-256]

A meta–analysis by Shobeiri & Jenabi[255] showed no association between PCOS and risk of breast cancer among five cohort studies (OR 1.18, 95% CI 0.93–1.43, no heterogeneity) or among three case–control studies (OR 0.87, 95% CI 0.44–1.31, low heterogeneity). The meta–analysis included over 45,000 participants, and study quality was assessed as moderate for four studies and low for four studies.[255]

A meta–analysis by Chittenden et al.[256] included one case–control study that was not included by Shobeiri & Jenabi.[255] The findings were consistent with those of Shobeiri & Jenabi,[255] showing no association between PCOS and risk of breast cancer in the meta–analysis of three case–control studies (OR 0.88, 95% CI 0.44–1.77).[256]

Table D.27 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.6 Exogenous hormones

4.6.1 Hormonal contraception—combined

Evidence summary

Evidence classification: Convincing (for current and recent use).

There is convincing evidence that current use of combined oestrogen–progestogen oral contraceptives (OCs) is associated with an increased risk of breast cancer. Meta–analyses of prospective studies indicate an increased risk of breast cancer among current users of OCs that increases with increasing duration of use. The increased risk has been estimated as 1.07 (95% CI 1.03–1.11) for every five years of use.[257] The increased risk attenuates after cessation of use. Different progestogen components of combined OCs may have differential effects on breast cancer risk.

Background

Combined OCs consist of an oestrogen and a progestogen.[258] The main contraceptive action of combined OCs is through preventing ovulation. Combined OCs inhibit the release of luteinising hormone releasing hormone. This suppresses levels of follicle stimulating hormone and luteinising hormone, thus preventing follicular development and ovulation. The progestogen component also inhibits endometrial proliferation (reducing the receptivity of the endometrium to implantation) and has an effect on cervical mucus (impairing sperm migration into the cervix).[258] Combined hormonal contraceptives are available in numerous combinations of the oestrogen and progestogen components, dosages and modes of delivery.

Oestrogen and progestogen may influence breast cancer risk though one or more hormone receptor–mediated pathways or through hormone–induced DNA damage.[259, 260]

IARC

The International Agency for Research on Cancer (IARC)[260] classified combined oestrogen–progestogen oral contraceptives as '*carcinogenic to humans (Group 1)*' and concluded that there is '*sufficient evidence in humans for the carcinogenicity of combined oestrogen–progestogen oral contraceptives*' and '*combined oestrogen–progestogen oral contraceptives cause cancer of the breast*'. IARC also concluded that combined oestrogen–progestogen oral contraceptives cause cancer of in–situ and invasive cancer of the uterine cervix, and cancer of the liver, and that an inverse relationship has been established for cancers of the endometrium, ovary and colorectum.

The evaluation for breast cancer was based on human epidemiological studies published up to 2008, including updated results of two long term UK cohort studies,[261, 262] one cohort study conducted in China[263] and additional data from population–based and hospital–based case–control studies. The evidence considered by IARC[260] for breast cancer built on evidence previously reviewed by IARC.[258] The earlier review, published 2007, included the pooled analysis of 54 studies (including six cohort studies) by the Collaborative Group on

Hormonal Factors in Breast Cancer,[264] as well as data from five cohort studies published between 2000 and 2004, and 13 case–control studies published between 1977 and 2001. The pooled analysis reported an increased risk of breast cancer among current users (RR 1.24, 95% CI 1.15–1.33) and recent users (summary RR for 1–4 years after stopping 1.16, 95% CI 1.08–1.23), but not 'ever users', compared with never users of combined OCs. Effects were most notable for women under 35 years of age at diagnosis who had initiated use when aged <20 years (summary RR 1.07, SD 0.035).[264] The increased risk was not evident 10 years after cessation of use.

Recent evidence

Long term follow–up (44 years) of the UK Royal College of General Practitioners' Oral Contraception Study (46,022 women)[265] showed that recent users (less than five years since cessation of use) had a significantly increased risk of breast cancer (incidence rate ratio 1.48, 99% CI 1.10–1.97), which attenuated with longer duration post use. Incidence of breast cancer in the cohort of 'ever users' of combined OCs was not significantly higher than in the general population.

A meta–analysis by Gierisch et al.[266] included eight cohort studies and 15 case–control studies. Recent use, determined as 0–5 years since cessation of use, was associated with a significantly increased risk of breast cancer (OR 1.21, 95% CI 1.04–1.41) with significant heterogeneity across studies, but this raised risk attenuated and was no longer significant with longer time post use. A borderline significant association was reported for ever versus never use of combined OCs (OR 1.08, 95% CI 1.00–1.17) with evidence of significant heterogeneity. Gierisch et al.[266] did not find a significant trend for duration of use up to 121+ months. A significant trend was observed with 'time since last use' in a subgroup analysis of 11 studies.

Two additional systematic reviews with meta–analyses published since the review by IARC[257, 267] included many of the same studies reviewed by Gierisch et al.[266] It was not clear how many studies contributed to the meta–analysis of combined OC use conducted by Anothaisintawee et al.,[267] which reported a summary estimate for breast cancer risk associated with ever versus never use of combined OCs of 1.10 (95% CI 1.02–1.19; significant heterogeneity). Zhu et al.[257] included only prospective studies, and the summary estimate for breast cancer associated with ever versus never use of combined OCs was not significantly different (RR 1.08, 95% CI 0.99–1.17). A dose–response meta–analysis of five studies suggested an increased risk for every five years of use (summary RR 1.07, 95% CI 1.03–1.11), with no evidence of significant heterogeneity among studies.

The Nurses' Health Study reported a HR for current use of OCs (any type—that is, including progestin–only) of 1.33 (95% CI 1.03–1.73).[268] The risk was slightly larger with longer duration of use, but was not maintained beyond four years after cessation of use. Hunter et al.[268] also reported risk according to type of progestin formulation among current OC users (any type). It concluded current use of triphasic preparations containing levonorgestrel as the progestin was associated with a higher risk than use of other formulations. Recent use (in past 12 months use) of combined or progestogen–only OCs was associated with an increased risk of postmenopausal breast cancer compared with past use of 10 or more years (HR 1.38, 95% CI 1.18–1.61) in the French Teachers Cohort (E3N).[44]

Table D.28 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.6.2 Hormonal contraception—progestogen only

Evidence summary

Evidence classification: Inconclusive.

The evidence for an association between the use of progestogen-only contraceptives and risk of breast cancer is inconclusive. There are insufficient, poor-quality studies examining the association. Most of the available studies, although limited in sample size and by poor measurement of exposure, indicate no association between use of progestogen–only contraceptives and risk of breast cancer.

Background

Progestogen–only contraceptives contain synthetic compounds designed to mimic some of the effects of natural progesterone. These compunds may be structurally related to progesterone (e.g. medroxyprogesterone acetate (MPA), dydrogestrone) or to testosterone (e.g. levonorgestrel) and are used by women who are breastfeeding or have other contraindications to oestrogen therapy (such as in the postpartum period). They are available as oral preparations or as injections, implants, hormone–releasing intrauterine devices and emergency contraceptives.[269] Progestogen–only contraceptives can suppress ovulation. However, their main contraceptive action is through an effect on cervical mucus (impairing sperm migration into the cervix) and, to a lesser extent, reducing the receptivity of the endometrium to implantation.[258] Progestogens may influence breast cancer risk through a hormonal–mediated effect on cell proliferation in breast tissue but may also have anti–proliferative effects.[259]

IARC

The International Agency for Research on Cancer (IARC) overall evaluation was that '*Progestogen-only contraceptives are possibly carcinogenic to humans (Group 2B)*'. IARC concluded that there was '*inadequate evidence in humans for the carcinogenicity of progestogen–only contraceptives*' and '*there is no evidence of an increased risk of breast cancer*',[269] based on the results of eight case–control studies. Breast and endometrial cancers are the only context in which the carcinogenicity of pharmacological progesterone has been investigated by IARC.

Recent evidence

A limited number of studies have examined the association between use of progestogen–only oral contraceptives (OCs) and breast cancer risk since those reviewed by IARC, and these vary according to dose and route of administration. Two cohort studies[270, 271] and one case–control study[272] examined oral progestogen–only use, two case–control studies have examined injectable/implantable progestogen–only use, and one cohort study has examined use of a progestogen–releasing intrauterine system (Levonorgestrel).[273]

Oral progestogen

Kumle et al.[271] reported that after eight years of follow–up in the Women's Lifestyle and Health Cohort Study in Norway and Sweden (103,027 women aged 30–49 years at recruitment in 1991), the RR for ever versus never use of progestogen–only contraceptives was 1.1 (95% CI 0.8–1.7)) and the increased risk was higher for current/recent use versus never use (RR 1.6, 95% CI 1.0–2.4), with no significant difference in the association for women aged 30–39 or 40–49 years at the start of follow–up.

No increased risk for ever use or current use of oral progestogen contraception among premenopausal women over the age of 40 years was found after nine years of follow–up in the French Teacher's Cohort (E3N) (73,664 women).[270] In interpreting the findings from the E3N cohort, note that in France, oral progestogen alone is prescribed to premenopausal women for other purposes, as well as for oral contraception; it is also prescribed for menstrual disorders, and benign uterine, ovarian and breast diseases.[270]

The population–based case–control study similarly reported a null association[272] for both ever use and current use versus never use of progestogen–only oral contraceptives.

Injectable and implantable progestin only

Current use compared with never use of an injectable progestogen–only contraceptive was associated with an increased risk of breast cancer (OR 1.6, 95% CI 1.1–2.3), in a non–population–based case–control study conducted of South African women aged 20–54 years.[274] However, ever versus never use was not associated with risk of breast cancer in the same study.

A larger population–based study conducted in the United States of women aged 35–64 years reported a null association between ever use of injectable or implantable progestogen–only contraceptive use and risk of breast cancer.[275]

Levonorgestrel–releasing intrauterine system

Among a cohort of 17,360 Finnish women ever or currently using the Levonorgestrel–releasing intrauterine system, the overall and age–specific incidence of breast cancer was not significantly different to the general population.[273] In addition, there was no apparent association between the length of time elapsed from the intrauterine system insertion up to 10 years and the yearly incidence of breast cancer.

Table D.29 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.6.3 Menopausal hormone therapy—combined

Evidence summary

Evidence classification: Convincing.

The evidence for an association between use of combined oestrogen-progestogen menopausal hormone therapy (combined MHT) and increased risk of breast cancer is convincing. A randomised controlled trial (RCT) and numerous cohort studies show an increased risk of breast cancer among current users compared with never users of combined MHT. The increased risk of current versus never use of combined MHT has been estimated in a

large meta–analysis of 30 observational studies and two RCTs as 1.72 (95% CI 1.55–1.92).[276] The risk among current users of combined MHT increases with increasing duration of use and is higher among women who start using combined MHT close to menopause.[277] The RCT showed a possible persistence in effect post–use, however, observational studies show no persistence in effect, except perhaps for certain formulations of combined MHT.

Background

Combined MHT involves the co–administration of an oestrogen and a progestogen to perimenopausal or menopausal women.[260] In the 1970s it was shown oestrogen–only therapy was associated with increased risk of endometrial cancer. Progestogens were added to mitigate this risk.

Combined MHT is used to mitigate the effects of diminishing circulating oestrogens and progesterone in menopause. Many observational studies suggested oestrogen reduces the incidence of coronary heart disease and osteoporotic fractures in postmenopausal women.

Combined MHT use may influence breast cancer risk through hormonal–mediated pathways, extending exposure to oestrogen and progestogen.[260]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)[11] stated '*Hormone therapy (also known as hormone replacement therapy) (containing oestrogen with or without progesterone) increases the risk of breast cancer, and the risk is greater with combined oestrogen plus progesterone preparations*'. Combined MHT is listed as 'an established cause of breast cancer'.

IARC

The International Agency for Research on Cancer (IARC)[258, 260] classified combined oestrogen-progestogen menopausal therapy as '*carcinogenic to humans (Group 1)*' and concluded that there is '*sufficient evidence in humans for the carcinogenicity of combined [MHT]*', and '*combined [MHT] causes cancer of the breast*'. Evidence for an increasing risk of breast cancer with increasing duration of use among current users was noted. The IARC[260] evaluation for breast cancer included the human epidemiological evidence from four systematic reviews, three clinical trials (including two reports from the Women's Health Initiative (WHI) trial), 15 cohort and 11 case–control studies.

Recent evidence

Long term follow–up of the WHI trial has shown an increased risk of breast cancer from use of combined MHT.[278, 279] Of 27,347 postmenopausal women aged 50–79 years with an intact uterus, women who received conjugated equine oestrogens plus medroxyprogesterone acetate had a significantly increased risk of breast cancer in the intervention phase (mean of 6.8 years) (HR 1.24, 95% CI 1.01–1.53). In the early postintervention phase—within 2.75 years from intervention—there was a sharp decrease in breast cancer incidence with combined MHT use, although the risk was higher than 1 (HR 1.23, 95% CI 0.90–1.70); the HR

was below 1 for follow-up of less than 2 years (HR 0.71, 95% CI 0.47–1.08). This was attributed to a therapeutic influence of change in hormone environment.

Two systematic reviews with meta–analyses[267, 276] published since the IARC review reported an increased risk of 1.34 (95% CI 1.24–1.46) and 1.33 (95% CI 1.30–1.36) respectively, for ever versus never use of combined MHT. The risk was higher among current users (RR 1.72, 95% CI 1.55–1.92).[276] Munsell et al.[276] reported a positive association between both current or ever use of combined MHT and oestrogen receptor positive/progesterone receptor positive (ER+PR+) breast cancer, but not oestrogen receptor negative/progesterone receptor negative (ER–PR–) breast cancer. However, in a review article published in 2015, Cheblowski & Anderson indicate that current concepts indicate that increased risks are observed across breast cancer subtypes.

Reported increased risks among current versus never users of combined MHT have been higher in recent cohort studies. Jones et al.,[280] for example—using a robust study design examining biases from a single baseline measurement of MHT use—reported a risk of 2.96 (95% CI 2.19–3.99) for women enrolled in the United Kingdom Generations Cohort Study, with a median duration of 5.4 years of current use. Román et al.[281] reported an increased risk of 2.74 (95% CI 2.55–2.95) among women in a Norwegian cohort who were current users of oestradiol–norethisterone acetate, followed for an average of 4.8 years.

The increased risks observed in the WHI trial[278, 279] during the intervention period (current use) remained elevated for the post–intervention period up to a median of 13.2 years (HR for cumulative follow–up 1.28, 95% CI 1.11–1.48).[278] However, earlier findings involving shorter term follow–up of the WHI trial showed an attenuation of risk year–by–year after cessation of MHT use. [278, 282] None of the cohort studies, including Fournier et al.,[283] Román et al.,[281] and Jones et al.,[280] reported persistence in risk post–use. One of the largest cohort studies—the Million Women Study—also observed a decreased risk of breast cancer to levels seen in never-users of MHT following cessation of treatment (RR 1.00; 95% CI 0.97–1.03)[277]. Further, the meta–analysis by Munsell et al.[276] reported no risk among past users of combined MHT (RR 1.02, 95% CI 0.92–1.14).

Fournier et al.[283] noted a persistence in effect among long term users (>five years of use) up to 10 years post–use only among users of combined MHT that included 'other progestogens' and not for users of MHT composed of oestrogen and progesterone/dydrogesterone.

A longer duration of use among current users of combined MHT is associated with a higher increased risk of breast cancer. This effect was noted in the meta–analyses by Collins et al.[284] and Shah et al.,[285] cited by IARC.[260] These meta–analyses reported an increased risk of 1.53 (95% CI 0.88–2.18) and 1.63 (95% CI 1.22–2.18) for current users of longer than five years, compared with 1.15 (95% CI 0.78–1.52) and 1.35 (95% CI 1.16–1.57) for users of less than five years, respectively. Data from the Breakthrough Generations Study in the United Kingdom showed a significant trend with increasing duration of use. The risk of breast cancer for current versus never users of combined MHT was 2.96 (95% CI 2.19–3.99) for a median duration of 5.4 years of current use, increasing to 3.69 (95% CI 1.73–7.90) at ≥15 years of use.[280] Increased risks were more moderate for longer term use in other cohort studies. Lee et al.,[286] for example, reported increased risks of 1.43 (95% CI 1.06–1.93), 1.82 (95% CI 1.53–2.17) and 2.18 (95% CI 1.86–2.56) for up to five, 10 and more than 10 years of use, respectively. Similarly, Bakken et al.[287] reported increased risks of 1.44 (95% CI 1.09–1.89), 1.81 (95% CI 1.44–2.29) and 1.98 (95% CI 1.12–3.50) for less than one year, 3–5 years and more than 10 years of use, respectively.

In the Million Women Study, time since menopause appeared to influence MHT–related breast cancer risk. Women starting combined MHT less than five years since menopause had an increased risk of breast cancer (RR 2.04, 95% CI 1.97–2.12) compared to women initiating MHT more than five years since menopause (RR 1.53, 95% CI 1.38–1.69).[277] This higher risk of breast cancer associated with starting combined MHT close to menopause has been observed in the Women's Health Initiative trial[288, 289] and the French E3N cohort[290]; with the latter study showing increased risks of breast cancer even after a short duration of use (≤2 years) initiated within the first 3 years following menopause onset.

Three cohort studies reported on different formulations and different routes of administration of MHT.[281, 287, 291] In the Norwegian cohort study, Román et al.[281] reported similarly increased risks for both continuous (every day) (RR 2.80, 95% CI 2.59–3.02) and sequential (cyclic) (RR 2.31, 95% CI 1.88–2.83) MHT use. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort[287] and the Women's Health Study in the United States[291] suggested the risk associated with continuous regimes was higher. The Norwegian study[281] suggested transdermal delivery of the combined estradiol–norethisterone acetate was associated with a non–significant increased risk of breast cancer, when compared with oral delivery, although the analyses were based on a small number of users, and this was contrary to findings from the EPIC cohort.[287] Fournier et al.,[283] in the French Teacher's Cohort (E3N), reported risk of breast cancer associated with combined MHT was less elevated when it contained micronised progesterone (a bioidentical hormone with a molecular structure identical to that of endogenous progesterone produced by the ovary) or dydrogesterone (HR 1.22, 95% CI 1.11–1.35) rather than 'other progestogens' (HR 1.87, 95% CI 1.71–2.04).

Table D.30 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.6.4 Menopausal hormone therapy—oestrogen only

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between oestrogen–only menopausal hormone therapy (MHT) and risk of breast cancer is inconclusive. The evidence is inconsistent across studies. Although an increased risk of breast cancer was found with 'ever use' versus 'never use' of oestrogen–only MHT in a meta–analysis of cohort and case–control studies—and among current users in some, but not all, more recently published cohort studies—there is no evidence of a dose–response relationship. Evidence from a randomised controlled trial (RCT) does not support an increased risk of breast cancer among oestrogen–only MHT current or past users.

Background

Oestrogen–only MHT, also known as oestrogen–only hormone therapy, is also known as unopposed oestrogen MHT and refers to the administration of an oestrogen without a progestogen to perimenopausal or menopausal women.[260] It is used to mitigate the effects of diminished circulating oestrogens in menopause and is mainly prescribed to women who have had a hysterectomy,[260] since unopposed oestrogen increases the risk of cancer of the

endometrial cancer.[260] Proposed pathways for an association with breast cancer relate to the generally longer duration of exposure to oestrogen over a lifetime among oestrogen–only MHT users compared with non–users.

IARC

The International Agency for Research on Cancer (IARC) classified oestrogen–only menopausal therapy *as 'carcinogenic to humans (Group 1)'* and concluded that '*oestrogen–only menopausal therapy causes cancer of the endometrium and of the ovary*'. An inverse relationship has been established for cancer of the colorectum. IARC noted that '*a positive association has been observed between exposure to oestrogen–only menopausal therapy and cancer of the breast*' but a causal relationship was not determined.[260] The IARC evaluation for breast cancer included human epidemiological studies published between 1996 and 2008, including one systematic review,[292] one randomised controlled trial and over 20 cohort and case–control studies.

Recent evidence

A systematic review not cited by IARC[260] that was published in 2005 reported that the evidence from RCTs did not support an association between use of oestrogen–only MHT and risk of breast cancer (0.78, 95% CI 0.61–1.01). However, the observational studies suggested a small but significantly increased risk associated with 'current use', but not 'ever use', of oestrogen–only MHT (summary estimate 1.18, 95% CI 1.01–1.38).[284] This increased risk among current users did not vary according to duration of use (less than five years, five or more years).

More recent findings from an RCT are those from a longer term follow–up of the Women's Health Initiative (WHI) trial. This study showed that, among 10,739 postmenopausal women aged 50–79 years with a prior hysterectomy, there was an indication of a decreased risk of breast cancer among women who received conjugated equine oestrogens (CEE) alone compared with women receiving a placebo, both in the intervention phase (median 5.6 years) (HR 0.79, 95% CI 0.61–1.02) and in the post–intervention phase (HR 0.80, 0.58–1.11),[ix] with a mean follow–up of 13 years.[278]

One meta–analysis has been published since the IARC review.[267] This meta–analysis reviewed the evidence in 29 cohort and case–control studies published up to 2011, with substantial overlap in studies included in the meta–analysis conducted by Greiser et al.[292] (reviewed by IARC).[260] The summary estimate for breast cancer risk associated with 'ever' versus 'never use' of oestrogen–only MHT was 1.09 (95% CI 1.06–1.12).

Several reports from cohort studies[280, 281, 283, 287] have been published subsequent to the IARC review[260] that were not included in the meta–analysis by Anothaisintawee et al.[267]

The UK Generations Cohort Study (39,183 postmenopausal women) reported no association between 'ever use' of oestrogen–only MHT and breast cancer risk.[280] Similarly, Roman et al.,[281] in a large population–based cohort of Norwegian women, did not find an increased

[ix] The data presented in the text of the paper indicated that 'for women assigned to CEE alone, the risk reduction became statistically significant during cumulative follow–up (HR 0.79, 0.65–0.97)'.

risk of 'ever use' of oestradiol or oestriol formulations, although 'current use' of oestradiol was associated with a significant increased risk (HR for 1 mg preparation 1.52, 95% CI 1.11–2.10; and 1.68, 95% CI 1.30–2.15 for 2 mg preparations).

An increased risk of breast cancer was associated with current use of oestrogen–only MHT among the women in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (HR 1.42, 95% CI 1.23–1.64) but there was no dose–response relationship with longer duration of use.[287] Route of oestrogen delivery (oral versus transdermal) did not modify the association. Fournier et al.,[283] using data from the French Teacher's Cohort (E3N), did not find an increased risk of breast cancer associated with current use of oestrogen–only MHT (HR 1.17, 95% CI 0.99–1.38), either for short term (up to five years) or long term (more than five years) users.

Table D.31 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.6.5 Hormonal infertility treatment

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between hormonal treatment for infertility and risk of breast cancer is inconclusive. The evidence is limited by substantial methodological issues. However, the majority of the evidence from a large number of cohort studies shows no association between risk of breast cancer and hormonal infertility treatment, either with or without in vitro fertilisation (IVF).

Background

Hormonal treatment for infertility encompasses stimulation of ovulation in women with ovulatory disorders using agents such as selective oestrogen receptor modulators (for example, clomiphene citrate and tamoxifen), follicle–stimulating hormone, gonadotropins and gonadotropin–releasing hormone (GnRH) analogues, without IVF, and progestogens. It also encompasses IVF and other assisted reproductive technologies (ARTs) that use hormonal treatment as part of the treatment protocol.[293]

Hormonal infertility treatments result in levels of oestrogen that are higher than those during natural menstrual cycles.[294] It has been hypothesised that the prolonged or uninterrupted exposure to these higher levels of oestrogen may be associated with breast cancer.

Recent evidence

Recent meta–analyses and additional cohort studies have investigated any association between breast cancer and hormonal fertility treatment, with and without IVF.

Methodological limitations include differences in the choice of reference population, which has considerable bearing on inference. For example, some studies used the general population as the reference category, rather than a population of infertile women not

exposed to fertility treatment. Using the general population as the reference category means that an independent effect of infertility on breast cancer risk cannot be excluded. Other limitations include the changes in fertility treatment protocols that have occurred over time, the relatively short follow–up times in some studies, and potentially inaccurate measurements of the hormonal doses prior to and during the treatment regimes compared with those in the general population.[293, 294] There are also many potential confounders, such as age at menarche, age at treatment, body mass index (BMI), previous infertility treatment, pre–eclampsia, and multiple births. Studies have varied in their approaches to adjusting for these and other variables.[293]

A recent meta–analysis of 20 cohort studies with a total of over 200,000 participants investigated any association between breast cancer risk and hormonal fertility treatment, with and without IVF.[295] There was no association between hormonal treatment for infertility and breast cancer risk (summary RR 1.05, 95% CI 0.96–1.14).[295] There was also no association between breast cancer risk and IVF (summary RR 0.96, 95% CI 0.80–1.14) based on seven studies with moderate heterogeneity. However, an increased risk of breast cancer was observed among women treated without IVF in three studies (summary RR 1.26, 95% CI 1.06–1.50, moderate heterogeneity). There was an increased breast cancer risk associated with hormonal infertility treatment for longer versus shorter duration of follow–up (≥10 years versus <10 years): summary RR 1.13 (95% CI 1.02–1.26) versus RR 0.95 (95% CI 0.85–1.06).[295]

An earlier meta–analysis by Sergentanis et al.[293] investigated breast cancer risk and IVF. Eight cohort studies were included, all of which were also included in the meta–analysis by Gennari et al.[295]

Cohort studies published since the search dates for the meta–analyses include a large Swedish cohort study by Lundberg et al.[296] In this study, a decreased risk of breast cancer was observed among infertile women who gave birth after ART compared with parous women who had no infertility (HR 0.84, 95% CI 0.74–0.95) and among infertile women who gave birth after spontaneous conception compared with fertile parous women (HR 0.83, 95% CI 0.77–0.89). Similarly, in a cohort study of over 100,000 women in the United States, with mean follow–up of 4.87 years,[297] women treated with ART had a lower risk of breast cancer than the expected incidence in the general population (SIR 0.83, 95% CI 0.75–0.91).[297] However, in the Swedish study, among a separate cohort of women born between 1960 and 1992, there were no differences in breast cancer incidence among parous women who received controlled ovarian stimulation (HR 0.86, 95% CI 0.69–1.07) or other hormonal treatment for infertility (HR 0.79, 95% CI 0.60–1.05), compared with parous women with no infertility–related diagnosis or treatment.[296]

In a Norwegian cohort study of over 1,300,000 women with median follow–up of 11 years, ART was not associated with risk of breast cancer either in nulliparous (HR 1.11, 95% CI 0.75–1.66) or parous women (HR 0.96, 95% CI 0.76–1.22).[298] In the latter study, treatment with clomiphene citrate was associated with an increased breast cancer risk in parous women (HR 1.26, 95% CI 1.03–1.54) but no dose–response relationship was observed.

In an historical cohort study of over 25,000 women from the Netherlands by van den Belt–Dusebout et al.,[294] with median follow–up of 21 years, breast cancer risk in women treated with IVF prior to 1995 was no different than that of the general population (SIR 1.01, 95% CI 0.93–1.09) or than the risk in a non–IVF sub–fertile comparison group, HR 1.01 (95% CI 0.86–1.19).[294] There was also no association with longer time since treatment either in the IVF group or in the non–IVF group and risk of breast cancer.

Table D.32 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.6.6 DES in utero

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to diethylstilboestrol (DES) in utero and risk of breast cancer inconclusive. Initial findings from pooled analyses of cohort studies in the United States indicated an increased risk of breast cancer among women exposed to DES in utero who were aged over 40 years at diagnosis. However no significant differences between risk of breast cancer among exposed versus unexposed women were found in longer term follow–up of these cohorts, nor in a large cohort study in the Netherlands, among women overall or by age at diagnosis.[299, 300]

Background

DES is a synthetic non–steroidal oestrogen that was commonly prescribed to women from the late 1940s to the early 1970s, to prevent complications of pregnancy, including spontaneous abortion and premature delivery. It works by stimulating the synthesis of oestrogen and progesterone in the placenta.[260, 300] It was also used as an emergency contraceptive (morning after pill) and less commonly for other indications such as treatment of hypogonadism or dysfunctional menstrual cycles.[260] The use of DES declined after studies in the 1950s showed it was not effective in preventing the problems.[301] Following repercussions from a 1971 publication by Herbst et al.[302] prenatal DES exposure to a rare vaginal cancer in girls and young women, the Food and Drug Administration (FDA) issued a drug bulletin to physicians, stating that DES in contra–indicated for use in pregnant women. Use in some countries did not cease until the early 1980s. DES is no longer registered for use in Australia. It has been estimated that 15,000 Australian women used the drug during pregnancy.[303]

Exposure to DES as a potential risk factor for breast cancer can be through one of two routes: maternal exposure, where a woman has taken DES while pregnant (section 4.6.7); and in utero exposure when the woman was a foetus. This evidence summary reports on the association between in utero exposure to DES and risk of breast cancer.

DES is known to be an endocrine–disrupting chemical, one of a number of substances that interfere with the endocrine system to increase risk of cancer, birth defects and other developmental abnormalities. These effects are pertinent when exposure occurs during foetal development.[304]

In utero exposure to oestrogen may plausibly be associated with an increased risk of breast cancer later in life.[305] Studies in mice have provided some evidence that DES exposure in utero permanently alters hormonal responsiveness in the breast tissue.[260] In utero exposure also influences immune function in both animals and humans.[260]

IARC

The International Agency for Research on Cancer[260] concluded that there is '*sufficient evidence in humans for the carcinogenicity of DES (Group 1)*'. In utero exposure to DES causes clear cell adenoma of the cervix and vagina.[260] IARC reviewed the human epidemiological evidence for an association between in utero exposure to DES and breast cancer, and found little evidence of an association. The human epidemiological evidence included three cohort studies published between 1998 and 2007.[306-308] Only one of the studies reported an increased incidence of breast cancer, and only among women aged over 40 years exposed to DES in utero compared with those not exposed (IRR 1.91, 95% CI 1.09–3.33 for women aged ≥40 years; IRR 3.85, 95%CI 1.06–14.0 for women aged ≥ 50 years).[308] It was noted that women at these ages would have been exposed during the period of peak usage, and when high doses of DES were prescribed.

Recent evidence

The most recently published data from the Diethylstilbestrol (DES) Combined Cohort Follow–up[299] in the United States (the NCI DESAD study, the Dieckmann clinical trial cohort, and offspring of women from the Women's Health Study (WHS)) added 10 more years of follow–up data to those previously reported by Troisi et al.[307] The SIR for breast cancer for the exposed women was 1.17 (95% CI 1.01–1.36), compared with SIR 1.06 (95% CI 0.83–1.33) in the unexposed women. When adjusted for risk factors in the Gail model, the SIR declined to 1.07 (95% CI 0.89–1.25) in the exposed women, comparable to that in the unexposed participants. Given these results, the authors suggested any excess risk in exposed women might be due to DES effects on established risk factors. The HR for exposure to DES in utero and risk of breast cancer adjusted for major confounders was 1.07 (95% CI 0.80–1.44). No significant differences were found by age or by menopausal status, although risks were highest among women aged 40–49 years at diagnosis, compared with women aged less than 40 years or older than 49 years at diagnosis. The data across cancer types did not support a diathesis of cancers in DES–exposed female offspring.

Findings from earlier analyses of these cohort studies were reported by Hoover et al.,[309] Troisi et al.[307] and Palmer et al.[308] Hoover et al.[309] reported a significantly increased risk of breast cancer at 40 years of age or older in women exposed to DES in utero, compared with those not exposed (HR 1.82, 95% CI 1.04–3.18). Risk was higher among women with vaginal epithelial changes (VEC), a histological marker of high–dose DES exposure, compared with women without VEC. Troisi et al.[307] also reported an excess risk for breast cancer among women aged 40 years or older (RR 1.83, 95% CI 1.1–3.2) and no excess risk in women aged less than 40 years. Similar data were reported on the same cohorts by Palmer et al.[308]

A large cohort study conducted in the Netherlands compared breast cancer incidence in 12,091 women exposed to DES in utero with the incidence of breast cancer in the general population.[300] No overall risk of breast cancer risk was found (SIR 1.05, 95% CI 0.90–1.23). Nor was there any difference when stratified by age: SIR 0.95 (95% CI 0.69–1.29) among those aged <40 years at diagnosis, and compared with SIR 1.09 (95% CI 0.91–1.31) among those ≥40 years at diagnosis.

Table D.33 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.6.7 DES maternal exposure

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that exposure to diethylstilboestrol (DES) during pregnancy is associated with an increased risk of breast cancer. There is consistent evidence from cohort studies. The increased risk has been estimated as RR 1.27 (95% CI 1.07–1.52) in extended follow–up of the Dieckmann clinical trial cohort and the Women's Health Study.[310]

Background

DES is a synthetic non–steroidal oestrogen that was commonly prescribed to women from the late 1940s to the early 1970s, to prevent complications of pregnancy, including spontaneous abortion and premature delivery. It works by stimulating the synthesis of oestrogen and progesterone in the placenta.[260, 300] It was also used as an emergency contraceptive (morning after pill) and less commonly for other indications such as treatment of hypogonadism or dysfunctional menstrual cycles.[260] The use of DES declined after studies in the 1950s showed it was not effective in preventing the problems.[301] Following repercussions from a 1971 publication by Herbst et al.[302] prenatal DES exposure to a rare vaginal cancer in girls and young women, the Food and Drug Administration (FDA) issued a drug bulletin to physicians, stating that DES in contra–indicated for use in pregnant women. Use in some countries did not cease until the early 1980s. DES is no longer registered for use in Australia. It has been estimated that 15,000 Australian women used the drug during pregnancy.[303]

Exposure to DES can be through one of two routes: maternal exposure, where a woman has taken DES while pregnant; and in utero exposure when the woman was a foetus. This summary reports on the association between maternal exposure to DES (DES mothers) and risk of breast cancer. Further information about in utero exposure to DES can be found in section 4.6.6.

DES induces chromosomal breaks and other chromosomal aberrations in human and animal cells, in a process mediated largely by oestrogen receptors in susceptible breast tissue during pregnancy, and which most likely accounts for the main carcinogenic effect.[260]

IARC

The International Agency for Research on Cancer (IARC)[260] classified exposure to DES as '*carcinogenic to humans (Group 1)*' and concluded that there is '*sufficient evidence in humans for the carcinogenicity of DES*', and '*Diethylstilboestrol causes cancer of the breast in women who were exposed while pregnant*'. The evaluation for breast includedhuman epidemiological studies published between 1978 and 2001, including data from the Dieckmann study,[311] the Women's Health Study (WHS),[312, 313] and several other small cohort studies. The Dieckmann study was a clinical trial that examined the effects of DES on pregnancy outcomes.[311]

Recent evidence

The most recently published and largest study to examine the association, by Titus–Ernstoff et al., was included in the IARC evaluation.[310] This study included data from extended follow–up of the Dieckmann clinical trial cohort, and the WHS, with a total of 3,844 exposed women and 3,716 unexposed women. An increased risk of breast cancer was observed (RR 1.27, 95% CI 1.07–1.52) that was not modified by reproductive history, menopausal status, or exogenous hormone use (including oral contraceptives, menopausal hormone therapy use). Breast cancer incidence in exposed women was slightly elevated compared with the general population (SIR 1.10, 95% CI 0.98–1.23), but this comparison is limited because the combined study cohort included only parous women. The data, in aggregate, do not support a dose–response relationship. However, exposure to DES is brief, even among women with multiple exposed pregnancies.[310]

Table D.34 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7 Lifestyle factors

4.7.1 Adiposity

Evidence summary

Evidence classification—body fatness in young adulthood (18–30 years) (marked by BMI) and decreased risk of premenopausal and postmenopausal breast cancer: Probable.

Higher body fatness during young adulthood is probably associated with a decreased risk of premenopausal and postmenopausal breast cancer. The decreased risk of premenopausal and postmenopausal breast cancer per five units higher body mass index (BMI) (kg/m^2) during young adulthood (ages 18–30 years) is estimated to be 0.82 (95% CI 0.76–0.89) and 0.82 (95% CI 0.76–0.88), respectively.[11]

Evidence classification—adult body fatness before the menopause (marked by BMI, waist circumference and waist–hip ratio) and decreased risk of premenopausal breast cancer: Probable.

Higher adult body fatness before the menopause is probably associated with a decreased risk of premenopausal breast cancer. The decreased risk of premenopausal breast cancer per five units higher BMI before menopause is estimated to be 0.93 (95% CI 0.90–0.97).[11]

Evidence classification—adult body fatness throughout adulthood (marked by BMI, waist circumference and waist–hip ratio) and increased risk of postmenopausal breast cancer: Convincing.

There is convincing evidence that higher adult body fatness throughout adulthood is associated with an increased risk of breast cancer. The increased risk of postmenopausal breast cancer per five units higher BMI throughout adulthood is estimated to be 1.12 (95% CI 1.09–1.15).[11]

Background

BMI is an index of weight–for–height that is used to classify weight status categories in adults. It is defined as the weight in kilograms divided by the square of the height in metres (kg/m^2): <18.5 kg/m^2=underweight; 18.5–24.9 kg/m^2=normal weight; 25–29.9 kg/m^2=overweight; ≥30 kg/m^2=obese.[314]

Other measures of fat accumulation and/or distribution include waist circumference (WC) and waist–to–hip ratio (WHR). These measures can be used to identify individuals at increased risk of obesity–related diseases since abdominal fat mass can vary within a narrow range of BMI.[314]

The International Agency for Research on Cancer (IARC) indicated that obesity is associated with substantial metabolic and endocrine abnormalities, including alterations in sex hormone metabolism, insulin and insulin–like growth factor (IGF) signalling, and adipokines or inflammatory pathways.[315] Lauby–Secretan et al.[315] further noted that evidence for a role of sex hormone metabolism and of chronic inflammation in mediating the obesity–cancer relation is strong, and evidence for a role of insulin and IGF signalling is moderate. In relation

to breast cancer specifically, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)[11] have indicated that obesity in premenopausal women probably reduces ovarian progesterone production and therefore risk of premenopausal breast cancer, although they indicate that the mechanisms underlying the inverse association of early life body fatness and breast cancer risk are complex and not well–understood. In postmenopausal women, in whom ovarian oestrogen production is low, oestradiol production is increased by obesity through the action of aromatase in adipose tissue.[11] In addition, studies are increasingly implicating obesity as associated with a low–grade chronic inflammatory state and the activation of inflammatory cascades is one process that may predispose to carcinogenesis.

IARC

The International Agency for Research on Cancer (IARC)[316] concluded there '*is sufficient evidence in humans for the cancer–preventive effect of the absence of body fatness*' and, specifically with respect to breast cancer that, '*the absence of excess body fatness reduces the risk of cancer of the breast in postmenopausal women*'.[315, 316] The IARC review relied heavily on a meta–analysis conducted by Renehan et al.[317] that included 31 studies reporting on the association between BMI and postmenopausal breast cancer (RR 1.22, 95% CI 1.08–1.16) and 21 studies on premenopausal breast cancer (RR 0.92, 95% CI 0.88–0.97). The increased risk cited by Lauby–Secretan et al.[315] was 'approximately 1.1 per 5 BMI (kg/m^2) units', and an effect particularly for oestrogen receptor positive tumours was noted.

WCRF/AICR

Consideration was given separately to the evidence regarding body fatness in young adulthood (ages 18–30 years) and to body fatness throughout adulthood.[11] Measures of body fatness included BMI, WC and WHR.

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) considered that '*greater body fatness (marked by BMI) in young women (aged about 18–30 years) probably protects against premenopausal breast cancer and postmenopausal breast cancer*'.[11] Twelve and 17 studies contributed to dose–response meta–analyses (per 5 unit BMI increase), respectively. The summary risk estimates were of the same magnitude (RR per 5 kg/m^2 0.82, 95% CI 0.76–0.89 and 0.82, 95% CI 0.76–0.88, respectively).

In consideration of body fatness during adulthood, WCRF/AICR considered that '*greater body fatness before menopause (marked by BMI, WC and WHR) probably protects against premenopausal breast cancer*', and that '*greater body fatness throughout adulthood (marked by BMI, waist circumference and waist–hip ratio) is a convincing cause of postmenopausal breast cancer*'.[11]

Thirty–seven studies contributed to a dose–response meta–analysis for the association between BMI throughout adulthood and risk of premenopausal breast cancer (RR per 5 unit increase in BMI 0.93, 95% CI 0.90–0.97; significant heterogeneity). Fifty–six studies (including four pooled analyses) contributed to a dose–response meta–analysis for the association between BMI throughout adulthood and risk of postmenopausal breast cancer (RR per 5 unit increase in BMI 1.12; 95% CI 1.09–1.15; significant heterogeneity). The observed high heterogeneity was partly attributable to geographical locations of the cohorts. When stratified by use of menopausal hormone therapy (MHT) and breast cancer subtypes,

significant positive associations were observed only among never users of MHT or never/former user but not current or ever users. For hormone receptor status, BMI was associated with postmenopausal ER+, PR+ and ER+PR+ breast cancers.

Dose–response meta–analyses for waist circumference and risk of premenopausal breast cancer, showed no association in six studies unadjusted for BMI, however the association was significant among three studies adjusting for BMI (RR per 10 cm increase, 1.14, 95%CI 1.04–1.26; no heterogeneity).

For postmenopausal breast cancer, dose–response meta–analyses for waist circumference showed a significantly increased risk per 10 cm increase in waist circumference for studies not adjusted for BMI (RR 1.11, 95% CI 1.09–1.13; 11 studies; no heterogeneity), and for studies adjusted for BMI (RR 1.06, 1.01–1.12; 5 studies; high heterogeneity).

Dose–response analyses for waist–hip ratio (WHR) showed no association for premenopausal breast cancer among studies unadjusted for BMI but a positive association among the nine studies adjusted for BMI (RR per 0.1 unit increase 1.15, 95% CI 1.01–1.31). Conversely for postmenopausal breast cancer, but there was a positive association with WHR among15 studies unadjusted for BMI (RR 1.10, 95% CI 1.05–1.16), but no association between WHR and risk of postmenopausal breast cancer in a dose–response meta–analysis of ten studies adjusted for BMI.

Recent evidence

The effect of weight status on risk of breast cancer among premenopausal women aged 18–54 years was examined in a large multicentre pooled analysis using individual–level data from 758,592 premenopausal women from 19 prospective cohorts.[318] Medium follow–up was 9.3 years with 13,082 incident cases of breast cancer. BMI at all ages was negatively associated with risk of breast cancer in a dose–response relationship. Among 18–24 year olds the trend per 5 kg/m^2 BMI was 0.77 (95% CI 0.73–0.80) with a lower risk among those who were overweight (0.75, 95% CI 0.68–0.82) or obese (0.55, 95% CI 0.45–0.68) and a higher risk among those who were underweight (1.14, 95% CI 1.07–1.21), compared with those who were normal weight. This effect was attenuated in the older age groups. Associations were strongest for hormone receptor positive tumours.

Freisling et al.[319] demonstrated an increased risk of postmenopausal breast cancer with BMI in a meta–analysis of data from seven prospective cohort studies in the CHANCES consortium (The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) project). After adjustment for hip circumference (HC), WC and WHR, the estimated HR per 1–SD increase in BMI was 1.15 (95% CI 1.03–1.27). No significant multiplicative interactions were observed between BMI and any of the three measures of body fat distribution. In this analysis, women who had never used MHT had an approximately 20% higher risk of postmenopausal breast cancer per standard deviation of BMI, WC and hip circumference, compared with ever MHT users.

Similar findings were observed in the California Teachers Cohort of 109,862 women, which included only oestrogen receptor positive (ER+) breast cancer cases,[50] and in the earlier pooled analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC).[320] In the former study, compared with women with a BMI of <25 kg/m^2 at baseline, women with a BMI of ≥25 kg/m^2 or more and who had never used MHT had a

significantly increased risk of ER+ breast cancer (HR 1.21, 95% CI 1.07–1.37) while there was no association among non–users of MHT (HR 1.07, 95% CI 0.95–1.21). However, analyses of data from the Women's Health Initiative Clinical Trial cohort found no evidence of effect modification of the BMI–postmenopausal breast cancer relationship by MHT use.[321]

Table D.35 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.2 Adiposity—weight gain

Evidence summary

Evidence classification—postmenopausal breast cancer: Convincing.

Evidence classification—premenopausal breast cancer: Inconclusive.

There is convincing evidence that adult weight gain is associated with an increased risk of postmenopausal breast cancer. There is a dose–response relationship and the increased risk per 5 kg increase in weight has been estimated as 1.06 (95% CI 1.05–1.08) by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR).[11]

The evidence for an association between adult weight gain and risk of premenopausal breast cancer is inconclusive. Among the limited number of studies, there is no evidence of an association between adult weight gain and risk of premenopausal breast cancer.[11]

Background

Long term weight change in adults predominantly reflects change in fat mass, and thus weight gain is a measure of excess body fat storage.[11] Adult weight gain may influence breast cancer risk through the effect of adipose tissue on circulating hormone levels. Weight gain in postmenopausal women is inversely associated with serum hormone binding protein levels, which results in higher levels of circulating oestrogen.[322]

IARC

The International Agency for Research on Cancer (IARC)[323] concluded there was '*sufficient evidence in humans for a cancer–preventive effect of the avoidance of weight gain for postmenopausal breast cancer*'. IARC also indicated that the available evidence on the avoidance of weight gain suggests a lack of cancer–preventive protective effect for premenopausal breast cancer. The evaluation was based on data from three cohort and seven case–control studies. Among these studies, higher weight gain was generally inversely associated with premenopausal breast cancer. Higher weight gain during young adulthood was associated with a 10–30% decrease in overall breast cancer risk in most, but not all, studies. The IARC working group noted the magnitude of the inverse association between weight gain and postmenopausal breast cancer risk was attenuated among current users of menopausal hormone therapy (MHT).

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) [11] considered there was convincing evidence—that is, the judgement was 'Strong–convincing'— that greater weight gain in adulthood is a cause of postmenopausal breast cancer, based on 22 studies. Fifteen of these studies contributed to a dose–response meta–analysis for postmenopausal breast cancer. The summary RR per 5 kg increase in weight was 1.06 (95% CI 1.05–1.08), with evidence of significant heterogeneity among the included studies. In subgroup analyses the increased risk associated with weight gain was significant only for ER+PR+ breast cancer (five studies), and not ER+PR– (three studies) or ER–PR– disease (five studies). Contrary to the IARC review, risk was not affected by use of MHT (three studies).

WCRF/AICR[11] made no conclusion about the association between adult weight gain and premenopausal breast cancer due to 'limited evidence'. Five studies contributed to a dose–response meta–analysis for premenopausal breast cancer risk with no significant association observed.

Recent evidence

Data from the Women's Health Initiative Clinical Trial cohort (Neuhouser et al.[321]) and from a Japanese cohort (Nitta et al.[51]) on the association between adult weight gain and postmenopausal breast cancer were published subsequent to the Continuous Update Project Systematic Literature Review in 2017.[10] Nitta et al.[51] reported a significantly increased risk of postmenopausal but not premenopausal breast cancer with weight gain after age 20 in a study among 38,610 Japanese women (HR for weight gain of 6.7–9.9 kg 2.48, 95% CI 1.40–4.41; HR for weight gain of ≥10.0 kg 2.94, 95% CI 1.84–4.70). A dose–response relationship was observed, consistent with the findings of WCRF/AICR.[10]

Among 67,142 women in the Women's Health Initiative Clinical Trial cohort, those who gained >5% of their baseline weight over a mean follow–up period of 13 years had a modest increased risk of breast cancer (HR 1.12, 95% CI 1.00–1.25) compared with weight stable women. Among women who gained >5% of their bodyweight during follow–up, women who were in the normal weight range (body mass index (BMI)<25 kg/m^2) at baseline had a significantly higher risk of breast cancer (HR 1.36, 95 % CI 1.10–1.65) than women who were already overweight or obese at baseline.[321]

Table D.36 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.3 Adiposity—weight loss

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between weight loss and risk of breast cancer is inconclusive. There are inconsistent findings from prospective studies regarding a possible association between adult weight loss and risk of breast cancer. The evidence base is limited by methodological issues, including whether the weight loss is intentional or non–intentional.

Background

As epidemiological associations have been observed between overweight and obesity and risk of postmenopausal breast cancer, it has been hypothesised that weight loss may reverse or reduce increased breast cancer risk in postmenopausal women. Weight loss has been hypothesised to lower risk of breast cancer through several possible pathways, including changes in oestrogen and testosterone levels and reduced inflammation.[324, 325]

There are particular methodological challenges in aetiologic studies of weight loss and risk of breast cancer. For example, it may be difficult to separate the effects of physical activity—which is important in maintaining weight loss, and has an independent protective effect on breast cancer risk—from the effects of weight loss in observational studies or weight loss trials.[325] Other challenges in determining the likelihood of any association between weight loss and risk of breast cancer include: the different means by which weight loss is achieved, for example, dietary intervention, physical activity or bariatric surgery; the difficulty in distinguishing intentional weight loss from non–intentional weight loss; and the issue that many of the prospective studies have not been designed specifically to investigate weight loss, and are thus very underpowered to identify true effects.[326] Further, unintentional weight loss may indicate a comorbid illness and may obscure any relationship between intentional weight loss and health benefit.

IARC

The International Agency for Research on Cancer (IARC) Handbook of Cancer Prevention on Weight Control and Physical Activity indicated that there was inadequate evidence in humans for a cancer–preventive effect of intentional weight loss for any cancer site.[323]

Recent evidence

In a meta–analysis by Winder et al.[327] of four controlled studies of bariatric surgery, there was no association with breast cancer risk for women who had undergone bariatric surgery (9,235 women) compared with controls (16,492 women; OR 0.59, 95% CI 0.25–1.39). Limitations identified included the high heterogeneity between studies, difficulty in identifying accurate controls, no monitoring and reporting of weight loss in the controls or surgical participants (outcome bias), and short follow–up.[327]

Among over 60,000 postmenopausal women followed for 11.4 years in the Women's Health Initiative (WHI) Observational Study (which tracks the health of postmenopausal women between the ages of 50 and 79), self–reported weight loss of ≥5% and of ≥15% compared with women who maintained a stable weight over three years was associated with decreased risk of postmenopausal breast cancer (HR 0.88, 95% CI 0.78–0.98; HR 0.63, 95% CI 0.45–0.90, respectively). There was no significant difference in breast cancer incidence observed in women with intentional or unintentional weight loss. Subgroup analyses by hormone receptor subtype, baseline body mass index (BMI), race/ethnicity and age group, indicated similar effects in all subgroups.[328]

In an earlier analysis of the WHI trial of over 67,000 postmenopausal women with a median of 13 years follow–up, among women who were already overweight or obese, there was no association between weight loss of either 2–5% or >5% (or weight gain) and risk of postmenopausal breast cancer (HR 1.00, 95% CI 0.89–1.12; HR 1.00, 95% CI 0.95–1.21,

respectively). There was also no association between weight loss and postmenopausal breast cancer risk for subgroups stratified by baseline BMI compared with women whose weight was stable during follow–up (<25, 25–<30, 30–<35, ≥35 kg/m^2). The WHI trials encompassed three randomised controlled trials (hormone trials and dietary intervention trial) and it was noted that the weight loss data could reflect both intentional and unintentional weight loss.[321]

A systematic review by Birks et al.[326] on the impact of weight loss on breast cancer risk identified seven prospective cohort and three case–control studies, but did not include a meta–analysis. In four prospective cohort studies, weight loss was associated with decreased risk of postmenopausal breast cancer, and in three prospective cohort studies there was no association.

Table D.37 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.4 Alcohol consumption

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that alcohol consumption is causally related to breast cancer.[329, 330] The evidence for daily alcohol consumption has been classified as 'Strong–convincing' for risk of postmenopausal cancer and as 'Strong–probable' for risk of premenopausal breast cancer by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR).[11] There is a dose–response relationship and no threshold for regular consumption is observed. The summary RR for every 10 g/day increase in alcohol consumption has been estimated as 7% (RR 1.07, 95% CI 1.05–1.09) for breast cancer overall and 9% (RR 1.09, 95% CI 1.07–1.12) for postmenopausal breast cancer.

Background

Exposure has generally been measured as grams of alcohol per day; one 'standard' drink contains approximately 10 g of alcohol. Binge drinking has been rarely researched.

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that there are robust mechanisms operating in humans for an association between alcohol consumption and risk of breast cancer.[11] The postulated mechanisms through which alcohol may affect risk of breast cancer are several and include both hormone–dependent and hormone–independent pathways. Alcohol acts as a lipid solvent, facilitating the movement of carcinogens into cells. It has important effects on lipid metabolism and in the generation of free radical oxygen species.[331] These oxygen species are associated with DNA damage and thus with carcinogenesis.[10] Also, genetic polymorphisms for ethanol metabolism can affect breast cancer risk.[10] In addition, alcohol consumption has been associated with higher serum oestrogen concentrations.[332]

IARC

The International Agency for Research on Cancer (IARC)[333] has concluded that alcohol consumption is '*carcinogenic to humans (Group 1)*' and that there is '*sufficient evidence in humans for the carcinogenicity of alcohol consumption*' and that '*alcohol consumption causes cancer of the female breast*'. Alcohol consumption is also causally associated with cancers of the oral cavity, pharynx, larynx, oesohpagus, and liver, and colorectal cancer. IARC noted the presence of a linear dose–response relationship in the human epidemiological evidence for breast cancer, citing the evidence from the Million Women's Study[334] where risk of breast cancer increased by 12% (95% CI 9–14%) for every 10 g/day increase in alcohol consumption. The IARC review concluded that there was consistent evidence that the increased risk of breast cancer associated with alcohol consumption did not vary significantly by beverage type.[333] The earlier IARC 2010[329] evaluation of the evidence included more than 100 epidemiological studies and cited a pooled analysis of 53 studies reporting a dose–response relationship of 7% increase in risk for every 10 g/day increase in alcohol consumption.[335]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) [11] judged that there was 'Strong–convincing' evidence that alcohol consumption increases risk of postmenopausal breast cancer and 'Limited–probable' evidence that alcohol increases risk of premenopausal breast cancer.

The judgements were based on evidence from the WCRF Continuous Update Project systematic literature review (CUP Breast SLR) which included 62 studies (randomised controlled trials, cohort, case–control, and nested case–control studies).[10] Twenty–three studies were included in the dose–response meta–analysis: 10 for premenopausal and 22 for postmenopausal breast cancer. The summary RR for every 10 g/day increase in alcohol consumption was 7% (RR 1.07, 95% CI 1.05–1.09) for breast cancer overall, 5% (RR 1.05, 95% CI 1.02–1.08) for premenopausal breast cancer and 9% (RR 1.09, 95% CI 1.07–1.12) for postmenopausal breast cancer. There was no evidence of a non–linear association or of a threshold effect, with an increased risk evident even at low levels of daily consumption. The increased risk did not differ materially across types of beverages (beer, wine, liquor) although the risk per 10 g/day increase in consumption was statistically significant only for alcohol intake from beer and wine. There was an indication among postmenopausal women that the increased risk of breast cancer from daily alcohol consumption is not apparent for oestrogen receptor negative/progesterone receptor negative (ER–PR–) tumours.

Recent evidence

The findings of four meta–analyses[332, 336-338], a large pooled analysis of 20 cohort studies[339] and five individual cohort studies[340-343] all support alcohol consumption as a risk factor for breast cancer.

The two largest meta–analyses included overlapping study populations and examined the association between 'light drinking' (defined as <12.5 g of ethanol per day or less than one standard drink per day) and breast cancer risk.[332, 338] Sietz et al.[332] included 113 studies (39 cohort and 74 case–control studies) and reported a significant association (RR for less than one standard drink per day 1.05, 95% CI 1.02–1.08). Bagnardi et al.[338] included 110 studies (39

cohort and 71 case–control studies) and reported a significant association of the same magnitude (RR for less than one standard drink per day 1.05, 95% CI 1.02–1.08). The two smaller meta–analyses[336, 337] included 26 and 16 studies respectively, and focused on specific alcohol exposures. Chen et al.[336] reported on consumption of wine only, while Jayasekara et al.[337] reported on the association between long term alcohol consumption and breast cancer risk. Both reviews reported significant associations with highest versus lowest consumption and positive dose–response relationships that did not reach statistical significance. Chen et al.[336] reported a significant association between wine drinking and risk of premenopausal but not postmenopausal breast cancer (RR 1.79, 95% CI 1.34–2.40 and 1.20, 95% CI 0.94–1.53, respectively).

Jung et al.[339] reported that, when breast cancer was classified jointly by oestrogen–receptor (ER) and progesterone–receptor (PR) status, there were only statistically significant associations with alcohol consumption for ER+PR+ and ER+PR– disease, which supported the findings of the 2017 WCRF CUP Breast SLR.[10] This pooled analysis of prospective studies found no effect modification according to menopausal hormone therapy (MHT) use,[339] in accordance with inconclusive findings for an effect of MHT use in studies reviewed by IARC in 2012.[333]

Table D.38 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.5 Bras

Evidence summary

Evidence classification: Inconclusive.

The evidence of any association between aspects of bra wearing and risk of breast cancer is inconclusive. A very limited amount of evidence, which is of low quality, is available. The single population–based case–control study does not support an association between any aspect of bra wearing and increased breast cancer risk.

Background

'Bra' is universally understood to refer to a form–fitting undergarment designed to support or cover the wearer's breasts. The proposed mechanisms for a link between bra use and breast cancer include impeding lymphatic drainage from the breast. This hypothesis has been shown to lack biological plausibility.[344]

Recent evidence

There are no published cohort studies examining an association between any aspects of wearing a bra and risk of breast cancer.

Only one population–based, case–control study, by Chen et al, has examined an association between any aspect of bra wearing and risk of breast cancer.[75] Multiple potential confounders were examined in this study, which included 454 postmenopausal women with invasive ductal carcinoma (IDC), 590 postmenopausal women with invasive lobular

carcinoma (ILC) and 469 age–matched controls. There was no association between any aspect of bra wearing—including average number of hours/day worn, average lifetime hours/day worn, age at first regular use, wearing a bra with an underwire—and risk of either IDC or ILC.

A systematic review and meta-analysis on aspects of bra wearing and risk of breast cancer has been published; but the 11 studies included in the review, in addition to that by Chen et al., were all hospital-based case-control studies of very low quality. [345] The main other included study, by Hsieh & Trichopoulos[346], is often reported in the literature. This study noted a suggested increased risk of breast cancer among premenopausal women who did not wear bras. However, this finding wasn't statistically significant and was indicated to be likely due to these women being thinner and having smaller breasts.

Table D.39 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.6 Coffee, tea, caffeine

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between coffee and/or tea intake and risk of breast cancer is inconclusive. There is some inconsistency in findings across studies. However, in meta–analyses of prospective cohort studies no association has been found between coffee consumption and risk of breast cancer or between tea consumption and risk of breast cancer overall.[10, 11] There is some evidence from meta–analyses that coffee consumption may be associated with a small decreased risk of postmenopausal breast cancer in a linear dose–response relationship.[10, 11, 347] The upper confidence interval, however, is close to or equal to 1.00, limiting confidence in the association. A recent meta–analysis of nine prospective studies reported no association between highest versus lowest intakes of caffeine and risk of breast cancer.

Background

Coffee and tea contain caffeine, a naturally occurring plant alkaloid. One cup of coffee contains approximately 100 mg of caffeine (instant coffee 80 mg/250 ml cup, espresso 145 mg/50 ml cup) and black and green tea contains 50 mg/250 ml cup.[348]

Potential pathways hypothesised for any association between coffee and/or tea consumption and decreased risk of breast cancer have been linked to the caffeine content. This includes an increase in sex hormone-binding globulin thereby lowering the circulating free levels of oestrogens, and reduced levels of bioavailable testosterone with high intake of caffeine.[349]

In addition, there are compounds other than caffeine in coffee and tea—such as polyphenols—that may have anti-carcinogenic effects via antioxidant actions, inhibiting oxidative stress and oxidative damage.[349, 350]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) has judged the evidence for any association between consumption of coffee or tea and risk of breast cancer as 'Limited—no conclusion', for both premenopausal and postmenopausal breast cancer.[11]

In dose–response meta–analyses undertaken in the WCRF Continuous Update Project systematic literature review (CUP Breast SLR), there was a borderline association for 1 cup/day increments in coffee consumption with decreased risk of breast cancer (RR 0.99, 95% CI 0.98–1.00, 14 studies, low heterogeneity).[10] There was no association for premenopausal breast cancer (RR 1.00, 95% CI 0.97–1.03, seven studies, moderate heterogeneity) and a borderline association for decreased risk of postmenopausal breast cancer (RR 0.98, 95% CI 0.95–1.00, seven studies, moderate heterogeneity).

For tea, in dose–response meta–analyses undertaken in the SLR, there was no association for one cup/day increments with breast cancer risk (RR 1.03, 95% CI 0.98–1.09, six studies, high heterogeneity). There was no association for premenopausal breast cancer (RR 1.00, 95% CI 0.96–1.05, four studies, no heterogeneity), or for postmenopausal breast cancer (RR 1.05, 95% CI 0.99–1.11, five studies, high heterogeneity).[10]

For green tea, in dose–response meta–analyses undertaken in the SLR there was no association with breast cancer risk (RR 0.99, 95% CI 0.97–1.02, six studies, no heterogeneity).[10]

Recent evidence

Studies have focused on coffee consumption. A meta–analysis by Lafranconi et al.[347] of coffee intake and breast cancer risk included a total of 21 prospective studies including the findings from recent cohort studies by Hashibe et al.,[350] Oh et al.,[351] Bhoo–Pathy et al.[352] and Lukic et al.[353] The authors noted that their meta–analysis was an update of the reviews by Jiang et al.[354] and Li et al.[355]

Lafranconi et al.[347] reported the findings of Jiang et al.[354] and Li et al.[355] as follows: '*The meta–analysis performed by Li and colleagues, on 16 cohort and 10 case–control studies, showed a borderline significant inverse association between coffee intake and the risk of breast cancer (RR 0.96, CI 95% 0.93–1.00 for highest versus lowest analysis; RR 0.98, CI 95% 0.97–1.00 for an increment of 2 cups per day). Statistical significance was reached only for those women without oestrogen receptor (ER–negative, RR 0.81, 95% CI 0.67–0.97). In our [Lafranconi et al 2018] study, such a finding was not confirmed. The work carried out by Jiang and colleagues, which included 17 prospective and 20 case–control studies, found no significant association between coffee consumption and breast cancer risk (highest versus lowest analysis: RR 0.98, CI 95% 0.95–1.02; dose–response analysis: RR 0.98, 95% CI 0.92–1.05 for an increment of 2 cups per day)*.'

Lafranconi et al.[347] conducted a dose–response analysis of 13 studies and reported a significant linear association between coffee consumption and risk of breast cancer. This association was stronger among postmenopausal women. Relative risks for one to seven cups of coffee/day were 0.97 (95% CI 0.95–1.00), 0.95 (95% CI 0.90–1.00), 0.92 (95% CI 0.86–1.00), 0.90 (95% CI 0.82–0.99), 0.88 (95% CI 0.78–0.99), 0.85 (95% CI 0.74–0.99), and 0.83 (95% CI 0.70–0.99) respectively compared with no coffee consumption. In addition, an association between highest versus lowest consumption of coffee was observed only among

postmenopausal women (RR 0.92, 95% CI 0.88–0.98) and not for premenopausal breast cancer or breast cancer overall.

Some studies have reported on caffeine intake, as opposed to coffee and/or tea intake and risk of breast cancer. A meta–analysis by Grosso et al.[349] included nine prospective studies where caffeine intake was determined. A descreased risk of 0.99 (95% CI 0.94–1.04) for the highest versus lowest intakes of caffeine was observed.

Table D.40 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.7 Diet—calcium

Evidence summary

Evidence classification: Suggestive (for dietary calcium).

The evidence is suggestive of an association between dietary calcium and decreased risk of breast cancer. There is limited but generally consistent evidence from two meta–analyses that dietary calcium intake is associated with decreased risk of breast cancer.[10, 356] No association between intake of calcium supplements and breast cancer risk was found in two meta–analyses, based on a very limited amount of evidence.[10, 356]

Background

Calcium is an essential mineral in the diet and is found in many foods. Foods high in calcium include dairy products, such as milk, yoghurt and cheese, dark green vegetables, some soy products, fish, nuts, and legumes. Some foods such as fruit juices and drinks, tofu and cereals, may be fortified with calcium.[357] In addition to dietary intake, calcium may also be taken as a supplement. Calcium supplements may be taken concurrently with vitamin D supplements.

Potential mechanisms for associations between calcium intake and breast cancer risk include calcium's role in regulating cell proliferation, differentiation, and programmed cell death (apoptosis). This is supported by evidence from animal studies suggesting that calcium has anti–proliferative and pro–differentiation actions in breast cells that would reduce risk of developing cancer. The effects of calcium on breast cancer risk may also involve its interactions with vitamin D.[356]

Methodological limitations for studies of calcium intake include measurement error associated with assessment of dietary calcium intake using food frequency questionnaires, and potential multiple confounders (such as age, reproductive factors, body mass index (BMI) and alcohol consumption) that were adjusted for in most studies.[10, 356]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged the evidence for an association between diets high in calcium with decreased risk of both premenopausal and postmenopausal breast cancer as 'Limited–suggestive'.[11]

For dietary calcium, in dose–response meta–analyses undertaken in the WCRF Continuous Update Project systematic literature review (CUP Breast SLR), there was no association between dietary calcium intake and overall breast cancer risk (RR per 300 g/day 0.97, 95% CI 0.94–1.00; five studies with low heterogeneity).[10] Dietary calcium intake was associated with decreased risk of premenopausal breast cancer (RR per 300 g/day 0.87, 95% CI 0.76–0.95; five studies with high heterogeneity) and with decreased risk of postmenopausal breast cancer (RR per 300 g/day 0.96, 95% CI 0.94–0.99; six studies with no heterogeneity). All studies in the dose–response meta–analyses were adjusted for age, alcohol intake, BMI and reproductive factors, except for one study that did not adjust for alcohol intake.[10]

For calcium supplements, the WCRF CUP Breast SLR reported that one meta–analysis of six randomised controlled trials (none of which were designed to investigate cancer risk as the primary outcome) found no association between supplemental calcium intake and breast cancer risk. No associations were reported in cohort studies between breast cancer risk and calcium supplements, except in one study for decreased breast cancer risk in women who used calcium supplements compared with non–users. Dose–response meta–analyses were not conducted due to the low number of studies.[10] For concurrent calcium and vitamin D supplements, the WCRF CUP Breast SLR identified one randomised controlled trial and one prospective cohort study. No associations were reported between breast cancer risk and concurrent calcium and vitamin D supplementation.[10]

For total calcium (calcium from food and supplements), the WCRF CUP Breast SLR identified one meta–analysis and four cohort studies. No associations were reported in cohort studies between total calcium intake and breast cancer risk, except in one study for decreased premenopausal breast cancer risk associated with highest compared with lowest total calcium intake. Dose–response meta–analyses were not conducted due to the low number of studies.[10]

Recent evidence

A meta–analysis by Hidayat et al.[356] examining any association between calcium intake (dietary and/or supplemental calcium) and risk of breast cancer included 11 prospective cohort studies, 10 of which were also included in the WCRF CUP Breast SLR in 2017.[10] The meta–analysis by Hidayat et al.[356] also noted an association between dietary calcium and decreased breast cancer risk. For dietary and/or supplemental calcium intake, a high versus low intake of calcium was associated with a decreased breast cancer (RR 0.92, 95% CI 0.85–0.99; 11 studies with moderate heterogeneity), with a decreased risk of premenopausal breast cancer (RR 0.75, 95% CI 0.59–0.96) and a decreased risk of postmenopausal breast cancer (RR 0.94, 95% CI 0.87–1.01). In subgroup analyses by type of intake, intake of dietary calcium but not total or supplemental calcium was associated with a decreased risk of breast cancer (RR 0.90, 95% CI 0.84–0.97, nine studies; RR 0.93, 95% CI 0.84–1.03; six studies and RR 0.98, 95% CI 0.92–1.03; four studies).[356]

Table D.41 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.8 Diet—dairy

Evidence summary

Evidence classification: Suggestive.

The evidence is suggestive of an association between dairy intake and decreased risk of breast cancer. There is limited, but generally consistent, evidence that intake of dairy products may be associated with a decreased risk of breast cancer (overall and premenopausal breast cancer) from three meta–analyses, including a dose response association.[10]

No association between dairy intake and risk of postmenopausal breast cancer was found in the meta–analysis by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR).[11]

No associations have been observed between intake of total milk or whole milk and risk of breast cancer.

Background

Dairy products are foods produced from the milk of mammals such as cows, sheep and goats. Dairy products include milk (whole milk, low–fat milk, skim milk), butter, cheese (natural and processed), cultured products (yoghurt, cottage cheese) and products such as ice–cream. Dairy products contain calcium and fat, however, these components are considered as separate exposures (sections 4.7.7 and 4.7.18).

The potential mechanism for any association between dairy intake and breast cancer risk may be via dietary calcium, because dairy products are a major source of calcium, or via fortification of dairy products with vitamin D.[11, 358] For yoghurt, the presence of probiotics and the effects of fermentation in yoghurt production may be potential mechanisms for any association with breast cancer risk.[358]

Methodological issues in studies of dairy intake include the measurement error associated with assessment of intake using food frequency questionnaires—a commonly used method—which can differ between studies and are often self–administered.[10, 358] There are multiple possible confounders, such as age, reproductive factors, body mass index (BMI) and alcohol consumption; most studies have adjusted for these.[10] Fat intake could confound any association of breast cancer risk with dairy intake, since a diet with high diary consumption may also have high total fat intake, particularly saturated fat.[358]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged the evidence for intake of dairy products as 'Limited–suggestive' for an association with reduced risk of premenopausal breast cancer, and as 'Limited–no conclusion' for an association with risk of postmenopausal breast cancer.[11]

In dose–response meta–analyses undertaken in the WCRF Continuous Update Project systematic literature review (CUP Breast SLR), dairy product intake was associated with a

decreased risk of breast cancer overall (RR per 200 g/day 0.96, 95% CI 0.94–0.99; six studies, no heterogeneity).[10] Dairy intake was also associated with decreased risk of premenopausal breast cancer, RR per 200 g/day 0.95 (95% CI 0.92–0.99; seven studies, no heterogeneity) but there was no association with postmenopausal breast cancer, RR per 200 g/day 0.97 (95% CI 0.93–1.01; eight studies, moderate heterogeneity). Dose–response meta–analyses indicated no associations between total milk intake or whole milk intake and risk of breast cancer.[10]

WCRF/AICR[11] reported on a pooled analysis of eight studies which was excluded from the CUP analysis because fluid and solid intake were reported separately.[359] No significant dose–response associations were observed for total dairy fluids or for total dairy solids and risk of breast cancer.

Recent evidence

A meta–analysis by Wu et al.[360] included analyses of specific types of dairy products but did not include any more recent additional studies than the WCRF CUP Breast SLR. The meta–analysis indicated that decreased risk of breast cancer was associated with consumption of skim milk and yoghurt: RR for highest versus lowest intake of skim milk was 0.93 (95% CI 0.85–1.00, eight studies with moderate heterogeneity) and RR for highest versus lowest intake of yoghurt was 0.90 (95% CI 0.82–1.00, seven studies with no heterogeneity).[360] There was no association with breast cancer risk for consumption of total milk (18 studies) or whole milk (nine studies).[360]

A meta–analysis by Zang et al.[358] on dairy intake and breast cancer risk, that included case–control (five studies, all conducted in Asia) not included in the WCRF CUP Breast SLR, and 22 prospective cohort studies, reported findings consistent with the WCRF CUP Breast SLR. High and modest dairy consumptions (>600 and 400–600 g/day, respectively) were associated with decreased breast cancer risk, compared with low dairy consumption (<400 g/day): RR for high consumption was 0.90 (95% CI 0.83–0.98) and RR for modest consumption was 0.94 (95% CI 0.91–0.98).[358]

Table D.42 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.9 Diet—dietary fibre

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between dietary fibre intake and breast cancer risk is inconclusive. Meta–analyses have indicated a possible association between increased intake of dietary fibre and decreased risk of breast cancer overall and postmenopausal breast cancer, but not premenopausal breast cancer; and an association of soluble fibre intake but not insoluble fibre intake with decreased breast cancer risk overall.[10]

Background

Dietary fibre comprises plant cell wall constituents (carbohydrate polymers, such as cellulose) that are not digested in the small intestine and includes both naturally–occurring and added fibre in food.[361] There are two types of dietary fibre: soluble fibre (found in oat bran, barley, nuts, seeds, beans, lentils, peas, and some fruits and vegetables) that absorbs water; and insoluble fibre (found in wheat bran, vegetables and whole grains) that adds bulk. The source of fibre, such as legumes, cereal, vegetable or fruit, can also be used to classify dietary fibre.[361]

Potential mechanisms for any association between dietary fibre intake and decreased risk of breast cancer include via decreased levels of oestrogens, through inhibition of intestinal reabsorption, and increased faecal excretion of oestrogens.[362] Other potential mechanistic effects of dietary fibre may include delayed gastric emptying and increased small intestine transit time, resulting in slower glucose absorption and reduced insulin secretion.[362]

WCRF/AICR

The World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) judged the evidence for the association between dietary fibre intake and risk of breast cancer as 'Limited–no conclusion' for both premenopausal and postmenopausal breast cancer.[11]

In the WCRF Continuous Update Project systematic literature review (CUP Breast SLR), dose–response meta–analyses indicated that dietary fibre intake was associated with decreased risk of breast cancer overall (RR per 10 g/day increase 0.95, 95% CI 0.93–0.98; 16 studies with no heterogeneity).[10] There was no association in dose–response meta–analyses with dietary fibre intake for premenopausal breast cancer (RR per 10 g/day increase 0.91, 95% CI 0.75–1.10; four studies with moderate heterogeneity). However, dietary fibre intake was associated with decreased risk of postmenopausal breast cancer (RR per 10 g/day increase 0.95, 95% CI 0.92—0.99); 11 studies with no heterogeneity).[10] Decreased risk of breast cancer overall was associated with intake of soluble fibre (RR per 10 g/day 0.74, 95% CI 0.63–0.88; five studies with no heterogeneity) but not insoluble fibre (RR per 10 g/day 0.97, 95% CI 0.87–1.07; six studies with low heterogeneity). Analyses by sources of dietary fibre (legume fibre, cereal fibre, vegetable fibre and fruit fibre) indicated no associations of different dietary fibre sources with breast cancer risk.[10]

Recent evidence

A meta–analysis by Chen et al.[363] of 24 prospective cohort and case–control studies included all 16 cohort studies in the WCRF SLR (2017) and an additional four studies (one of which was published after the cut–off date for the WCRF SLR). The meta–analysis indicated that dietary fibre intake was associated with decreased risk of breast cancer overall (RR 0.88, 95% CI 0.83–0.93; 24 studies with moderate heterogeneity) and with decreased risk of premenopausal (RR 0.78, 95% CI 0.62–0.94) and postmenopausal breast cancer (RR 0.88, 95% CI 0.79–0.97). In dose–response meta–analysis, dietary fibre intake was associated with decreased risk of breast cancer (RR per 10 g/day increase 0.96, 95% CI 0.92–0.98).[363]

A cohort study by Narita et al.,[364] published since the meta–analyses, included 44,444 Japanese women who were followed for an average of 14 years. There was no association reported between dietary fibre intake (total fibre, soluble fibre, insoluble fibre) and risk of breast cancer overall, or for premenopausal or postmenopausal breast cancer. However, the median level of fibre intake for this cohort was low, ranging from a median of 7.9 g/day in the lowest quartile of intake to 18.1 g/day in the highest quartile.[364]

Table D.43 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.10 Diet—fruit

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between fruit intake and breast cancer risk is inconclusive. The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) has judged the evidence to be 'Limited–no conclusion'; although meta–analyses have indicated a possible association of increased fruit intake with decreased overall breast cancer risk and with decreased risk of postmenopausal, but not premenopausal breast cancer.[10] A more recent large cohort study reported no association between fruit intake and breast cancer risk,[365]however another large cohort study with long-term follow–up has shown a positive association.[366]

Background

Fruit, used as a culinary term, refers to the edible part of a plant, tree, bush or vine that contains the seeds and pulpy surrounding tissues and has a sweet or tart taste.[11] As a botanical term, fruit, more broadly, refers to the edible part of a plant that consists of seeds and surrounding tissues.

Fruit includes apples, bananas, berries, figs, grapes, mangoes, melons, citrus fruits and dried fruits.

Fruits are a source of dietary fibre, vitamins and minerals and other bioactive compounds such as phytochemicals. Nutrient levels of fruit vary with the species and the environment and may be affected by how they are produced (including when they are harvested), stored and prepared.[11]

Potential mechanisms for any association between fruit intake and breast cancer risk may be via components of fruits, such as vitamins C and E, minerals, fibre and other bioactive compounds (for example, antioxidants and polyphenols in berries).[365] These compounds may reduce breast cancer risk by mechanisms such as reducing oxidative damage to DNA, increasing programmed cell death (apoptosis) or increasing the activity of enzymes able to detoxify carcinogens.[367]

Methodological issues in studies of fruit intake include the measurement error associated with assessment of intake using food frequency questionnaires—a method commonly used—which can differ between studies and are often self–administered.[10] There are multiple

possible confounders, such as age, reproductive factors, BMI and alcohol consumption, and, while most studies have adjusted for these, residual confounding is possible as women who eat a lot of fruit and vegetables might have healthier lifestyles.[366]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) noted in the 2018 Continuous Update Project Third Expert Report that the evidence for any association between fruit intake and risk of breast cancer was previously judged as 'Limited–no conclusion' in the Second Expert Report (2010)[368], and that it remained the same.[11]

In the WCRF Continuous Update Project systematic literature review (CUP Breast SLR), dose–response meta–analyses indicated that fruit intake was associated with decreased risk of breast cancer overall (RR per 200 g/day increase 0.94, 95% CI 0.90–0.98; 12 studies with low heterogeneity). However, fruit intake was associated with decreased risk of postmenopausal breast cancer (RR per 200 g/day 0.92, 95 % CI 0.87–0.98; eight studies with low heterogeneity).[10] There was no association in dose–response meta–analyses with fruit intake for premenopausal breast cancer (RR per 200 g/day 1.00, 95% CI 0.81–1.23; three studies with moderate heterogeneity).

WCRF/AICR reported on a pooled analysis by Jung et al.[369] from the Pooling Project of Prospective Studies of Diet and Cancer. This study included data from 993,466 women from 20 cohort studies followed for 11 to 20 years, with 19,869 ER+ and 4,821 ER– breast cancer cases. There was no association between highest versus lowest amounts of fruit intake and risk of breast cancer (RR 0.99, 95% CI 0.95–1.03), or by breast cancer hormone–receptor sub–types, and no evidence of a dose–response.[369]

Recent evidence

A meta–analysis by Fabiani et al.[370] published since the WCRF SLR reported that apple intake was associated with a decreased risk of breast cancer in case–control studies (OR for highest versus lowest level of apple consumption 0.79, 95% CI 0.73–0.87; five studies with low heterogeneity) but there was no association between apple consumption and breast cancer risk in cohort studies (RR 0.97, 95% CI 0.94–1.01; three studies with no heterogeneity).

Two large cohort studies on associations between fruit intake and breast cancer risk have been published since the WCRF SLR. A prospective cohort study by Emaus et al.[365] from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (335,054 women with median follow–up of 11.5 years) reported no association between fruit intake and breast cancer risk (HR for highest (399–565 g/day) versus lowest (36–86 g/day) quintile of intake 1.01, 95% CI 0.94–1.09). There were also no associations between total fruit intake and breast cancer hormone–receptor subtypes.[365]

Farvid et al.,[366] from an analysis of data from the prospective Nurses' Health Study (90,476 premenopausal women), reported that high versus low fruit consumption during adolescence (ages 13–18 years) was associated with a lower risk of breast cancer (HR for highest (median intake of 2.9 servings/day) versus lowest (median intake of 0.5 serving/day) quintile of intake 0.75, 95% CI 0.62–0.90). However, total fruit intake during early adulthood (age 27–44 years) was not associated with a lower risk of breast cancer (HR for highest versus lowest quintile of intake 0.96, 95% CI 0.85–1.09).[366]

Longer term follow–up of the Nurses' Health Study I and II, as reported by Farvid et al.,[371] and with repeated measures of dietary intake, showed that, among 182,145 premenopausal women at baseline, after a mean of 23.7 years of follow–up, that total fruit intake was associated inversely with breast cancer incidence (HR >2.5 servings/day versus ≤4 servings/week of fruits 0.91, 95% CI 0.84–0.99). Fruit juice consumption was not associated with breast cancer risk. Higher consumption of fruits and vegetables rich in vitamin C, alpha–carotene, β–carotene and lutein, was each associated with lower risk of ER–negative (ER–) breast cancer. Higher consumption of fruit juice was associated with higher risk of ER–breast cancer (data were not provided). Examining individual fruits, higher intakes of blueberries and strawberries were associated with decreased risk of ER– breast cancer.

Total fruit and vegetable consumption was associated with decreased breast cancer risk 8–12 years after exposure but not for shorter latency periods. Total fruit consumption was more strongly associated with breast cancer risk for longer time lags, 12–16 years after exposure. Shorter exposures were associated with decreased risk of ER– breast cancers.

Table D.44 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.11 Diet—vegetables

Evidence summary

Evidence classification: Suggestive (for intake of non–starchy vegetables and decreased risk of oestrogen receptor negative (ER–) breast cancer).

The evidence is suggestive of an association between intake of non-starchy vegetables and decreased risk of oestrogen receptor negative (ER–) breast cancer. There is limited but generally consistent evidence from one meta–analysis, one pooled analysis and two additional cohort studies. The decreased risk associated with increased intake of non–starchy vegetables for ER– breast cancer has been estimated as 0.79 (95% CI 0.63–0.98).[11]

Background

The term 'vegetables' refers to the edible parts of plants and includes edible leaves, roots, tubers, bulbs, stems and stalks, flowers and grains used as vegetables (for example, sweetcorn, tomatoes, eggplant and zucchini). It does not include nuts, seeds and most grains.[11] Vegetables are sources of dietary fibre, vitamins and minerals, and other bioactive compounds such as phytochemicals. Nutrient levels of vegetables vary with species and environment, and may be affected by how they are produced, stored and prepared (as most forms of cooking reduce the nutrient content of vegetables).[11] One serve of vegetables is equivalent to approximately 100 grams.

Vegetables can be classified as starchy and non–starchy. Both contribute to a healthy diet. Starchy vegetables are higher in carbohydrate content and include some tubers and roots such as potatoes, sweet potatoes, cassava, sago and taro. Non–starchy vegetables have a lower carbohydrate content and include green leafy vegetables (spinach and lettuce), carrots, broccoli, cabbage, and onions. The WCRF/AICR has separated its review of evidence on starchy and non–starchy vegetables.[11] Specific exclusion of starchy vegetables

has been made by studies, such as exclusion of potatoes by Jung et al.,[369] and exclusion of legumes, potatoes and other tubers by Emaus et al.[365]

Potential mechanisms for any association between vegetables intake and breast cancer risk include through components of vegetables, such as vitamins C and E, minerals, fibre and other bioactive compounds (for example, glucosinolates in cruciferous vegetables).[365] It has been suggested the effect of bioactive components may be more detectable in ER– cancers than in oestrogen receptor positive (ER+) cancers, where the effect of oestrogens may obscure a smaller effect from vegetables.[11] A potential mechanism may be through reduction of the epidermal growth factor receptor by phytochemicals in vegetables. [11]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged the evidence for the association between the intake of non–starchy vegetables and decreased risk of ER– premenopausal and postmenopausal breast cancer as 'Limited—suggestive'.[11]

Dose–response meta–analyses included in the WCRF Continuous Update Project systematic literature review (CUP Breast SLR) indicated non–starchy vegetables intake was not associated with risk of breast cancer overall (RR per 200 g/day increase 0.98, 95% CI 0.93–1.02; 12 studies, low heterogeneity), or with risk of premenopausal breast cancer (RR per 200 g/day increase 0.96, 95% CI 0.83–1.11; three studies, no heterogeneity) or postmenopausal breast cancer (RR per 200 g/day increase 1.03, 95% CI 0.97–1.09; eight studies, no heterogeneity).[10]

However, meta–analysis of breast cancer risk by hormone receptor subtype of three studies—including data from the large European Prospective Investigation into Cancer and Nutrition (EPIC) study by Emaus et al.[365]—indicated that non–starchy vegetables intake was associated with decreased risk of ER–PR– breast cancer (RR per 200 g/day increase 0.79, 95% CI 0.63–0.98; moderate heterogeneity). There was no association with breast cancer risk for ER+PR+ breast cancer (RR per 200 g/day increase 0.89, 95% CI 0.79–1.01) or for ER+PR– breast cancer (RR per 200 g/day increase 0.96, 95% CI 0.81–1.13).[10]

WCRF/AICR reported on a pooled analysis by Jung et al.[369] from the Pooling Project of Prospective Studies of Diet and Cancer. This study included data from 993,466 women from 20 cohort studies followed for 11 to 20 years, with 19,869 ER+ and 4,821 ER– breast cancer cases. Vegetable intake was associated with a decreased risk of ER– breast cancer (pooled RR for highest versus lowest quintile of total vegetable consumption 0.82, 95% CI 0.74–0.90). For ER– breast cancer, a dose–response analysis resulted in a pooled RR per 300 g/day of 0.88 (95% CI 0.81–0.95)[369]. There was no association between vegetable intake and ER+ breast cancer risk (RR 1.04, 95% CI 0.97–1.11).[369]

Recent evidence

A prospective cohort study by Emaus et al.[365] from the EPIC cohort (335,054 women with median follow–up of 11.5 years), reported vegetables intake was associated with decreased risk of breast cancer (HR for highest versus lowest quintile of vegetable intake 0.87, 95% CI 0.80–0.94). Although the study was published after the WCRF CUP Breast SLR publication search date, the results from the study for breast cancer risk by hormone receptor subtype

were included in the WCRF hormone receptor breast cancer subtypes meta–analysis (summarised above).

An early analysis of data from the Nurses' Health Study (90,476 premenopausal women) reported no association with risk of breast cancer between total vegetables intake during adolescence or early adulthood and risk of breast cancer (HR for highest verses lowest vegetables intake at ages 13–18 years 0.86, 95% CI 0.73–1.01), or in early adulthood (HR for highest versus lowest vegetables intake age 27–44 years 0.96, 95% CI 0.86–1.07).[366]

Longer term follow–up of the Nurses' Health Study I and II, as reported by Farvid et al.,[371] and with repeated measures of dietary intake, showed that, among 182,145 premenopausal women at baseline, after a mean of 23.7 years of follow–up, that total vegetables consumption was inversely associated (borderline significant) with breast cancer incidence (>4.5 versus ≤1.5 servings/day of vegetables; HR 0.91, 95% CI 0.84–1.00). There were also significant inverse associations with cruciferous vegetables consumption (>5 versus ≤2 servings/week; HR 0.92, 95% CI 0.85–0.98) and those rich in vitamin C (>1 servings/day versus ≤2 servings/week; HR 0.89, 95% CI 0.82–0.95), α–carotene (≥3 servings/week versus <2 servings/month; HR 0.91, 95% CI 0.84–0.98;), and β–carotene (>1 servings/day versus ≤2 servings/week; HR 0.87, 95% CI 0.80–0.94). Although there was significant heterogeneity among individual vegetables in associations with breast cancer risk, the association for carrots remained significant using step–wise selection analysis. Higher intakes of carrots, lettuce, winter squash, broccoli, cabbage, and cauliflower were also significantly associated with lower incidence of breast cancer. In analyses by tumour hormone receptor status, higher consumption of green leafy, yellow/orange, cruciferous, tomato, and other vegetables, as well as fruits and vegetables rich in vitamin C, alpha–carotene, β–carotene, and lutein was each associated with lower risk of ER–negative (ER–) breast cancer. Overall intake of total vegetables was especially associated with lower risk of ER– tumours (HR per 2 additional servings per day 0.85, 95% CI 0.77–0.93).

Various findings also related similar types of vegetables consumption with HER2–enriched and basal–like breast cancers. The study authors noted that the positive findings in their study may have been due to the latency period. The long follow–up period in this study showed that fruit and vegetables intake may be important 8 or more years before diagnosis. Total fruit and vegetables intake was associated with decreased risk of breast cancer 8–12 years after exposure but not for shorter latency periods. Total vegetables intake was associated with decreased risk 8–12 years and 12–16 years after exposure. Shorter exposures were associated with decreased risk of ER– breast cancers.

Table D.45 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.12 Diet—foods high in carotenoids

Evidence summary

Evidence classification: Suggestive.

The evidence is suggestive of an association between intake of foods high in carotenoids and decreased risk of breast cancer. The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged the evidence to be 'Limited–suggestive' of an

association between circulating carotenoids and decreased risk of breast cancer. Although there are mixed findings across the range of carotenoids and across studies, this may be partly due to differences in measurement of exposure. Moreover, dose–response analyses have generally been in the direction of an inverse association.[11]

Background

Carotenoids are naturally occurring pigments and are the sources of the yellow, orange and red colours of many plants. Fruit and vegetables provide most of the 40–50 carotenoids found in the human diet. The most common carotenoids in the western diet are alpha–carotene, beta–carotene, beta–cryptoxanthin, lutein, zeanthin and lycopene. Alpha–carotene, beta–carotene and beta–cryptoxanthin are pro–vitamin A carotenoids and can be metabolised to retinol.

The systemic and breast metabolism of carotenoids may have an impact on processes related to cell growth, differentiations and apoptosis, thereby altering the carcinogenic processes (WCRF/AICR[11] citing Zhang et al.[372]). Some evidence suggests carotenoids may have a direct impact on breast carincogenesis. Carotenoids have antioxidant properties, for example, and may quench reactive oxygen and various free radicals, providing protection against DNA damage (WCRF/AICR[11] citing Elliot[373]). Any anti–cancer properties of specific carotenoids may, therefore, result variously from their anti–oxidant properties, interactions with cellular (including growth control) signaling cascades, and/or altering gene expression.[374]

The evidence for the exposure to dietary carotenoids often includes exposure as circulating carotenoids. Considering measurement error in studies estimating carotenoid intake, the bioavailability of carotenoids from different foods, and individual differences in absorption and metabolism, circulating carotenoids as biomarkers of intake may be better indicators of underlying carotenoid exposure.[11]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged the evidence to be suggestive of an association between circulating carotenoids and decreased risk of breast cancer. The WCRF Continuous Update Project systematic literature review (CUP Breast SLR) identified studies on dietary beta–carotene and circulating beta–carotene, alpha–carotene, total carotenoids, lutein, beta–cryptoxanthin, and lycopene and had sufficient data to conduct meta–analyses on all of these exposures.[10] An additional published pooled analysis was also reported on for beta–carotene and for other dietary carotenoids by hormone receptor status.[372]

Significant inverse dose–response associations were observed for circulating beta–carotene, circulating total carotenoids and circulating lutein (RR per 50 µg/dL 0.78, 95% CI 0.66–0.92; RR per 100 µg/dL 0.82, 95% CI 0.71–0.96; RR per 25 µg/dL 0.72, 95% CI 0.55–0.93). No significant associations were observed for circulating alpha–carotene, β–cryptoxanthin and lycopene, although results for each of these exposures were all in the direction of an inverse association. There was no association between dietary β-carotene and risk of breast cancer in 18 studies (RR 1.00, 95% CI 0.98–1.02).

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) [11] report on findings by hormone receptor status from the pooled analysis by Zhang et al.[372] and other individual studies and noted an overall stronger association with oestrogen receptor negative (ER–) breast cancers although the findings vary by type of carotenoid.

Recent evidence

Longer term follow up of the Nurses' Health Study I and II with repeated measures of dietary intake showed that, among 182,145 premenopausal women at baseline and after a mean of 23.7 years of follow–up, there were significant inverse associations with vegetables and fruits containing α–carotene (≥3 servings/week versus <2 servings/month; HR 0.91, 95% CI 0.84–0.98;), and β–carotene (>1 servings/day versus ≤2 servings/week; HR 0.87, 95% CI 0.80–0.94). These associations were stronger for ER– disease. There was also an association between consumption of fruit and vegetables rich in lutein and risk of ER– and HER2–enriched disease (data were not provided). [371]

Data from a large case–control study nested in the European Prospective Investigation into Cancer and Nutrition cohort (521,000 participants from 10 European countries; 1502 breast cancer cases including 462 ER– cases) suggested that higher plasma concentrations of α–carotene and β–carotene were inversely associated with ER– breast cancer risk (OR for quintile 1 of intake compared with quintile 5 of intake 0.61, 95% CI 0.39– 0.98; and 0.41, 95% CI 0.26–0.65; respectively).[375] Higher levels of vitamin C were associated with a decreased risk of oestrogen receptor positive/ progesterone receptor positive (ER+PR+) breast cancer. No association was observed between retinol or tocopherols and breast cancer risk.

A case–control study nested in the Cancer Prevention Study II (CPSII) Nutrition cohort (98,000 women) reported that higher levels of plasma concentration of alpha–carotene, but not beta–carotene, beta–cryptoxanthin, lycopene, lutein + zeaxanthin or total carotenoids, were significantly inversely associated with postmenopausal breast cancer (OR for the highest quintile versus the lowest quintile 0.50, 95% CI 0.29–0.85).[376]

Table D.46 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.13 Diet—Mediterranean diet

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between a Mediterranean diet and risk of breast cancer is inconclusive. While a randomised trial and the majority of cohort studies have indicated a possible association between a Mediterranean diet and decreased risk of postmenopausal breast cancer, there are methodological limitations to the evidence.

Background

Dietary patterns, such as the Mediterranean diet, integrate the contributions of individual dietary components, enabling simultaneous assessment of the effects of individual nutrients

and their potential interdependencies.[377, 378] A Mediterranean diet is characterised by high consumption of whole grains, vegetables, fruits, nuts and legumes and regular intake of fish and seafood, but low amounts of meat, eggs, high–fat dairy and sugar. Olive oil is the main source of fat, and moderate alcohol consumption, preferably as red wine consumed with meals, can be included as an indicator.[377, 378]

Definitions of a Mediterranean diet have changed over time and can vary.[377, 379] Different indices used to assess adherence to a Mediterranean diet include the Mediterranean diet index, and the modified–, alternate– and relative–Mediterranean diet indices.[377] Since alcohol is an established risk factor for breast cancer, some studies have excluded alcohol from the Mediterranean diet score.[378]

Potential mechanisms for any associations of a Mediterranean diet and breast cancer risk include reduction in total and low density lipoprotein cholesterol, body weight, blood pressure, fasting plasma glucose and C–reactive protein, and antioxidant and anti–inflammatory effects.[379]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged the evidence for any association between breast cancer risk and dietary patterns, or culturally defined diets, as 'Limited—no conclusion' for both premenopausal and postmenopausal breast cancer. No classification of evidence was made specifically for the Mediterranean diet.[11]

The WCRF Continuous Update Project systematic literature review (CUP Breast SLR) identified 10 cohort studies on Mediterranean diet score, or modified/alternate Mediterranean diet score, and breast cancer risk. Some studies excluded alcohol consumption from the score, or examined scores both with and without alcohol. No dose–response meta–analyses were undertaken due to the low number of studies.[10]

The WCRF CUP Breast SLR reported inconsistent results from individual studies for Mediterranean diet score—with and without alcohol—and overall risk of breast cancer and risk of premenopausal breast cancer. For postmenopausal breast cancer (eight cohort studies), there was decreased risk associated with Mediterranean diet score, with and without alcohol, except for one pooled study from the United Kingdom. In analysis by hormone receptor subtype, one cohort study reported decreased risk of oestrogen receptor negative/ progesterone receptor negative (ER–PR–) postmenopausal breast cancer associated with highest compared with lowest Mediterranean diet score. There were no other associations with other subtypes of postmenopausal breast cancer.[10]

Recent evidence

A meta–analysis by[377] on Mediterranean diet and breast cancer risk included one randomised controlled trial (RCT), seven prospective cohort studies, 16 observational studies and nine case–control studies. The RCT included was the PREDIMED trial from Spain,[380] which is described separately below. In the meta–analysis, high adherence to Mediterranean diet pattern was associated with decreased risk of breast cancer in cohort studies (RR 0.94, 95% CI 0.90–0.99; seven studies with low heterogeneity) and also case–control studies (RR 0.89, 95% CI 0.85–0.94; nine studies with low heterogeneity).[377] This meta–analysis included the

cohort study by van den Brandt & Schulpen[378] described separately below, which was not included in the WCRF CUP Breast SLR.[10]

A meta–analysis by[379] included trials and cohort studies on Mediterranean diets with no restriction on fat intake. Meta–analysis of 13 cohort studies indicated no association between breast cancer risk and the highest versus lowest levels of adherence to a Mediterranean diet (RR 0.96, 95% CI 0.90–1.03).[379]

In a cohort study of over 62,000 postmenopausal women from the Netherlands with 20 years follow–up, high versus low adherence to a Mediterranean diet (excluding alcohol) was associated with decreased risk of ER– postmenopausal breast cancer (HR 0.60, 95% CI 0.39–0.95).[378] A meta–analysis of these results with those from other cohort studies also indicated association of Mediterranean diet adherence with decreased risk of ER– postmenopausal breast cancer (HR 0.73, 95% CI 0.57–0.93) and with ER–PR– postmenopausal breast cancer (HR 0.77, 95% CI 0.63–0.94), for high versus low adherence.[378]

The PREDIMED cardiovascular disease prevention trial from Spain randomised 4,282 postmenopausal women at high cardiovascular disease risk to a Mediterranean diet supplemented with extra–virgin olive oil or to a Mediterranean diet supplemented with mixed nuts, or to a control diet (with advice to reduce dietary fat).[380] In a pre–specified secondary analysis after median 4.8 years follow–up, risk of breast cancer was lower in the Mediterranean diet with extra–virgin olive oil group compared with the control group (HR 0.32, 95% CI 0.13–0.79). However, this trial was not powered for breast cancer as a primary end point and there were only 35 confirmed incident cases of breast cancer.[380]

Table D.47 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.14 Diet—phytoestrogens

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between intake of phytoestrogens and risk of breast cancer is inconclusive. The evidence is inconsistent. However, meta–analyses of the higher–quality prospective cohort studies show no association with breast cancer risk for intake of any specific groups of dietary phytoestrogens including ‘isoflavones’ and ‘soy and soy products’.

Background

Phytoestrogens are naturally occurring plant–derived compounds, the molecules of which have structural similarities to oestrogens. The major classes of phytoestrogens include isoflavones (from soy beans, soya products and vegetables), flavanoids (from red and yellow fruits and vegetables), lignans (from flaxseed, whole grains, fruits and vegetables), coumestans (from peas, beans, alfalfa and sunflower seeds), and stilbenes (from red wine).[381]

Phytoestrogens have been investigated primarily as protective agents for breast cancer. The hypothesis that soy isoflavones and other phytoestrogens could reduce risk of breast and

endometrial cancer comes from the low incidence of breast and endometrial cancer in Asian countries where soy products are prevalent in the diet, and from certain animal models.[382] Phytoestrogens bind weakly to oestrogen receptors and therefore have weak (anti)oestrogenic effects, which is a potential mechanism for reducing breast cancer risk.[381, 383] Other effects of phytoestrogens that may be involved in potential mechanisms for reducing cancer risk include inhibiting cell growth and proliferation, interacting with growth factor and cytokine signaling pathways, regulating cell cycle and apoptosis pathways, and antioxidant and anti–inflammatory effects.[381, 383]

The (anti)oestrogenic properties of phytoestrogens have also raised concern in relation to increased risk of breast cancer because they might act as endocrine disruptors.[384]

WCRF/AICR

The World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) judged the evidence for any association between breast cancer risk and 'phytoestrogens', 'isoflavones', and 'soya and soya products' as 'Limited–no conclusion' for both premenopausal and postmenopausal breast cancer.[11] One study was identified on total phytoestrogens which found no association with breast cancer risk. For isoflavones, seven cohort studies were identified, with inconsistent findings. A dose–response meta–analysis of six of these seven studies, with high heterogeneity, showed no association of dietary isoflavones with postmenopausal breast cancer risk (RR per 3 mg/day 0.99, 95% CI 0.98–1.00). There were insufficient data for meta–analysis of intake of isoflavones with risk of (any) breast cancer or with premenopausal breast cancer. Three cohort studies of lignans were included in the review and no associations were found with breast cancer risk.[10] No association was identified between intake of soy products (including soy milk) overall (five cohort studies), miso soup intake (three cohort studies), or tofu intake (three cohort studies) and risk of breast cancer.

Recent evidence

A review by Grosso et al.[349] included 16 prospective studies and 23 case–control studies on the relationship between dietary phytoestrogens and risk of breast cancer. As per the WCRF Continuous Update Project systematic literature review (CUP Breast SLR),[10] there were generally small numbers of studies, particularly prospective studies, for intake of the various types of phytoestrogens. A meta–analysis of the 39 studies showed no association between highest versus lowest intakes of total dietary flavonoids and risk of breast cancer (RR 0.96, 95% CI 0.89–1.0). In addition, there were no associations with breast cancer risk for any of the individual dietary flavonoids investigated using prospective studies, including total flavonoids (three studies), flavonols (four studies), flavanones (three studies), isoflavones (eight studies), proanthocyanidins (three studies), or lignans (four studies).

A meta–analysis by Wu et al.[360] on breast cancer risk and dietary protein sources such as soy food included only prospective studies. There was no association with breast cancer risk for highest versus lowest intake of soy food (RR 0.92, 95% CI 0.84–1.00) in 10 studies, or in dose–response analysis per serving increase (RR 0.91, 95 % CI 0.84–1.00) in seven studies.[360]

Baglia et al.[385] have reported extended follow–up results from the Shanghai Women's Health Study cohort, for which earlier results were included in the WCRF CUP Breast SLR analysis.[10] In this cohort of 70,578 women after median 13 years follow–up, adult soy intake was

associated with decreased breast cancer risk (HR for fifth versus first quintile soy protein intake 0.78, 95% CI 0.63–0.97) and with decreased risk of premenopausal breast cancer (HR 0.46, 95% CI 0.29–0.74).[385]

Table D.48 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.15 Diet—glycaemic index

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between glycaemic index and risk of breast cancer is inconclusive. Although there is an indication of a possible association between glycaemic index and increased risk of postmenopausal breast cancer, the evidence is currently heterogeneous. Meta–analyses by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and others, and more recent cohort studies, indicate no associations between glycaemic index and overall risk of breast cancer or premenopausal breast cancer. There is no evidence for an association between glycaemic load and risk of breast cancer.[11]

Background

Glycaemic index (GI) is a relative ranking of the carbohydrate in foods according to how the carbohydrate affects blood glucose levels. GI indicates the extent to which a carbohydrate food raises blood glucose levels after it is eaten, compared with glucose as a reference. Foods with a high GI are quickly broken down during digestion and produce a higher peak in blood glucose and a larger overall blood glucose response after eating, than do foods with a low GI.[386] Glycaemic load (GL) incorporates the effect of the amount of carbohydrate consumed and is calculated as the product of a food's GI and the weight of consumed carbohydrate. The GL of a mixed meal or diet is the sum of the GL values for all the carbohydrate foods consumed and is a measure of the total glycaemic effect of the diet.[386]

Sieri & Krogh[386] hypothesised that the underlying mechanism for any association between GI or GL with increased cancer risk is chronically high blood glucose resulting in chronically elevated blood insulin. Increased insulin results in increased bioactivity of insulin–like growth factors, such as IGF–1, which can promote tumour development. Cancer risk may also be increased via other conditions associated with chronically high blood sugar, such as insulin resistance, obesity and diabetes.[386]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged the evidence for any association between GI and GL with breast cancer risk as 'Limited—no conclusion', for both premenopausal and postmenopausal breast cancer.[11]

For GI, dose–response meta–analyses undertaken in the WCRF Continuous Update Project systematic literature review (CUP Breast SLR) showed an association between GI (per 10 GI

units/day) and increased risk of postmenopausal breast cancer (RR 1.06, 95% CI 1.02–1.10; 10 studies with moderate heterogeneity)[10] No associations were identified for (any) breast cancer (RR 1.02, 95% CI 0.96–1.10; five studies with high heterogeneity) or for premenopausal breast cancer (RR 1.01, 95% CI 0.93–1.10; six studies with moderate heterogeneity). There were no associations of GI with risk of breast cancer subgroups defined by hormone receptor status.[10]

The WCRF CUP Breast SLR identified no associations between GL and risk of breast cancer in dose–response meta–analyses. For meta–analysis per 50 units GL/day, the relative risk for breast cancer was RR 1.02 (95% CI 0.93–1.11; six studies with high heterogeneity); for premenopausal breast cancer RR 1.07 (95% CI 0.92–1.24; seven studies with high heterogeneity); and for postmenopausal breast cancer RR 1.02 (95% CI 0.99–1.06; 10 studies with low heterogeneity).[10] There were no associations of GL with risk of breast cancer defined by hormone receptor status.[10]

Recent evidence

Schlesinger et al.[387] conducted meta–analyses by menopausal status, hormone receptor status and body mass index (BMI) of the studies also identified in the WCRF CUP Breast SLR. GI was associated with increased risk of postmenopausal breast cancer, consistent with the WCRF CUP Breast SLR. No significant differences in relative risks for GI were identified between hormone receptor subtypes or between groups stratified by BMI. GL was associated with increased postmenopausal breast cancer for oestrogen receptor negative (ER–) tumours (RR 1.28, 95% CI 1.08–1.52), compared with oestrogen receptor positive (ER+) tumours (RR 0.99, 95% CI 0.95–1.03). No significant differences in relative risks for GL were identified between groups stratified by BMI.

Sieri et al.[386] found no association of either GI or GL with risk of breast cancer, using the European Prospective Investigation into Cancer and Nutrition (EPIC) Italian prospective cohort study of over 30,000 women after median 15 years follow–up. However, in a subgroup analysis that excluded participants who reported that they were dieting at recruitment, high GL was associated with increased breast cancer risk (HR 1.34, 95% CI 1.02–1.76 highest versus lowest quintile; P trend 0.049).

Makarem et al.[388] found no association for GI or GL with breast cancer risk in age– and multivariate–adjusted models (non–significant HR ranged from 0.54 to 0.91; study of 1,689 women from the prospective Framingham Offspring cohort).

Table D.49 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.16 Diet—total energy

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between total energy intake and risk of breast cancer, and of any association between dietary energy density and risk of breast cancer, is inconclusive. There are inconsistent findings across studies.

Background

Total energy intake refers to the total dietary intake of energy (expressed as kcal/day) from all food types, including carbohydrate, fat and protein, and alcohol intake. Total energy intake can be challenging to assess, and methods used (such as food frequency questionnaires) have measurement errors and often differ across studies.[389]

Dietary energy density is a related measure of diet quality: it is the amount of energy per unit of food consumed (kcal per gram).[390]

There may be a complex interplay of total energy intake with other correlated and confounding factors, such as body mass index (BMI) / obesity / body fatness and physical activity.[390] In addition, different total energy intakes may be associated with different dietary patterns—for example, high energy intake may be associated with high fat consumption and low fruit and vegetable consumption—and these dietary components may have independent effects on breast cancer risk.[390]

Potential biological mechanisms for any association between breast cancer risk and total energy intake may include insulin insensitivity, elevated levels of insulin–like and other growth factors, elevated levels of sex steroid hormones, chronic inflammation and altered adipokines.[390]

WCRF/AICR

The World Cancer Research Fund / American Institute for Cancer Research (WCRF/AICR) judged the evidence for any association between breast cancer risk and energy intake as 'Limited—no conclusion', for both premenopausal and postmenopausal breast cancer.[11]

A dose–response meta–analysis by the WCRF Continuous Update Project systematic literature review (CUP Breast SLR) found no association between total energy intake (500 kcal/day increments) and risk of postmenopausal breast cancer (RR 1.02, 95% CI 0.97–1.06) in nine studies with moderate heterogeneity.[10] Meta–analyses were not conducted for any breast cancer (16 studies identified with inconsistent results) or for premenopausal breast cancer (five studies identified with inconsistent results), because there were not enough new studies with sufficient data.[10]

Recent evidence

Two prospective cohort studies published since the WCRF Continuous Update Project systematic literature review investigated dietary energy density and breast cancer risk.[390, 391]

Hartman et al.[390] studied over 56,000 postmenopausal women from the Cancer Prevention Study II Nutrition Cohort. They found an increased risk of postmenopausal breast cancer associated with total dietary energy density for the highest compared with the lowest quintile of intake (RR 1.17, 95% CI 1.03–1.33), after multivariable adjustment, including BMI. They found

no association between the quantity of high energy density foods consumed and risk of breast cancer.[390]

Thomson et al.[391] studied over 90,000 postmenopausal women from the Women's Health Initiative. They also found no association between dietary energy density and postmenopausal breast cancer risk (age–adjusted sub–hazard ratio 1.06, 95% CI 0.97–1.10 for the highest compared with the lowest quintile of intake).

Table D.50 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.17 Diet—sugar

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between dietary sugar intake and risk of breast cancer is inconclusive. Meta–analyses of a small number of prospective studies indicate no association between total sugar intake, fructose intake or consumption of sugar–sweetened beverages and risk of breast cancer.

Background

Sugar intake can refer to the dietary intake of sucrose (which is commonly referred to as 'sugar'), the dietary intake of all simple sugars (such as glucose, sucrose, fructose, maltose and lactose), or the intake of sugary drinks. The mechanisms for any association between sugar intake and breast cancer risk may be similar to the mechanisms suggested for any association with glycaemic index or glycaemic load (section 4.7.15). These mechanisms include elevated insulin levels and increased bioactivity of insulin–like growth factors such as IGF–1. They also include other conditions associated with chronically high blood sugar, such as insulin resistance, obesity and diabetes.[386]

WCRF/AICR

The World Cancer Research Fund / American Institute for Cancer Research (WCRF/AICR) judged the evidence for any association between breast cancer risk and sugar (sucrose), other sugars, sugary drinks and foods as 'Limited—no conclusion', for premenopausal and postmenopausal breast cancer.[11] The evidence was previously considered too limited to draw conclusions in the 2007 WCRF/AICR Second Expert Report and was not updated as part of the Continuous Update Project.[11]

Recent evidence

Schlesinger et al.[387] undertook a meta–analysis of prospective studies of sugar intake (total sugars and specific sugars) and breast cancer risk, using searches used by the WCRF Continuous Update Project systematic literature review (CUP Breast SLR). The number of studies was limited, however, and the authors could not perform a stratified analysis by either

menopausal status or hormone receptor status.[387] In four studies with moderate heterogeneity, no association was found between breast cancer risk and total sugar intake (for increments of 10 g/day, RR 0.99, 95% CI 0.98–1.01). In three studies with moderate heterogeneity, there was no association with breast cancer risk and fructose intake (for increments of 10 g/day, RR 0.99, 95% CI 0.96–1.01). For other specific sugars (sucrose, glucose, lactose and maltose), there were not enough studies to conduct meta–analyses, and none of the individual studies reported a statistically significant association between intake and breast cancer risk.[387]

A recent large cohort study in Australia[392] showed a borderline significant dose–response association between consumption of sugar–sweetened soft drinks and risk of postmenopausal breast cancer (HR 1.26, 95% CI 1.00–1.58; linear model). No association was observed for consumption of artificially sweetened soft drinks and risk of postmenopausal breast cancer (HE 0.92, 95% CI 0.71–1.18).

A meta–analysis by Boyle et al.[393] on associations with sweetened, carbonated beverage consumption had identified only two retrospective studies on breast cancer risk which found no association between consumption of colas or sugar–sweetened beverages and breast cancer risk (no risk estimate provided).

Table D.51 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.18 Diet—fat

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between dietary fat intake and risk of breast cancer is inconclusive. Findings are inconsistent across studies but randomised trials and cohort studies that adjusted for known confounders have shown no association between total fat intake and risk of breast cancer.

Background

Total fat intake can be measured as absolute intake (grams per day) and is often expressed as intake relative to total energy intake (percentage of energy). Suggested mechanisms for any association between total fat intake and breast cancer risk include the increased production of endogenous oestrogens or other hormones, or the regulation of immune function.[394] Established breast cancer risk factors such as body mass index (BMI), family history and reproductive factors may confound any association between total fat intake and breast cancer risk.[394]

WCRF/AICR

The World Cancer Research Fund / American Institute for Cancer Research (WCRF/AICR) judged the evidence for any association between breast cancer risk and total fat intake as 'Limited—no conclusion', for both premenopausal and postmenopausal breast cancer.[11]

Total dietary fat had previously been classified in the 2010 WCRF/AICR Breast Cancer Report as 'Limited—suggestive' for postmenopausal breast cancer risk, but in the updated 2018 report the evidence was judged to be less consistent.[11, 368]

The WCRF Continuous Update Project systematic literature review (CUP Breast SLR) included two randomised dietary intervention trials and 34 cohort studies.[10] Dose–response meta–analyses found no association with breast cancer risk for either total fat intake (RR per 20 g/day 1.02, 95% CI 0.97–1.07; 12 studies) or fat as a percentage of energy (RR per 5% of energy 1.01, 95% CI 0.99–1.02; 13 studies), with low heterogeneity across studies. In four studies that analysed by hormone receptor subtype, total fat was associated with increased risk of ER+ breast cancer and decreased risk of ER– subtype.[10]

Recent evidence

A meta–analysis of prospective cohort studies by Cao et al.[395] did not include any cohort studies additional to those included in the WCRF CUP Breast SLR. The 20 studies with moderate heterogeneity determined an association between the highest versus the lowest category of total fat intake and risk of breast cancer (RR 1.10, 95% CI 1.02–1.19).[395] No association was observed in studies adjusting for risk factors of breast cancer, such as family history of breast cancer, BMI and reproductive factors.[395]

Chlebowski et al.[396] reported on extended follow–up from the Women's Health Initiative Dietary Modification trial. Earlier results from this randomised controlled trial of dietary intervention were included in the WCRF CUP Breast SLR.[10] The trial randomly assigned over 48,000 postmenopausal women to either a low–fat diet that had the goal of reducing fat intake to 20% of energy and increasing fruit, vegetable and grain intake, or to no intervention. After a median of 16.1 years of cumulative follow–up, postmenopausal breast cancer incidence was not found to be associated with the low–fat dietary intervention compared with the usual diet control group (HR 0.97, 95% CI 0.90–1.04).[396]

Table D.52 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.19 Diet—processed meat

Evidence summary

Evidence classification: Suggestive.

There is suggestive evidence of an association between processed meat intake and increased risk of breast cancer. Although earlier evidence was inconsistent, several recent meta–analyses of good–quality studies have reported a positive association between high versus low levels of processed meat consumption and risk of breast cancer. This association is observed for breast cancer overall, and for postmenopausal breast cancer, but possibly not for premenopausal breast cancer.

Background

Processed meat refers to meat that has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation (for example, ham, sausages, corned beef, biltong, beef jerky, canned meat).[397, 398] Processed meats predominantly contain pork or beef but can include other red meats, poultry, offal or meat by–products such as blood.[397, 398]

There is no established mechanism for a link between the consumption of processed meat and breast cancer risk.[398] Processing meat can result in the formation of carcinogenic chemicals, including N–nitroso–compounds (NOC) and polycyclic aromatic hydrocarbons (PAH).[399] Cooking processed meat, particularly at high temperatures can also produce known or suspected carcinogens, including heterocyclic aromatic amines (HAA) and PAH.[399] Other potential mechanisms for a carcinogenic effect relate specifically to red meat (section 4.7.20).

IARC

The International Agency for Research on Cancer[397] (IARC) concluded that consumption of processed meat is '*carcinogenic to humans (Group 1)*', noting sufficient evidence in humans that the consumption of processed meat causes colorectal cancer. The IARC Working Group considered the human epidemiological evidence from 10 cohort studies (including case–control studies nested in the cohorts) and 16 case–control studies. The cohorts had large sample sizes, accurate exposure assessment and adequate adjustment for confounding.[397] Four of the 10 cohort studies reported a statistically significant positive association for the consumption of red and processed meat combined. The case–control studies provided inconsistent evidence. There were insufficient data to evaluate the association separately for premenopausal and postmenopausal breast cancer, or by hormone receptor status.[397]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged the evidence for any association between processed meat and risk of breast cancer as 'Limited—no conclusion', for premenopausal and postmenopausal breast cancer.[11] The WCRF Continuous Update Project systematic literature review[10] (CUP Breast SLR) evaluated 15 studies and a single meta–analysis[400] reporting on the association between processed meat consumption and breast cancer risk. Thirteen studies were included in a dose–response meta–analysis, which reported a null association (summary RR per 50 g/day increment 1.08, 95% CI 0.96–1.22), but with evidence of significant heterogeneity. In subgroup dose–response analyses, no association was observed for premenopausal (four studies) or postmenopausal (eight studies) breast cancer (summary RR 1.02, 95% CI 0.84–1.24 and 1.13, 95% CI 0.99–1.29, respectively). There was substantial overlap in studies included in the IARC[397] evaluation and the WCRF CUP Breast SLR.[10]

Recent evidence

In a meta–analysis of prospective cohort, nested case–control and clinical trial studies, Farvid et al.[401] showed high compared with low intake of processed meat was associated with

overall breast cancer risk (RR 1.09, 95% CI 1.03–1.16; 15 studies) and postmenopausal breast cancer risk (RR 1.10, 95% CI 1.03–1.17; 10 studies), but not with premenopausal breast cancer risk (RR 1.09, 95% CI 0.95–1.25; seven studies). The non–significance of the latter association was considered possibly attributable to lack of statistical power.

Data from the UK Biobank cohort study were combined with data from 10 previous cohort studies, involving 40,257 incidence breast cancers among 1.65 million women in a meta–analysis by Anderson et al.[402] In congruence with the findings by Farvid et al.,[401] processed meat consumption was associated with overall breast cancer (RR 1.06, 95% CI 1.01–1.11) and postmenopausal breast cancer (RR 1.09, 95% CI 1.03–1.15), but not premenopausal (RR 0.99, 95% CI 0.88–1.10) breast cancer.

An earlier meta–analysis by Wu et al.[360] included 14 cohort studies. A summary RR of 1.07 (95% CI 1.01–1.14) for the highest category of processed meat consumption compared with the lowest category of consumption, and a statistically significant dose–response relationship (summary RR per 50 g/day increment 1.09, 95% CI 1.02–1.17), with low heterogeneity; was reported. In subgroup dose–response analyses, no association was observed for premenopausal breast cancer (four studies) or postmenopausal breast cancer (six studies) (summary RR 1.09, 95% CI 0.94–1.26 and summary RR 1.10, 95% CI 0.97–1.26, respectively). All cohort studies included in the dose–response meta–analysis were also evaluated by the IARC[397] Working Group and included in the WCRF CUP Breast SLR.[10]

Diallo et al.[403] reported no association between processed meat consumption and risk of breast cancer overall, or for premenopausal or postmenopausal breast cancer in the French NutriNet–Santé cohort of adult women. Processed meat consumption was relatively low in this study, however, which decreased the ability to detect any association.

Table D.53 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.20 Diet—red meat

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between red meat intake and risk of breast cancer is inconclusive. There is a substantial amount of evidence from a large number of cohort studies and meta–analyses. The findings are inconsistent in effect, and differential in their evidence of a dose–response and/or comparison of lowest versus highest consumption categories.

Background

Red meat refers to all mammalian muscle meat, including, beef, veal, pork, lamb, mutton, horse and goat.[397, 398] There is no established mechanism for a link between the consumption of red meat and breast cancer risk.[398] One hypothesis is a link though the carcinogenic effect of byproducts formed when red meat is cooked at high temperatures—for example, heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons.[360] A second hypothesis

relates to a carcinogenic effect of certain components of red meat—including fat, haem iron and the animal sugar molecule *N*–glycolylneuraminic acid—that individually or collectively may promote inflammation and oxidative stress.[360] Hormone residues in beef cattle may increase risk of oestrogen receptor positive (ER+) tumours.[401, 402]

IARC

The International Agency for Research on Cancer (IARC)[397] concluded that consumption of red meat is '*probably carcinogenic to humans (Group 2A)*'. IARC also concluded that there is '*limited evidence in humans for the carcinogenicity of consumption of red meat*' and that '*positive associations have been observed between consumption of red meat and cancers of the colorectum, pancreas, and prostate*'. A large number of cohort and case–control studies examining the association between consumption of red meat and risk of breast cancer were included in the human epidemiological evidence considered by IARC but breast cancer was not mentioned in the overall evaluation.

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged the evidence for any association between breast cancer risk and red meat consumption as 'Limited—no conclusion', for premenopausal and postmenopausal breast cancer.[11]

The WCRF Continuous Update Project Systematic Literature Review (CUP Breast SLR)[10] evaluated 12 studies (nine cohort and three nested case–control studies) reporting on the association between red meat consumption and breast cancer risk. Six studies were included in a dose–response meta–analysis, which reported a 12% increase in breast cancer risk for each 100 g/day increment of red meat intake (RR 1.12, 95% CI 1.01–1.24). There was no evidence of significant heterogeneity or publication bias. In subgroup dose–response analyses, no association was observed for premenopausal (three studies) or postmenopausal (five studies) breast cancer (RR 1.04, 95% CI 0.84–1.29 and RR 1.11, 95% CI 0.97–1.27 respectively). In a meta–analysis of highest versus lowest consumption categories, no significant associations were observed for breast cancer overall, or for pre– or postmenopausal breast cancer.

Recent evidence

In a meta–analysis of prospective cohort, nested case–control and clinical trial studies, Farvid et al.[401] found red meat consumption was not associated with risk of overall breast cancer (RR for highest versus lowest category of consumption 1.06, 95% CI 0.99–1.14; 13 studies). The studies had moderate inconsistencies. There was similarly no significant association for risk of premenopausal breast cancer (RR 1.07, 95% CI 0.97–1.18; six cohort studies) or postmenopausal breast cancer (RR 1.08, 95% CI 0.99–1.17; nine studies). Further, consumption of red meat was not associated with either the fast or slow NAT2 acetylator genotypes. This finding does not support the hypothesis on the carcinogenic HCAs formed in red meat during cooking in the aetiology of breast cancer, although Farvid et al.[401] noted the limitations of the findings of the included studies.

Data from the UK Biobank cohort study were combined with data from 10 previous cohort studies, involving 40,257 incidence breast cancers among 1.65 million women in a meta–analysis by Anderson et al.[402] In line with the findings reported by Farvid et al.,[401] red meat consumption was not associated with premenopausal (RR 1.02, 95% CI 0.92–1.11) or postmenopausal (RR 1.03, 95% CI 0.97–1.08) breast cancer.

Earlier, Wu et al.[360] examined consumption of 'fresh red meat', and included 12 cohort studies (23,667 women with breast cancer) in a highest versus lowest category analysis. Seven of the 12 cohort studies were also included in the WCRF evaluation.[10] The summary RR was 1.07 (95% CI 0.98–1.17), with evidence of significant heterogeneity but not of publication bias. Eight studies were included in a dose–response meta–analysis, and the summary RR for breast cancer per 120 g/day was 1.13 (95% CI 1.01–1.26) with significant heterogeneity.

Diallo et al.[403] reported on more recent data on risk of breast cancer associated with red meat consumption in a cohort of 45,930 adult French women (the French NutriNet–Santé study). Compared with women in the lowest category of consumption, women in the highest category had an increased risk of breast cancer (HR 1.83, 95% CI 1.33–2.51). The association was observed for both premenopausal (HR 2.04, 95% CI 1.03–4.06) and postmenopausal breast cancer (HR 1.79, 95% CI 1.26–2.55). The significantly raised risk remained in sensitivity analyses excluding breast cancer cases that occurred in the first year of follow–up, and in analyses restricted to invasive breast cancers. There was no evidence of a significant dose–response relationship.

Table D.54 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.21 Environmental tobacco smoke

Evidence summary

Classification: Inconclusive.

The evidence for any association between exposure to environmental tobacco smoke and risk of breast cancer is inconclusive. The evidence is inconsistent. Some case–control studies have reported positive associations between exposure to environmental tobacco smoke and breast cancer risk. However, the more robust evidence from cohort studies does not support an association.

Background

Environmental tobacco smoke (ETS; also referred to as secondhand smoking/smoke, passive smoking/smoke or involuntary smoking/smoke) is the combination of 'mainstream' and 'sidestream' smoke; that is, the smoke exhaled by a smoker and the smoke given off by a burning tobacco product.[333] ETS contains the same carcinogens that are inhaled by smokers, although the concentrations of individual components vary according to how easily the smoke can be dispersed into the environment.[404]

IARC

Although secondhand tobacco smoke is classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen,[333] the evidence for an association between ETS and breast cancer was considered to be inconsistent for breast cancer overall and for premenopausal breast cancer. IARC examined an additional 16 studies (three cohort studies and 12 case–control studies) published since the prior IARC evaluation conducted in 2002.[404] In the previous evaluation, IARC[404] also concluded that the evidence was inconsistent, highlighting that the findings of large cohort studies did not support a causal association.

However, IARC noted that there have been concerns expressed regarding inherent biases in the data, because the information on exposure to secondhand tobacco smoke relies heavily on recall of past exposures outside the home.[333] Concerns were also raised that lifetime exposure to tobacco smoke may have been ignored or underestimated in cohort studies and that these women were included in the referent group, diluting the contrast between exposed and 'non–exposed' women.[333]

Recent evidence

Five systematic reviews with meta–analysis examining the association between ETS and breast cancer risk have been published since 2012. The most recently published review included 47 studies conducted between 1985 and 2015 (15 cohort studies, 30 case–control studies and two nested case–control studies).[405] Definitions of ETS exposure varied markedly across studies. The summary estimate for breast cancer risk associated with ETS (all studies) was 1.15 (95% CI 1.07–1.23), with evidence of significant heterogeneity between studies. However, the increased risk was restricted to case–control studies (RR 1.26, 95% CI 1.13–1.41). There was no evidence of an association for the meta–analysis of 15 prospective studies (RR 1.02, 95% CI 0.97–1.07). Various exposures to ETS were examined including spouse, home, workplace, adulthood, and childhood, and the findings were consistent with the primary analysis of a suggestion of an increased risk only in case–control studies. Seven cohort studies presented effect estimates stratified by menopausal status, showing an increased risk of breast cancer among premenopausal (RR 1.36, 95% CI 1.15–1.60) but not postmenopausal women.

A meta–analysis published in 2015 included 31 studies,[406] most of which were included in the meta–analysis by Lee & Hamling.[405] The analysis reported an increased risk of breast cancer associated with ever having passively smoked among 11 prospective studies (RR 1.07, 95% CI 1.02–1.13; no heterogeneity) and among 20 retrospective studies (RR 1.30, 95% CI 1.10–1.54). The authors noted that the evidence for a moderate increase in risk with passive smoking was more substantial than in previous years.

Two meta–analyses were restricted to Chinese populations. Chen et al.[407] included eight case–control studies published between 2001 and 2011 and reported a summary OR of 1.67 (95% CI 1.27–2.21). Chen et al.[407] included studies published between 2010 and 2013 (two cohort studies and 25 case–control studies) and reported an overall summary estimate associated with passive smoking of 1.60 (95% CI 1.39–1.82). As observed in the other meta–analyses, the increased risk was observed only in case–control and not in cohort studies. This study was the only one to analyse by dose, noting a possible but not statistically significant increased magnitude of effect for heavy versus light passive smoking.

A meta–analysis of 10 prospective studies published in 2013[408] reported a null association; all of these cohorts were included in the meta–analysis by Lee & Hamling.[405]

Table D.55 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.22 Tobacco smoking

Evidence summary

Evidence classification: Suggestive.

The evidence is suggestive of an association between tobacco smoking and risk of breast cancer. The evidence from a large number of cohort studies is generally consistent in showing a positive association between current or former tobacco smoking versus never having smoked tobacco and risk of breast cancer. There is some evidence to indicate that starting smoking at a young age or before first birth is associated with an increased risk of breast cancer. However, the evidence for a dose–response effect is inconsistent.

Background

Tobacco smoking is the practice of burning tobacco and inhaling the smoke (consisting of particle and gaseous elements). Tobacco is prepared by curing the leaves of the tobacco plant, which is of the family Solanaceae and genus Nicotiana. Tobacco smoke is a complex mixture of over 5,300 compounds, including toxicants and known carcinogens. To date, the International Agency for Research on Cancer (IARC) has found sufficient evidence for the carcinogenicity (in either animals or humans) of over 70 components of tobacco smoke. There are other likely carcinogens that are yet to be evaluated, including polycyclic aromatic hydrocarbons (PAHs), tobacco–specific N–nitrosoamines, aromatic amines, aldehydes and certain volatile organic compounds.[404]

The exposure includes inhalation of tobacco smoke through smoking cigarettes, cigars and pipes but excludes chewing tobacco and e–cigarettes. It also excludes environmental exposure to tobacco smoke (section 4.7.21).

There are a number of potential biological mechanisms through which tobacco smoking may influence breast cancer risk. Several fat–soluble compounds found in tobacco smoke have been found to induce mammary tumours in rodents,[409] including PAHs and aromatic amines, and some of these compounds have been found in human breast milk.[410] Conversely, there is evidence that tobacco smoke may exert an antioestrogenic effect,[411] and can alter oestrogen metabolism[412] such that potential carcinogenic effects may be attenuated or offset. Tobacco smoking is also inversely associated with obesity,[413] and may influence risk indirectly through the association between obesity and increased risk of postmenopausal breast cancer (section 4.7.1).

IARC

The International Agency for Research on Cancer[333] concluded that, although there is sufficient evidence in humans of the carcinogenicity of tobacco smoking (Group 1

carcinogen), breast cancer is not on the list of cancers for which there is sufficient evidence for causality. A positive association between tobacco smoking and female breast cancer was acknowledged.

For breast cancer, IARC examined the findings from over 130 epidemiological studies, including seven reports on cohort studies and 12 on case–control studies published since the previous IARC evaluation.[404] Three of the seven cohort studies included in the more recent review reported increased risk of breast cancer associated with current smoking, with risk estimates ranging from 1.12 to 1.32. Former smoking was significantly associated with breast cancer in one cohort study only. In general, longer time since smoking cessation did not result in lower risk estimates. However, longer duration of smoking compared with shorter duration was associated with a significantly higher incidence of breast cancer in five of seven cohort studies. Across all studies considered, the association between age at initiation of smoking and breast cancer risk was inconsistent. Findings were inconsistent for the 19 case–control studies.

Recent evidence

A large pooled analysis of individual data from 14 international cohort studies (36,060 women with breast cancer) participating in the National Cancer Institute (NCI) Cohort Consortium[414] showed a summary hazard ratio for breast cancer associated with current smoking of 1.07 (95% CI 1.04–1.10), with moderate heterogeneity between included studies. The hazard ratio for former smoking was 1.06 (95% CI 1.04–1.09), with low heterogeneity between included studies. There was no evidence of effect modification by menopausal status and after adjusting for alcohol consumption, neither longer duration nor higher intensity of smoking was associated with breast cancer incidence. That is, a dose–response relationship was not observed. Those who started smoking more than 10 years before their first birth had the highest risk of breast cancer compared with those who had never smoked (HR 1.18; 95% CI 1.12–1.24).

A meta–analysis published in 2015 which included 71 studies (27 cohort studies and 44 case–control studies) reported summary RRs for breast cancer associated with ever having smoked versus never having smoked of 1.10 (95% CI 1.09–1.12) for 27 cohort studies (no heterogeneity) and 1.08 (95% CI 1.02–1.14) for case–control studies (significant heterogeneity).[406] Summary RRs for current active smoking were 1.13 (1.09–1.17) and 1.08 (0.97–1.20) for 27 prospective and 22 retrospective studies, respectively.

An earlier meta–analysis published in 2013 included only cohort studies[414] some of which were also included in the pooled analysis by Gaudet et al.[414] Fifteen cohort studies contributed to the meta–analysis. The summary HR for breast cancer associated with current smoking was 1.12 (95% CI 1.08–1.16), and 1.09 (95% CI 1.04–1.15) for former smokers compared with those who had never smoked. Stronger associations were observed in women who started smoking before their first birth.

A single cohort study, the UK–based Generations Study Cohort, published subsequent to the meta–analyses and pooled analysis, included 102,927 women who were followed for an average of 7.7 years.[415] The HR for invasive breast cancer in relation to ever having smoked versus never having smoked was 1.14 (95% CI 1.03–1.25), after adjusting for attained age, alcohol consumption and other potential confounders. The HR was 1.24 (95% CI 1.08–1.43) and 1.23 (95 % CI 1.07–1.41) for starting smoking at ages <17 years and for starting smoking 1–

4 years after menarche, respectively. A significant linear trend of increased magnitude of risk was observed with increasing pack–years of smoking and number of cigarettes smoked per day, but not with duration of smoking; with an effect only observed after 10+ years' duration of smoking versus never having smoked.

Data from the E3N–EPIC prospective cohort study involving 67,634 participants and 497 cases of premenopausal and 3,138 cases of postmenopausal breast cancer showed no association between smoking and risk of breast cancer among current or previous smokers;[44] although the E3N population is not representative of the general population and is prone to a healthy cohort effect.

Table D.56 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.23 Physical activity

Evidence summary

Evidence classification—vigorous physical activity: Probable.

Vigorous physical activity is probably associated with a decreased risk of premenopausal and postmenopausal breast cancer (RR 0.83, 95% CI 0.73–0.95 for premenopausal and RR 0.90, 95% CI 0.85–0.95 for postmenopausal breast cancer for the highest versus lowest levels of vigorous physical activity).[11]

Evidence classification—physical activity (including vigorous, occupational, recreational, walking and household activity) and postmenopausal breast cancer: Probable.

Total physical activity is probably associated with a decreased risk of postmenopausal breast cancer (RR 0.87, 95% CI 0.79–0.96 for the highest versus lowest levels of physical activity).[11]

Evidence classification—physical activity (including occupational, recreational, walking and household activity) and premenopausal breast cancer: Suggestive.

The evidence is suggestive of an association between physical activity and risk of premenopausal breast cancer.

Background

Physical activity is defined as any bodily movement produced by skeletal muscle that requires energy expenditure.[323] Evaluating the association between physical activity and cancer is hampered by differences in exposure definition across studies. Physical activity can be categorised into occupational, recreational or other types of activity, and measured in terms of frequency, duration and intensity. Different types of activity are commonly equated through metabolic equivalents (MET); one MET is considered to represent resting energy expenditure.

The World Health Organization defines moderate–intensity physical activity as any activity with an MET value between 3 and 5.9 and vigorous–intensity physical activity as ≥6 MET.[416] Physically inactive people are those who are performing insufficient amounts of moderate– and vigorous–intensity activity.[417] Sedentary behaviour is not the same as physical inactivity

and is defined as any waking behaviour characterised by an energy expenditure ≤1.5 METs while in a sitting, reclining or lying posture.[417]

There are a number of potential mechanisms through which physical activity may influence breast cancer risk. These include through alterations in levels of circulating sex hormones, metabolic hormones, and adipokines, or via an effect on oxidative stress and immune function.[418] Regular physical activity has been shown to lower the levels of biologically available oestrogen, progesterone, and androgens.[419, 420]

IARC

The International Agency for Research on Cancer[323] concluded there was 'sufficient evidence' for a cancer–protective effect of physical activity for cancers of the breast. The conclusion was based on the findings of 14 cohort and 24 case–control studies published up to 2001.

WCRF/AICR

The World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR)[11] concluded that there was 'Strong–probable' evidence that being physically active (including vigorous activity) decreases the risk of postmenopausal breast cancer. For premenopausal breast cancer, the Working Group concluded there was 'Limited–suggestive' evidence that being physically active decreases risk, but 'Strong–probable' evidence that undertaking vigorous physical activity decreases risk. The conclusions were based on a review of over 40 cohort studies and meta–analyses published up to 2014[10] and a meta–analysis of 31 prospective studies.[421] There was substantial overlap between the cohort studies included in the WCRF Continuous Update Project systematic literature review (CUP Breast SLR)[10] and the meta–analysis by Wu et al.[421]

Due to heterogeneity between studies in the way in which physical activity was reported for some physical activity domains, dose–response meta–analyses were only possible for recreational physical activity (MET–hours/week) and vigorous physical activity (minutes/day). Other analyses included in the WCRF CUP Breast SLR[10] compared the highest versus lowest physical activity categories, noting the comparison categories varied across component studies.

Total physical activity

Seventeen studies contributed to the analysis of total physical activity and breast cancer risk. A significant protective effect was seen for postmenopausal breast cancer risk (highest versus lowest levels of physical activity; RR 0.87, 95% CI 0.79–0.96) but not for premenopausal breast cancer or breast cancer overall.[10]

Vigorous physical activity

Nineteen studies contributed to the dose–response meta–analysis of vigorous physical activity (VPA; per 30 minutes/day) and breast cancer risk. Non–significant inverse associations were reported for breast cancer overall (RR per 30 mins VPA per day 0.95, 95% CI 0.91–1.00; 6 cohort studies), and both premenopausal and postmenopausal breast cancer, with no evidence of significant heterogeneity. An association was observed for an analysis of 'per 10 MET hours/week' of 0.95 (95% CI 0.92–0.99). [10]

In the 'highest' versus 'lowest' meta–analysis, the inverse associations were significant (RR 0.83, 95% CI 0.73–0.95 for premenopausal and 0.90, 95% CI 0.85–0.95 for postmenopausal breast cancer).[10]

Occupational physical activity

Seventeen studies contributed to the analysis of occupational physical activity and breast cancer risk. A significant protective effect was seen for breast cancer overall (highest versus lowest levels of physical activity; RR 0.93, 95% CI 0.87–0.99) and for postmenopausal (RR 0.89, 95% CI 0.83–0.96) but not premenopausal breast cancer. Again, there was no evidence of significant heterogeneity.[10]

Recreational physical activity

Thirty–six studies examined recreational physical activity and breast cancer risk. A significant protective effect was observed for breast cancer overall (RR per 10 MET–hour/week 0.95, 95% CI 0.92–0.99) and for postmenopausal (RR 0.98, 95% CI 0.97–0.99) but not premenopausal breast cancer. There was evidence of significant heterogeneity in the association with breast cancer risk overall, but not with postmenopausal breast cancer risk.[10]

Walking

Eleven studies contributed to the meta–analysis of the association between walking and breast cancer risk. In the highest versus lowest comparison, a significant protective effect was seen for breast cancer risk overall (RR 0.88, 95% CI 0.81–0.96; no significant heterogeneity), but not postmenopausal breast cancer risk. No studies reported on premenopausal breast cancer risk only.[10]

Household activity

Five studies contributed to an examination of household activity and meta–analyses were not conducted. Generally inverse associations between higher levels of household activity and breast cancer risk were reported.[10]

Physical inactivity

Eight studies examined physical inactivity in relation to breast cancer risk. It was associated positively, but not significantly, with breast cancer overall and postmenopausal breast cancer (no studies had reported on premenopausal breast cancer).[10]

Sedentary behaviour

Evidence was too limited for any analyses or conclusions.

Recent evidence

Three meta–analyses[422-424] and one pooled analysis[425] examining the association between physical activity and breast cancer risk published since the WCRF CUP Breast SLR[10] were identified. All but one was restricted to prospective studies,[422] and there was substantial overlap of included studies in these analyses with those of the WCRF/AICR[11] and Wu et al.[421]

Neilson et al.[422] included 36 case–control and 13 cohort studies and reported a significant protective effect of 'moderate–vigorous' physical activity in relation to premenopausal (RR 0.80, 95% CI 0.74–0.87) and postmenopausal (RR 0.79, 95% CI 0.74–0.84) breast cancer risk. Kyu et al.[423] included 35 prospective studies and reported a significant dose–response relationship between any physical activity (measured in MET–minutes/week) and risk of breast cancer overall. Compared with women with insufficient activity levels (less than 600

MET minutes/week), the risk of breast cancer in women with low activity (600–3,999 MET minutes), moderate activity (4,000–7,999 MET minutes), and high activity (≥ 8,000 MET minutes) levels was estimated as 0.967 (95% CI 0.937–0.998), 0.941 (95% CI 0.904–0.981) and 0.863 (95% CI 0.829–0.900), respectively.

A meta–analysis by Pizot et al.[424] included 38 prospective studies and reported similarly protective effects of physical activity with evidence of a dose–response association and no threshold effect. Comparison of highest versus lowest levels of physical activity were associated with a decreased risk of breast cancer (RR 0.88, 95% CI 0.85–0.90). For vigorous physical activity, a meta–analysis of 11 prospective studies showed a significantly decreased risk of breast cancer for more than or equal to 5 hours/week of vigorous physical activity versus no or limited vigorous physical activity (RR 0.82, 95% CI 0.77–0.96). Pizot et al.[424] provided evidence of effect modification by menopausal hormone therapy (MHT) use, such that the protective effect was only significant for women who had never used MHT.

The collaborative analysis by Moore et al.[425] included 10 studies (35,178 breast cancer cases) and reported 'leisure–time' physical activity was protective against breast cancer overall (HR for 90th percentile versus 10th percentile 0.90, 95% CI 0.87–0.93). This association was not modified by either body mass index (BMI) or smoking status.

Recently published data from an occupational cohort study conducted in Sweden (29,524 women) showed a significantly increased risk of breast cancer associated with sedentary occupations (HR 1.20, 95% CI 1.05–1.37). After stratifying by age (<55/≥55 years), the effect was only evident for women younger than 55 years of age.[426]

In another Swedish cohort (31,514 women), Harris et al.[427] provided an estimate of breast cancer risk associated with meeting the WCRF/AICR recommendations for physical activity (that is, to be moderately active for at least 30 minutes/day), reporting a protective effect that did not reach statistical significance (HR 0.86, 95% CI 0.73–1.01).

Table D.57 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.7.24 Shift work disrupting circadian rhythm

Evidence summary

Evidence classification: Suggestive.

The evidence is suggestive of an association between shift work that involves a disruption of circadian rhythm and increased risk of breast cancer. However, the supportive evidence is mostly from case–control studies rather than the more robust cohort studies. There is some evidence of a dose–response relationship. The evidence is stronger for an increased risk of breast cancer either after more than 20 years of night shift work or after shorter periods with many consecutive shifts.[428]

Background

Shift work is defined in the scientific literature as any arrangement of daily working hours other than the standard daylight hours (7/8 am—5/6 pm).[429] Shift work can be permanent

(regular work on one shift only), continuous (all days of the week), discontinuous (interruption on weekends) and can variously include night work.[429] Definitions of the period of night work vary internationally[429] and the variety in assessment of exposure in epidemiological studies has been highlighted.[428]

Proposed mechanisms through which shift work may influence breast cancer risk are related to disruption of the circadian system and associated hormonal effects[429-431] hence studies are focused mainly on night shift work. Melatonin is regarded as a reliable measure of circadian dysregulation.[429] It has been shown to have anti–proliferative effects on human cancer cells cultured in vitro, with some evidence of an anti–oestrogenic effect.[429] There is also evidence from animal models that melatonin inhibits or reduces the induction of DNA damage by free radicals.[429] Despite the experimental evidence from animal studies supporting a role for melatonin in lowering risk of breast cancer, data from clinical trials are lacking.[432]

IARC

The International Agency for Research on Cancer (IARC)[429] concluded that shift work that involves circadian disruption is '*probably carcinogenic to humans (Group 2A carcinogen)*'. IARC indicated that there was '*sufficient evidence in experimental animals for the carcinogenicity of light at night*' and '*limited evidence in humans for the carcinogenicity of shift work that involves night work*'.

The evidence assessed by IARC[429] for risk of breast cancer included eight epidemiological studies: two prospective cohort studies, one national census–based cohort study, three nested case–control studies and two retrospective case–control studies. The definition of shift work varied across studies and, although six of the eight studies showed modestly increased risks, there was considerable heterogeneity regarding dose metrics and dose–response relationships.

In 2014, the IARC advisory group listed shift work (light at night) as a high priority for updating,[433] in light of new evidence from observational studies in humans (including in relation to disease subtypes and according to genetic variation), new mechanistic insights, and the consequent potential implications for public health and regulatory authorities. The advisory group noted that consideration should be given to the evaluation of shift work versus circadian disruption generally and in occupationally exposed groups separately to the general population.

Recent evidence

Since the IARC evaluation,[429] at least six systematic reviews with meta–analyses have examined the association between night shift work and breast cancer risk.[434-439] Two included only prospective studies.[434, 435]

The most recently published review included the latest data from three large cohort studies (the Million Women Study, the EPIC–Oxford cohort and the UK Biobank), combined in a meta–analysis with data from seven independent cohort studies.[434] The meta–analysis of the 10 prospective studies included 4,660 breast cancer cases and the pooled RRs were 0.99 (95% CI 0.95–1.03) for any night shift work, 1.01 (95% CI 0.93–1.10) for 20 or more years, and 1.00 (95% CI 0.87–1.14) for 30 or more years of shift work.[434] The largest contributing study was

the Million Women Study, which reported a null effect that was not modified by sleep patterns or established breast cancer risk factors.

The meta–analysis by Lin et al.[435] included data from 16 prospective studies (four of the largest of these were also included in the review by Travis et al.[434] with a total of more than 10,000 incident breast cancer cases. The pooled RR for night shift work versus daytime work was 1.09 (95% CI 1.02–1.17), with evidence of a dose–response trend. The pooled RR for 5–year incremental risk was 1.03 (95% CI 1.01–1.04), and the highest risk was seen in women with more than 20 years of exposure (pooled RR 1.09, 95% CI 1.01–1.17). The increased risk was apparent for rotating night shift work but not fixed–night shift work.

He et al.[436] reported that their meta–analysis of shift work included 15 studies, although only 14 were listed in the text (four cohort studies, three nested case–control studies and seven case–control studies). Three of the four cohort studies were also included in the review by Lin et al.,[435] and there was substantial overlap in the included case–control studies. The pooled RR for shift work was 1.19 (95% CI 1.08–1.32), with evidence of significant heterogeneity. A positive dose–response relationship was reported among the case–control (pooled RR per 10 years of shift work exposure 1.16, 95% CI 1.06–1.27), but not cohort studies (pooled RR per 10 years of shift work exposure 1.03, 95% CI 0.95–1.11) or overall (pooled RR per 10 years of shift work exposure 1.06, 95% CI 0.98–1.15).

Earlier reviews with meta–analyses included a subset of studies included in the later reviews and all reported increased risks for case–control but not cohort studies.[437-439]

A recent report from the Nurses' Health Study (NHS) I and II cohorts included new data (longer follow–up) regarding the timing of exposure (9,541 breast cancer cases).[440] For women recruited in the 1988 to 2012 cohort, the HR for breast cancer associated with 30 or more years of rotating shift work was 0.95 (95% CI 0.77–1.17) but for women recruited in the 1989–2013 cohort, who were younger at recruitment, the HR for breast cancer associated with 20 or more years of rotating shift work was 2.15 (95% CI 1.23–3.73). A second report from NHS II examined the association between outdoor light at night (LAN) and breast cancer incidence, reporting a significant association among premenopausal but not postmenopausal women (HR for incident premenopausal breast cancer with an interquartile range [IQR] increase in cumulative average outdoor LAN 1.07, 95% CI 1.01–1.14).[441] The association was stronger in women who had worked night shifts (HR per IQR increase in LAN 1.09, 95% CI 1.01–1.18) compared with those who had never worked night shifts (HR 1.03, 95% CI 0.97–1.09).

Table D.58 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8 Medical factors

4.8.1 Aspirin

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between use of aspirin and risk of breast cancer is inconclusive. The evidence is limited by marked heterogeneity between studies in the doses, frequencies and durations of aspirin use, and limited available data to enable dose–response analyses. A large randomised controlled trial (RCT) with a long follow–up period and meta–analyses of cohort studies suggests no association between aspirin use and risk of breast cancer. A small protective effect of aspirin use on risk of breast cancer has mainly been observed in case–control studies.

Background

Aspirin, or acetylsalicylic acid, is one of a group of anti–inflammatory medications called non–steroidal anti–inflammatory drugs (NSAIDs) that are used to treat pain, fever and inflammation. Aspirin has a similar mode of action to other NSAIDs, but additionally inhibits platelet aggregation and is therefore also used in the prevention of cardiovascular disease.[442]

The mechanism through which aspirin might influence cancer risk is unclear, but is thought to be through the inhibition of cyclooxygenase (COX), notably COX–2, enzymes.[443] The expression of COX–2 is increased in breast cancer, and is known to play a role in carcinogenesis, apoptosis, and angiogenesis.[444] Anti–inflammatory agents with selective activity or non–selective activity such as aspirin against COX–2 are thought to have potential for the chemoprevention of some cancers.[445] Aspirin has been recommended in the primary prevention of colorectal cancer under certain circumstances.[446]

Recent evidence

Regular use of low dose aspirin and risk of breast cancer was examined in a large randomised controlled trial (RCT), the Women's Health Study. Aspirin use of 100 mg every other day for 10 years was compared with placebo in 39,876 female health professionals aged 45 years or older.[447] After 18 years of follow–up, aspirin use was not associated with risk of breast cancer (HR 0.98, 95% CI 0.90–1.07).

In addition to the RCT, nine meta–analyses published since 2008 that reported on the association between aspirin use and breast cancer risk were identified. There was marked heterogeneity in the doses, frequencies and durations of aspirin use examined across the studies. Evidence of publication bias was noted in at least one meta–analysis.[448] These meta–analyses were generally based on observational studies (case–control and cohort studies) and, for one meta–analysis,[449] some small RCTs. There was varied but often considerable overlap in the included studies.

Five of eight meta–analyses found a small protective effect of aspirin use (various exposures mainly including 'users versus non–users') when all study types were included or among only case–control studies.[449-453] Three of the four meta–analyses that analysed the data according to study type, however, did not find an association between aspirin use and risk of breast cancer for cohort studies.[444, 449, 452] The most recently published meta–analysis, which included only large prospective cohort studies (13 studies), also reported a null association between overall use of aspirin and risk of breast cancer (pooled RR 0.94, 95% CI 0.87–1.01) with significant heterogeneity among the included studies.[454]

The data on duration of aspirin use and risk of breast cancer are limited. A marginally significant dose–response relationship was reported in the meta–analysis by Zhong et al.[451] and Lu et al.[454] noted a potential dose–response relationship for frequency and duration of aspirin use and risk of breast cancer, but could not perform a dose–response analysis due to the data limitations. Duration of aspirin use was not associated with risk of breast cancer in the meta–analyses by Bosetti et al.[444] or Zhao et al.[452]

After 10 years of follow–up in the California Teachers Study, current use of three or more tablets per week of low–dose aspirin (81 mg) compared with women not taking any NSAIDs was marginally protective against breast cancer (HRR 0.84, 95% CI 0.72–0.98). The protective effect was limited to breast cancer of the hormone receptor positive/human epidermal growth factor receptor negative subtype. There was no association between current use of regular dose aspirin (325 mg) at three tablets per week and breast cancer risk overall.[455]

Bardia et al.[456] reported on follow–up data[x] from the Iowa Women's Health Study. They showed aspirin use was associated with a lower incidence of breast cancer for women with a family history of the disease (HR for 6+ per week versus never use 0.62, 95% CI 0.41–0.93) and a personal history of benign breast disease (HR 0.69, 95% CI 0.50–0.95) among postmenopausal women aged 55–69 years. Inverse associations were also observed in low risk (but not high risk) subgroups for age at menarche, age at menopause, parity/age at first live birth or body mass index.

Table D.59 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8.2 Cardiac glycosides

Evidence summary

Evidence classification: Suggestive.

The evidence is suggestive of an association between use of cardiac glycosides from the plant genus *digitalis*, predominantly digoxin, and increased risk of breast cancer. There is consistent evidence from cohort and case–control studies of a positive association; however, there is a lack of adjustment for confounders in many of the studies.

[x] Earlier data were reported by Bardia et al. (2011); these data were included in the meta–analysis by Lu et al. (2017).

Background

Digoxin belongs to the family of cardiac glycosides used in the treatment of congestive heart failure and heart arrhythmias. It is an extract of the plant foxglove (*Digitalis lanata*), and there are three other isolated compounds in the market place: digitoxin, β–acetyldigoxin and methyldigoxin.[305] Digoxin represents at least 90% of the world market for digitalis glycosides but the literature can be non–specific about which of the four glycosides is the exposure in studies.[305]

The chemical structure of digoxin is similar to that of oestradiol and there has been concern that digoxin may promote the development of breast cancer through an oestrogen–receptor mediated mechanism.419 Digoxin use is primarily in elderly populations, and thus these concerns are most relevant when considering postmenopausal breast cancer risk.

IARC

The International Agency for Research on Cancer (IARC) concluded that digoxin is '*possibly carcinogenic to humans (Group 2B)*'.[457] As part of this overall evaluation, IARC noted the compelling nature of the human epidemiological data associating increased risk of cancer of the breast with use of digoxin.[457] IARC cited evidence from three cohort studies and four case–control studies in the narrative; however, a lack of other supportive evidence was noted.

Recent evidence

Two meta–analyses published subsequent to the IARC monograph (Karasneh et al.[458]; Osman et al.[459]) indicated an increased risk of breast cancer among digoxin users. An additional meta–analysis reported a significantly increased risk of the same magnitude for 'digitalis use'.[460] Five of the same cohort studies were included in each of the meta–analyses, three of which had been considered by IARC[457], and, overall, eight studies were included in all three meta–analyses.

The summary estimates for these three meta–analyses were similar: users compared with non–users of cardiac glycosides had 1.33–1.35 times the risk of breast cancer overall, with no evidence of significant heterogeneity among the included studies. The summary estimate for cohort studies was generally higher than for case–control studies. The findings were limited by lack of adjustment for potential confounders, such as body mass index (BMI), in several of the included studies.

The meta–analysis by Osman et al.[459] examined other cardiac glycoside exposure, as well as digitalis and digoxin separately. The summary HRs for breast cancer overall were of similar magnitude for all three exposures—approximately 1.30. A more recently published cohort study of 4,161 heart failure patients in Taiwan reported a similarly increased magnitude of risk of breast cancer among digoxin users compared with non–users (HR 1.30, 95% CI 1.05–1.62).[461]

Two of the three meta–analyses reported on the association between digoxin and breast cancer risk according to oestrogen receptor (ER) status (Karasneh et al.[458]; Osman et al.[459]), using data from two cohort studies (Ahern et al.[462]; Biggar et al.[463]). The analyses reported that digoxin use was significantly associated with ER+ (summary RR 1.33, 95% CI 1.25–1.42) but not ER– breast cancer (summary RR 0.98, 95% CI 0.61–1.58).

Table D.60 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8.3 HPV

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between infection with the human papillomavirus (HPV) and risk of breast cancer is inconclusive. The quality of the evidence is too poor to determine any association. There is a lack of biological plausibility for a causal association.

Background

HPVs are small, non–enveloped, double–stranded DNA viruses that infect mucosal and cutaneous epithelia in humans and induce cellular proliferation.[464] More than 100 types of HPV have been identified, and more than half of them infect the genital tract.[464] They can be classified into two main types: low–risk HPVs that can cause skin warts, and high–risk HPVs that can cause cancer (cervical, anal and head and neck cancers).[333]

The immune system clears most HPV infections within one to two years.[464] Persistence, which is 'long duration of detectable HPV infection', is uncommon compared with clearance. However persistence of infection with certain high–risk HPV types can lead to changes in cell functions that normally prevent cell proliferation and lead to carcinogenesis.[464] HPV DNA load may be an important determinant of pathogenicity. The mode of transmission of HPV to the breast is not known, and any mechanism by which HPV may cause breast cancer is unclear.[465] There are compelling arguments against an aetiologic link between HPV and breast cancer. Breast cancer incidence is not higher in immunosuppressed women, while cervical and head and neck cancers are raised two to six–fold compared with immunocompetent women[466] and HPV viral load in breast cancer is very low.[467]

IARC

The International Agency for Research on Cancer (IARC)[464] concluded that there was '*inadequate evidence in humans for the carcinogenicity of HPV in the breast*'. The IARC Working Group based its evaluation on a review of studies conducted up to 2005, reporting the prevalence of HPV, as detected by polymerase chain reaction (PCR), in breast cancer biopsies. Only one of the studies also reported on the presence of HPV in biopsies of normal breast tissue. In 2012, the IARC [333] reviewed a further four studies conducted up to 2009 that examined the prevalence of HPV in breast cancer tissue. The working group concluded there was contradictory evidence for the role of HPV in breast cancer.

Recent evidence

The most recently published systematic review included a meta–analysis of 22 case–control studies reporting on the association between HPV DNA–positivity in tissues and breast cancer risk.[468] The study reported a summary OR of 4.02 (95% CI 2.42–6.68), with evidence of

significant heterogeneity. No information on the method used to detect HPV DNA in the individual studies was included. In analyses according to HPV subtype (HPV 16, HPV 33, HPV 18), the highest summary OR was observed for HPV 16 (summary OR 5.67, 95% CI 2.21–14.52), but significantly raised risks were reported for all three HPV types. The funnel plot showed asymmetry (that is, fewer than expected small studies with negative findings); however, the test for publication bias was not significant.

Zhou et al.[469] included a subset of 16 case–control studies that were included in the more recent review by Bae & Kim.[468] Zhou et al.[469] reported a summary OR of 3.24 (95% CI 1.59–6.57), again with evidence of significant heterogeneity. The magnitude of the summary estimate varied according to method of HPV DNA detection (broad–spectrum primers, type–specific primers and combined primers) and tissue type (fresh/fixed).

A smaller meta–analysis of nine studies, of which eight were included in the other two meta–analyses, reported a higher summary OR of 5.90 (95% CI 3.26–10.7), with no evidence of significant heterogeneity.[470] A meta–analysis by Li et al.[471] included a subset of nine case–control studies included in the other three meta–analyses and reported a summary OR of 3.63 (95% CI 1.42–9.27).

Of the studies included in the meta–analyses, there was notable heterogeneity in HPV detection and identification techniques. Before 2000, only type–specific PCR primers were used to detect HPV in breast tissue; after 2000 the use of broad spectrum PCR and broad–spectrum primers became more common.[471] Many PCR–based studies do not meet the molecular criteria for verifying causality.[472] Of note, the more powerful next generation sequencing technologies do not support an aetiologic link between HPV infection and breast cancer despite demonstrated sensitivity and specificity in detecting viruses in known viral–caused cancers.[472]

Two recently published studies examined the prevalence of high–risk HPV types in breast tissue.[467, 473] Lawson et al.[465] reported on a retrospective cohort of 41 Australian women who had benign breast biopsies and later developed breast cancer, compared with 21 women with normal breast specimens. PCR was used for HPV detection in the samples. The prevalence of high–risk HPV types was significantly higher in benign breast biopsies (55%) and breast cancer biopsies (66%), compared with normal breast biopsies (29%). The authors reported the prevalence of high–risk HPV types in The Cancer Genome Atlas (TCGA) Breast Cancer Cohort (855 breast cancers) was 2.3%. A second study examined the prevalence of high–risk HPV types in 110 fresh breast tissue samples using PCR and Sanger sequencing. This study reported a prevalence of 42%, of which viral activity was confirmed in only five of 26 invasive breast cancer samples.[473] A low viral load of HPV in the breast cancer samples was reported.

Table D.61 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8.4 Hysterectomy

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between having had a hysterectomy and risk of breast cancer is inconclusive. There is inconsistent evidence from three large cohort studies. Two of these studies showed no association between hysterectomy without bilateral oophorectomy (hysterectomy alone) and risk of breast cancer. One study showed a decreased risk of breast cancer associated with hysterectomy alone.

Background

Hysterectomy is surgery to remove the uterus. Most hysterectomies are performed for non–cancerous conditions such as uterine fibroids, menstrual disorders and endometriosis.[474] Removal of one or both ovaries and the fallopian tubes (salpingo–oophrectomy) may also be undertaken at the time of hysterectomy. This evidence summary considers hysterectomy alone, that is, with conservation of at least one ovary.

The potential mechanism for any association between hysterectomy and risk of breast cancer may involve a reduction in ovarian blood supply following hysterectomy, resulting in compromised ovarian function and decreased levels of sex steroid hormones.[474, 475]

Recent evidence

A prospective cohort study by Altman et al.[474] investigated hysterectomy alone and cancer risk using nationwide health–care registers in Sweden between 1973 and 2009. The cohort included data from 111,595 women who had undergone hysterectomy and 5,379,843 women without a hysterectomy, with over 120 million person–years follow–up.[474] There was no association with risk of breast cancer after adjustment for age, calendar year, parity and education level (HR 0.97, 95% CI 0.93–1.01). Adjustment was not made for other potential confounders, including hormone therapy, alcohol or body mass index (BMI).[474]

Approximately 68,065 women aged 45–75 years from the Multiethnic Cohort study in the United States (recruited in Hawaii and Los Angeles) were followed for an average (median) of 7.7 years to examine any association between hysterectomy alone and risk of breast cancer.[476] Hysterectomy was not associated with breast cancer risk, compared with no hysterectomy among all women (RR 0.98, 95% CI 0.86–1.11), after multivariate adjustment, including age, BMI, family history, alcohol, reproductive factors and menopausal hormone therapy. Age at hysterectomy was not associated with risk of breast cancer. Hysterectomy status was self–reported, which could have resulted in misclassification of exposure.

The Gaudet et al.[475] study of the effect of hysterectomy alone on breast cancer risk included 66,802 postmenopausal women from the Cancer Prevention Study–II Nutrition Cohort in the United States. After a median follow–up period of 13.9 years, hysterectomy was associated with decreased risk of breast cancer overall (RR 0.86, 95% CI 0.76–0.96), compared with no surgery, after multivariate adjustment for age, reproductive factors, BMI, family history of breast cancer, hormone therapy and other factors.[475] Surgery was self–reported through regular follow–up questionnaires, and the authors acknowledged possible misclassification of bilateral salpingo–oophorectomy, but considered it would have minimal influence on the findings.

Table D.62 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8.5 Pregnancy termination

Evidence summary

Evidence classification: Evidence of no association.

There is evidence of no association between having had a pregnancy termination and risk of breast cancer. A meta–analysis and a pooled analysis of large numbers of cohort studies and record–linkage studies, which are not prone to measurement bias, have shown that pregnancies that end as a spontaneous or induced abortion are not associated with risk of breast cancer.

Background

Pregnancy termination (or induced abortion) is a medical procedure performed to end a pregnancy. A spontaneous miscarriage (or spontaneous abortion) is the loss of a baby before 20 weeks gestation.

Concern about a possible link between pregnancy termination or spontaneous miscarriage and breast cancer has been raised because of the interruption in the normal cycle of hormones that occurs during a full term pregnancy. The main potential mechanism postulated to link pregnancy termination or spontaneous miscarriage and breast cancer is that women who experience these events are exposed to high hormone levels in early normal pregnancy, but then do not experience the terminal differentiation that occurs in late pregnancy.[477] Breast epithelial cells undergo changes in late pregnancy in preparation for lactation, and the more highly differentiated cells are thought to be less vulnerable to DNA–damage.[12, 225]

Recent evidence

A meta–analysis of prospective studies published up to April 2014 reported on the association between abortion (spontaneous and induced) and breast cancer risk.[478] The meta–analysis included 15 prospective studies involving 31,816 cases, and included some of the studies included in the pooled analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC)[479] (see below), together with more recent data from several large cohort studies. These included the Nurses' Health Study,[480] the European Prospective Investigation into Cancer and Nutrition (EPIC),[481] the California Teachers' Study[477] and a large Scottish record linkage study.[482] The pooled RR for breast cancer risk from associated with induced abortion was 1.00 (95% CI 0.94–1.05; 14 studies) and with spontaneous miscarriage was 1.02 (95% CI 0.95–1.09; 12 studies). Significant heterogeneity was evident for both analyses. No associations were found in subgroup analyses: among nulliparous women, women exposed before and after a first full term pregnancy, women with one or two or more abortions, and women who experienced a first abortion after the age of 30 years.

The CGHFBC conducted a pooled analysis of 53 studies undertaken in 16 countries (83,000 women with breast cancer) and reported no significant overall increase in breast cancer risk associated with having had one or more pregnancies that ended either as a spontaneous miscarriage or as an induced abortion.[479] For the studies with prospective reporting of exposure (44,000 cases), the pooled RRs were 0.98 (95% CI 0.92–1.04; 12 studies) for

spontaneous miscarriage and 0.93 (95% CI 0.89–0.96; 13 studies) for induced abortion. For studies with retrospective reporting of exposure, the pooled RRs were 0.98 (SE 0.018; 40 studies) for spontaneous miscarriage and 1.11 (SE 0.025; 39 studies) for induced abortion. The study authors noted the following about the retrospective risk for induced abortion: '*collectively, the studies of breast cancer with retrospective recording of induced abortion yielded misleading results, possibly because women who had developed breast cancer were, on average, more likely than other women to disclose previous induced abortions*'.

Table D.63 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8.6 Previous cancer other than breast cancer

Evidence summary

Evidence classification: Suggestive.

The evidence is suggestive of an association between having had a previous cancer, other than breast cancer, and risk of breast cancer.

The cancers that have been most studied in relation to previous diagnosis or history and subsequent risk of breast cancer in the same woman are Hodgkin lymphoma (HL), non–Hodgkin lymphoma (NHL) and thyroid cancer. There is some evidence a personal history of HL and thyroid cancer may be associated with an increased risk of breast cancer independent of radiation treatment effects. Although the two identified cohort studies did not show a significant association between a previous diagnosis of ovarian cancer and risk of breast cancer, this may have been due to sample size issues; risks of ovarian cancer and breast cancer are increased if a woman carries a *BRCA1* or *BRCA2* mutation. There have been too few studies to make a classification regarding an association between previous history of other cancers and risk of breast cancer, although the various identified studies are indicative of an association across a range of cancers.

Background

An increased risk of breast cancer among women with a previous history of another cancer may be due to genetic susceptibility (including hereditary cancer syndromes—see section 4.3), cancer treatment–related effects or shared risk factors, depending on the site of the first cancer.[483, 484] Increased surveillance/screening of cancer survivors may also play a role.[485]

Recent evidence

Any other cancer diagnosis

A retrospective cohort study conducted in Queensland, Australia, reported women with a personal history of cancer other than breast had a significantly increased risk of developing breast cancer (SIR 1.32, 95% CI 1.27–1.37) compared with the incidence of breast cancer in the general population.[210]

Colorectal cancer

Four cohort studies that examined the association between a history of colorectal cancer and subsequent breast cancer reported inconsistent findings. Two studies reported significantly increased risks of breast cancer compared with the general population (SIR 1.21 for both studies).[210, 486] The remaining two studies reported a null association[487] and a non–significantly raised risk (SIR 1.22, 95% CI 0.97–1.47).[488] Two of the studies examined the risk separately for colon and rectal cancer, and the SIRs did not differ materially across sites.[486, 488]

Gastric cancer

Only two studies were identified that examined the association between history of gastric cancer and risk of breast cancer. Both studies were population–based and reported null findings. One was conducted in Taiwan[489] and the other in northern Portugal.[490]

Hodgkin lymphoma

A large meta–analysis and five cohort studies have examined the association between a history of Hodgkin lymphoma (HL) and breast cancer risk and shown a consistent positive association. A meta–analysis of 24 cohort studies (prospective, retrospective and linkage studies) reported a pooled RR of 8.23 (95% CI 5.43–12.47) with an absolute excess rate of 22.9/10,000 person–years.[491] The magnitude of risk varied across studies; however, 23 of 24 studies reported an increased risk. Importantly, the level of risk varied according to treatment therapy, with increased risk observed only for women treated with radiation therapy (with or without chemotherapy). This result suggested radiation therapy for HL accounts for the increased risk of breast cancer (section 4.10.6).

Radiation therapy's contribution to the increased risk of breast cancer among women with a previous diagnosis of HL is mixed in more recent cohort studies. Two studies reported estimates according to whether or not HL was treated with radiation therapy.[492, 493] Consistent with the meta–analysis, both reported higher risks for the radiation therapy group. Risk of breast cancer was increased in the non–radiation treated group in one study (SIR 1.4, 95% CI 1.1–1.8)[493] but not the other (SIR 1.0, 95% CI 0.3–2.2).[492]

Five cohort studies not included in the Ibrahim et al.[491] meta–analysis reported SIRs ranging from 1.39 to 17.2.[492-496] Dörffel et al.[495] and Schaapveld et al.[492] reported absolute risks of 14.9 and 54.3 per 10,000 person years, respectively.

The Ibrahim et al.[491] meta–analysis reported breast cancer risk was inversely related to age of diagnosis of HL, with the highest rate observed in young patients (<15 years old; RR 68.7, 95% CI 28.1–168.1). Risk was not significantly increased in women aged over 40 years.[491] Three cohort studies also reported inverse associations between age at HL diagnosis and risk of subsequent breast cancer.[493, 494, 496]

Non–Hodgkin lymphoma

A meta–analysis of 12 cohort studies examining the association between a history of non-Hodgkin lymphoma (NHL) and risk of subsequent breast cancer showed no association (1.10, 95% CI 0.88–1.37).[497] Two studies not included in the meta–analysis reported an increased risk of breast cancer among women with a NHL diagnosis, compared with the general population: SIRs of 1.13 (95% CI 1.05–1.22)[494] and 2.27 (95% CI 1.97–2.61).[496] The study by Baras et al.,[494] involving a large retrospective cohort of German women, reported a bi-directional relationship between NHL and breast cancer. That is, women diagnosed with breast cancer were at increased risk of subsequent NHL, suggesting the existence of shared risk factors.

Lymphohaematopoietic neoplasm

One Australian study reported a significantly raised risk of breast cancer following a diagnosis of lymphoid leukaemia, myeloid leukaemia and plasma cell tumours, compared with the general population. An approximate twofold increased risk for all three types of first primary cancer was observed (SIR 1.89, 95% CI 1.52–2.33; SIR 2.24, 95% CI 1.53–3.16; SIR 2.18, 95% CI 1.68–2.79, respectively).[496]

Oesophageal cancer

Two cohort studies showed no association with risk of breast cancer, compared with the general population.[498, 499] Chuang et al.[499] examined the histological subtypes of oesophageal cancer, adenocarcinoma and squamous cell carcinoma, separately. There was no statistical difference in the SIRs for breast cancer associated with the two histological subtypes.

Ovarian cancer

Two cohort studies observed non–significantly increased breast cancer incidence following a diagnosis of ovarian cancer, compared with the general population.[488, 500]

Other prior cancer types

A retrospective cohort study involving 355,966 cancer survivors in Japan reported SIRs for breast cancer subsequent to a first cancer of the stomach, liver, lung, uterus, kidney/urinary tract/bladder and blood. Compared with incidence in the general population, the study observed a significantly increased risk of breast cancer for women with a previous diagnosis of lung (SIR 1.66, 95% CI 1.10–2.21), stomach (SIR 1.63, 95% CI 1.34–1.91) and uterine cancers (SIR 1.40, 95% CI 1.10–1.71).[488]

Skin cancer

Two studies reported significantly increased risks of breast cancer, compared with the general population, among women with a history of melanoma (SIRs 1.07 and 1.19, respectively).[210, 501] A third study found no association.[502] Levi et al.[502] also found no association with risk of breast cancer following a diagnosis of keratinocyte skin cancer (basal cell carcinoma and squamous cell carcinoma).

Table D.67 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

Thyroid cancer

Five cohort studies reported on the association between past history of thyroid cancer and subsequent breast cancer, all reporting positive associations.[488, 503-506] Women who have had a thyroid cancer diagnosis have an increased risk of developing breast cancer, compared with the general population: SIRs ranging from 1.13 (95% CI 1.06–1.20)[505] to 1.97 (95% CI 1.34–2.61).[488]

Four of the studies were conducted in populations of Asian women,[488, 503, 504, 506] and the fifth study was a large record linkage study conducted in the United States,[505] hence it is uncertain whether the findings can be generalised to the Australian population. The association did not appear to vary materially by age at diagnosis of thyroid cancer,[506] year of diagnosis (between 1973 and 2008),[505] histologic subtype of thyroid cancer[505] or by treatment with radioisotopes/external beam radiation therapy.[503, 505] Lu et al.[506] reported the

increased risk was significant only up to five years after thyroid cancer diagnosis (SIR 4.44, 95% CI 3.24–5.95), but not beyond a five–year latency period.

Table D.64 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8.7 Silicone breast implants

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between silicone breast implants and risk of breast cancer is inconclusive.

Two meta–analyses have indicated that silicone–filled breast implants used for cosmetic augmentation are associated with decreased breast cancer risk, although the quality of these studies was limited by inadequate adjustment for confounders and a limited description of the types of implants employed.[507, 508]

Breast implants with a textured or polyurethane, rather than smooth surface, are associated with the rare lymphoma—anaplastic large cell lymphoma (ALCL)—which is likely a causal association.[509, 510] The risk of ALCL for women with breast implants has been estimated at between 1 in 1,000 and 1 in 10,000.[510]

Background

Breast implantation may be undertaken for cosmetic augmentation, reconstruction after breast cancer surgery, or for prophylactic mastectomy. There are different types of breast implants with different fillings (for example, silicone gel or saline), different surfaces or shell types (for example, textured, smooth, or polyurethane–coated), and different shapes (round or anatomical).[507]

Potential mechanisms underlying associations between breast implants and breast cancer include enhancement of the immune system due to the implant or the surgery, compression of glandular tissue—resulting in a decreased blood supply that may reduce cell proliferation, and a metabolic rate reduction resulting from a lower temperature of the breast tissue.[507]

IARC

Evaluation of the evidence by the International Agency for Research on Cancer (IARC)[511] indicated that there is a '*lack of evidence for carcinogenicity of silicone breast implants for breast cancer*'. The overall evaluation was that silicone breast implants are '*not classifiable as to their carcinogenicity in humans* (Group 3)'.

Recent evidence

Two meta–analyses have been undertaken of associations between breast implants and breast cancer. Both were restricted to women who received implants for cosmetic reasons.

The studies were limited by inadequate adjustment for possible confounders, such as raised body mass index (BMI), excess body weight/obesity, reproductive factors, alcohol consumption, and family history. In addition, women who undergo breast implantation may have other underlying differences such as socioeconomic factors, breast size and lifestyle factors, that may confound statistical associations with breast cancer.[507]

A meta–analysis by Balk et al.[507] included 11 longitudinal studies of primary breast cancer in women who had breast implants for augmentation. In each od the included studies, women with implants were at decreased risk of breast cancer. In the meta–analysis of studies with direct comparisons, implants were associated with decreased risk of breast cancer of 0.63 (95% CI 0.54–0.73; six studies with no heterogeneity). Also, in meta–analysis of studies reporting SIRs, implants were associated with a reduced risk (SIR) of 0.76 (95% CI 0.64–0.91; seven studies with high heterogeneity). Most studies did not adjust adequately for possible confounders. Other limitations included limited descriptions of: the type of implant (for example, silicone gel, double lumen, or saline); generation of the implant, manufacturer or brand; shell type (for example, textured, smooth, or polyurethane–coated); and shape (round or anatomical).[507]

A meta–analysis by Noels et al.[508] also reported a decreased risk of breast cancer associated with cosmetic breast implants. This meta–analysis included seven cohort studies and there was major overlap in the included studies with the meta–analysis by Balk et al.[507] Risk estimates for use of cosmetic breast implants and risk of breast cancer were: RR 0.63 (95% CI 0.56–0.71) among four cohort studies with no heterogeneity; and, SIR 0.69 (95% CI 0.56–0.85) among six cohort studies, with high heterogeneity.

Breast implants and anaplastic large cell lymphoma

An association of breast implants with increased risk of the rare lymphoma—anaplastic large cell lymphoma (ALCL)—has been observed across a number of studies and the evidence supports the likelihood of a causal association.[510] Breast implant–associated ALCL (BIA–ALCL)is a rare form of T–cell derived lymphoma (a cancer of the immune system) that can develop near breast implants.[509, 512, 513] It usually involves swelling of the breast due to accumulation of fluid or effusion near the implant. BIA–ALCL is not breast cancer. A potential mechanism for its development is a chronic bacterial biofilm infection on textured implants, which can increase lymphocyte activation and T–cell transformation.[509, 510]

BIA–ALCL has occurred in women with implants used for cosmetic reasons and for reconstruction after surgery. It typically presents 3–14 years after implant surgery.[509, 512] Cases of BIA–ALCL have been associated with breast implants that have a textured or polyurethane surface but not with implants with smooth surfaces.[509, 513, 514] The risk of ALCL for women with breast implants has been estimated at between 1 in 1,000 and 1 in 10,000.[510]

A recent case–control study from the Netherlands by de Boer et al.[514] reported 43 patients with BIA–ALCL, of whom 32 had ipsilateral breast implants. Breast implants were associated with increased cumulative risks of BIA–ALCL of 29 per million at age 50 years and 82 per million at age 70 years.[514]

The Australian Therapeutic Goods Administration is undertaking ongoing monitoring of the association between breast implants and ALCL and has provided expert advisory panel advice.[510] Up to May 2018, 72 cases of ALCL were reported in Australia.[510] A paper by Hopper et al.[509] indicated numbers of reported cases of ALCL in Australia to date and the role of the Australian Breast Device Registry in prospectively monitoring breast devices.

Table D.65 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8.8 Stress

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between stress and risk of breast cancer is inconclusive. The evidence from meta–analyses which included both case–control studies and cohort studies is inconsistent. When cohort studies are considered, adjusted for important potential confounding factors, there is no association between various exposures of psychological stress and risk of breast cancer. Case–control studies of stress have inherent limitations since studies that ask women about stress after cancer has been diagnosed, in other words retrospectively, are likely to be affected by recall bias. Other limitations to interpreting the available evidence include difficulty in quantifying exposures to psychological stress, and heterogeneity in exposure definition across studies.

Background

In the medical context, stress is defined as a state of mental or emotional strain or tension resulting from adverse or demanding circumstances. The body responds to stress by releasing stress hormones (such as epinephrine and norepinephrine) that increase blood pressure, heart rate and blood sugar levels. Stress can be caused by internal factors (for example, illness, psychological affect or personality type) and external factors (for example, bereavement, job loss or strain, and relationship breakdown).

Several biological pathways via which stress might influence breast cancer risk have been proposed, including an effect on oestrogen synthesis[515] and through alterations in immune function.[516] Stress may influence breast cancer risk indirectly through associations with other lifestyle factors that are known risk factors, including alcohol consumption. A person who experiences stress because of a cancer diagnosis in a relative may be at higher risk of cancer due to inherited genetic risk factors rather than as a result of the stress associated with the family member's diagnosis. In assessing the evidence for an association, therefore, the potentially confounding influence of other lifestyle factors as well as family history of disease must be considered.

Recent evidence

Four systematic reviews with meta–analyses have reported on the association between stress and breast cancer risk, and three cohort studies provide additional evidence. Exposure definitions varied across studies. In this report, stressful exposures reported in the literature have been classified into four broad areas: perceived stress/stressful life events; death of a partner/family member/friend; job strain/loss; and divorce/separation.

Perceived stress/stressful life events

Three systematic reviews with meta–analyses and three more recently published cohort studies have reported on perceived stress/stressful life events and risk of breast cancer. Lin et al.[517] examined stress related to 'striking life events', where a stress disorder was classified as an 'acute anxiety disorder'. This in turn was characterised by 'adverse anguishing experiences and physiological responses that develop after exposure to stressful life events'. The meta–analysis included four case–control and three prospective studies. The summary estimate for risk of breast cancer associated with 'striking life events' was OR 1.51 (95% CI 1.15–1.97) with evidence of significant heterogeneity between studies. Summary estimates were not provided according to study design, however individual study risk estimates ranged from 0.91 to 7.08 for case–control studies, and from 1.07 to 2.1 for prospective studies; factors adjusted for in individual studies were not reported. Six studies also reported on 'severe striking life events' and breast cancer risk; the summary estimate was OR 2.07 (95% CI 1.06–4.03) with significant heterogeneity among included studies.

An earlier meta–analysis published in 2009 examined 'high intensity stress' in relation to breast cancer risk.[518] The two cohort studies and three of the six case–control studies were also included in the review by Lin et al.[517] The summary estimate of breast cancer risk associated with 'high intensity stress' was RR 1.73 (95% CI 0.98–3.05) in six studies with no significant heterogeneity. No information about adjustment of factors in individual studies was reported. Similarly, a meta–analysis of 'stressful life events' and risk of breast cancer[519] reported a summary OR 1.77 (95 % CI 1.31–2.40) from 11 studies, including one prospective study also included in the more recent meta–analyses and four independent case–control studies.

Three cohort studies published subsequent to the inclusion dates of the meta–analyses have reported on the association between 'perceived stress' and breast cancer risk. Schoemaker et al.[520] and Sawada et al.[521]—after adjusting for known breast cancer risk factors including family history, alcohol consumption and body mass index—did not find any associations between 'perceived stress' and breast cancer risk. Similarly, the association between perceived stress over the previous 10 years and risk of breast cancer was null in the European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk cohort of 11,467 women in the United Kingdom, after adjustment for known risk factors.[522]

Death of a partner/family member/friend

The meta–analysis by Santos et al.[518] found no association between 'widowhood' and breast cancer risk with three studies (one cohort, two case–control studies) contributing to the summary estimate. The earlier meta–analysis by Duijts et al.[519] reported significantly increased risks of breast cancer associated with both 'death of a spouse' (four studies; no heterogeneity and no publication bias) and 'death of a relative or friend' (11 studies) of 37% (OR 1.37, 95% CI 1.10–1.71) and 35% (OR 1.35, 95% CI 1.09–1.68), respectively. Two cohort studies reported no association between loss events either collectively (deaths of first degree relatives)[522] or separately defined by type of loss (husband, close relative, close friend).[520] For both cohort studies, RRs were adjusted for important potential confounding factors.

Divorce/separation

Two of the systematic reviews[518, 519] and one of the cohort studies[520] examined the association between divorce/separation and breast cancer risk, all reporting no association.

Job loss/strain

A pooled analysis of individual participant data from 12 European cohort studies (Heikkila et al.[523]) reported no association between work stress and breast cancer risk after adjusting for BMI, alcohol consumption and other potential confounding factors. Similarly, Schoemaker et al.[520] reported no association in the UK cohort study between job loss and breast cancer incidence.

Table D.66 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8.9 Trauma to the breast

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between trauma to the breast and risk of breast cancer is inconclusive. Only a limited amount of poor quality evidence is available. The most reliable of the available studies indicates no association between trauma to the breast and risk of breast cancer. There is no plausible biological mechanism linking trauma to the breast and risk of breast cancer.

Background

Concerns have been raised about potential links between physical trauma to the breast and subsequent risk of breast cancer. A proposed mechanism is that tissue injury to areas containing in situ carcinoma might promote the dissemination of malignant cells.[524] There is, however, no research evidence to support this theory.[525] Song et al.[526] noted a hypothesised direct link between physical breast trauma and breast cancer[527] but indicated this theory is not widely accepted.

Trauma to the breast can lead to scarring that may show up on screening mammography and be difficult to differentiate from a neoplastic lesion. This could lead to a false positive diagnosis of breast cancer. Further, a visit to the doctor for an injury could lead to detection of a pre–existing breast cancer. Similarly, increased surveillance during recovery from physical trauma might disclose pre–existing breast cancer.

Recent evidence

Three very low quality studies have investigated a potential association between physical trauma to the breast and breast cancer risk.[526-528]

In a retrospective cohort study of 500 women presenting for breast examinations, of whom 102 were found to have breast cancer, women were asked about prior trauma to the breast.[528] No association was found between reported breast trauma and risk of breast cancer (OR 0.84, 95% CI 0.41–1.75).

A small retrospective case–control study (67 cases, 134 controls) reported that women with breast cancer were more likely to report physical trauma to the breast in the preceding five

years than women without breast cancer (OR 3.3, 95% CI 1.3–10.8).[527] These findings are unreliable, however, because they would have been vulnerable to recall bias, with women with breast cancer potentially recalling past trauma to the breast differently to those without breast cancer.

A systematic review of case reports, including 43 women who had breast injury from seat belt wearing in a road traffic accident, reported that five of 29 women who presented in a period between 3 weeks and 5 years from the time of the accident, had breast cancer.[526] This is not regarded as representing a causal relationship, particularly due to the short period of time between breast cancer diagnosis and time of the accident and the likelihood that increased observation as a result of the physical trauma led to the detection of the cancers in the short period post-injury.

Table D.67 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.8.10 Type 2 diabetes

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between having type 2 diabetes and risk of breast cancer is inconclusive. Several meta–analyses have shown a small positive association, particularly among postmenopausal women. The evidence is limited however by large heterogeneity between studies, a lack of adjustment for potential confounders, particularly adiposity, and a lack of differentiation between exposure to type 1 and type 2 diabetes. The few studies reported to be on type 1 diabetes show no association with breast cancer risk.

Background

Type 2 diabetes mellitus is a long term metabolic disorder characterised by high blood sugar, insulin resistance, and relative lack of insulin.[529] The major risk factors for type 2 diabetes are obesity and lack of physical activity, although genetic predisposition can also play a role.[529]

Mechanisms by which type 2 diabetes may be associated with breast cancer risk are not established.[530] Among the proposed mechanisms, the dysregulated glucose metabolism is suggested to play a major role. This factor concurs with a chronic pro–inflammatory condition and an associated oxidative stress to promote tumour initiation and progression.[531] Hyperinsulinaemia—both endogenous due to insulin–resistance and drug–induced—appears to promote tumour cell growth through a number of pathways. Other postulated mechanisms include hormonal pathways such as the signalling of insulin, the insulin–growth–factor system, and endogenous steroid hormones.[532] Type 2 diabetes may also be a marker of the adiposity–breast cancer association, as body mass index (BMI) is associated with type 2 diabetes and postmenopausal breast cancer.[533]

Alternative mechanisms have been postulated for a potential link between type 1 diabetes and breast cancer.[534]

Recent evidence

Four systematic reviews with meta–analyses[530, 534-536] have examined the association between type 2 diabetes and breast cancer risk, although the most recent and the oldest of these did not differentiate between type 1 and type 2 diabetes. There was significant overlap of studies included in the four meta–analyses.

Boyle et al.[530] included 14 studies and the summary risk estimate (for breast cancer incidence and mortality) was RR 1.16 (95% CI 1.04–1.29) with evidence of significant heterogeneity but not publication bias. The authors noted effect size was similar for incidence and mortality. For studies reporting on the association between type 2 diabetes and postmenopausal breast cancer, the summary risk estimate was RR 1.12 (95% CI 1.03–1.21). Hardefeldt et al.[535] included 10 studies (three cohort studies involving 152,503 cases; seven case–control studies involving 3,294 cases) reporting on the association between type 2 diabetes and breast cancer risk and reported a pooled estimate of OR 1.22 (95% CI 1.07–1.40). The largest of the included cohort studies by Bowker et al.[537] showed evidence of detection bias and no overall association between type 2 diabetes and breast cancer risk (RR 1.00, 95% CI 0.91–1.10; 84,506 cases).

The four meta–analyses showed similar summary risk estimates for women with either type 1 or type 2 diabetes and risk of breast cancer: HR 1.23 (95% CI 1.12–1.34);[534] RR 1.24 (95% CI 1.12–1.36);[530] OR 1.20 (95% CI 1.13–1.29);[535] and RR 1.23 (95% CI 1.18–1.27.[536] Analysis of studies that adjusted for family history, age and BMI resulted in a smaller effect size, although the association remained significant (OR 1.11, CI 95% 1.01–1.22).[535]

More recent data from two population–based cohort studies conducted in Italy[538] and China[539] reported increased risks of breast cancer in women with type 2 diabetes compared with the general population (SIR 1.24, 95% CI 1.00–1.52 and SIR 1.66, 95% CI 1.38–1.95 respectively). Contrary to the finding by Bowker et al.[537] the significant finding in the study by Gini et al.[538] was only among women where at least three years of latency was considered. Median follow–up time was less than four years for both studies. Both studies were retrospective record linkage studies, and the analyses were not able to account for the potentially confounding influence of BMI or other potential or known breast cancer risk factors.

Table D.68 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9 Chemical exposures

4.9.1 Bisphenol A (BPA)

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to bisphenol A (BPA) and risk of breast cancer is inconclusive. There is only a very limited amount of low level evidence available.

Background

Bisphenol A is an industrial chemical that has been used since the 1960s to produce certain plastic and resins.[540] It is found in polycarbonate plastics that are used to store food and beverages, such as water bottles, bottle tops and the coating inside food cans.[540] Consumer exposure via food can occur through migration of BPA from food and beverage contact materials.[540]

BPA is a synthetic oestrogen, and thus concerns have been raised about a potential link between exposure to BPA and breast cancer risk through a mechanism relating to endocrine disruption.[541] Experimental studies in animals have demonstrated BPA's endocrine disrupting potential. There is, however, controversy about whether the concentration of BPA detected in human blood is above the level required for biological activity.[542] Most experimental animal studies used higher doses of BPA.[542]

Recent evidence

No cohort studies were identified and only two case–control control studies were identified.[543, 544] An analysis of data from a population–based case–control study conducted in Poland did not find an association between urinary BPA measured at the time of diagnosis and postmenopausal breast cancer.[543] Yang et al.[544] similarly reported a null association between blood level of BPA measured at diagnosis and breast cancer risk in a smaller case–control study conducted in Korea.

A third case–control study did not examine BPA exposure specifically, but rather occupations including food canning and plastics manufacturing.[545] A significant association was observed between occupations in food canning and in the automotive plastics manufacturing sector and breast cancer risk. These occupations may involve exposure to other potentially carcinogenic compounds, however, and the findings should be interpreted accordingly.

Table D.69 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9.2 DDT exposure

Evidence summary

Evidence classification: Evidence of no association.

Large numbers of epidemiological studies overall show no association between exposure to DDT/DDE and risk of breast cancer. There is very limited evidence on early–life exposure to DDT/DDE and risk of breast cancer.

Background

Dichlorodiphenyltrichloroethane (*pp'*–DDT) is a non–systemic, broad–spectrum organochlorine pesticide that was used worldwide to control insects in agricultural systems, and to control mosquitoes to help prevent the transmission of malaria and other diseases.[546] DDT was used from the early 1940s, then phased out from the 1970s and 1980s in most countries.[542] The World Health Organization still recommends its use, however, for malaria control under specified conditions.[547]

DDT is a common and highly persistent environmental contaminant, found in foods, soils and sediments.[546] Exposure to DDT may occur during its production and application, or from ingestion of contaminated water and food.[546] *pp'*–DDT and its metabolites have been detected in breast milk and cord blood, and have been found to transport across the placenta to the foetus (studies cited by IARC).[548]

Dichlorodiphenyldichloroethylene (DDE or *p,p'*–DDE) is the main metabolite of *p,p'*–DDT, and DDT is rapidly converted to DDE in biological systems.[549]

There is strong experimental evidence in animals that DDT/DDE may influence cancer risk by suppressing immune function and disrupting endocrine pathways.[550] Experimental studies have shown DDT/DDE has oestrogenic properties[551] and specific effects on the development of breast tissue in rats when they are exposed in utero or during puberty.[542]

IARC

The International Agency for Research on Cancer (IARC)[548] classified DDT as '*probably carcinogenic to humans (Group 2A)*', based on *sufficient evidence* that DDT/DDE causes cancer in experimental animals but *limited evidence* of its carcinogenicity in humans. Positive associations were noted between DDT and cancers of the liver and testis, and non–Hodgkin lymphoma.

IARC[548] summarised more than 40 epidemiological studies conducted in North America, Latin America, Asia and Europe since 1993 that assessed the relationship between DDT exposure and risk of cancer of the breast. Almost all the studies used *p,p'*–DDE measurements in blood or adipose tissue as an exposure indicator, and some reported results for *p,p'*–DDT. Biological measurements of exposure were made at diagnosis or several years before. No association overall was found between *p,p'*–DDE or *p,p'*–DDT levels and breast cancer. Stratification by hormone–receptor status of the breast tumour, or menopausal status, did not modify the results. Several meta–analyses on *p,p'*–DDE exposure found the available studies supported the view that DDE is not associated with an increased risk of breast cancer in humans.

However, the potential influence of age at exposure to DDT remains of interest in relation to risk of breast cancer, as suggested by two studies that reported an increased risk of breast cancer in women highly exposed to DDT early in life.

Recent evidence

Four meta–analyses were cited by IARC[548] as having evaluated the association between cancer of the breast and DDT and/or DDE.[549, 551-553]

The most recently published meta–analysis included 10 nested case–control studies, 11 population–based case–control studies, and 16 hospital–based case–control studies examining DDT/DDE exposure (as measured in serum and plasma) and risk of breast cancer.[549] No association was found between DDT exposure and breast cancer (OR 1.03, 95% CI 0.95–1.12), although there was evidence of significant heterogeneity between studies and methodological limitations to the evidence base.

The meta–analysis by Ingber et al.[551] included 46 case–control or nested case–control studies, most of which had been included in the review by Park et al.[549] It was indicated to be an update of the review by Lopez–Cervantes et al.,[553] which found no association between DDE exposure and risk of breast cancer. Ingber et al.[551] examined the highest versus lowest levels of DDT or DDE in blood or adipose tissue. They reported no associations for exposure to either DDT (OR 1.02, 95% CI 0.92–1.13) or DDE (OR 1.05, 95% CI 0.93–1.18) and risk of breast cancer. Significant heterogeneity was not explained by study design, type of biological sample, study period or other factors, including menopausal status.

Table D.70 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9.3 Deodorant/antiperspirant

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between deodorants or antiperspirants and risk of breast cancer is inconclusive. The evidence is limited in amount and quality. Two case–control studies and narrative reviews of biological studies indicate no association between use of deodorants or antiperspirants and risk of breast cancer.

Background

Deodorants are topical products used to prevent body odour that is caused by the bacterial metabolism of the exudates of apocrine (sweat) glands (or perspiration).[554] Antiperspirants are a subgroup of deodorants that additionally prevent sweating by blocking the apocrine glands via the action of astringent agents such as aluminum salts.[554]

A link between the use of deodorants and antiperspirants and breast cancer risk has been proposed, mostly relating to the anatomic location of tumours (that is, in the upper right quadrant where there is more breast tissue)[555] and the demonstrated potential oestrogenic

activity of parabens (esters of p–hydroxybenzoic acid) in vitro.[555] Deodorants and antiperspirants contain parabens, which act as antimicrobial preservatives in many cosmetic products.[556] While parabens do mimic the activity of oestrogen, they lack the potency to cause genetic mutations unless at considerable concentrations.[535, 557] Further, Namer et al.[558] indicated that parabens are generally not present in deodorants/antiperspirants. Parabens as an exposure have been reviewed separately (see section 4.9.8).

In addition to parabens, antiperspirants contain aluminium salts, and other active non–ionic and ionic agents.[559] Limited experimental evidence has demonstrated a genotoxic potential of aluminium–containing compounds. Aluminium has been found in human breast cancer cells, although there is no direct evidence to suggest that it originated from antiperspirants.[559]

Recent evidence

There are limited data from studies in humans, with the bulk of relevant literature consisting of in vitro and in vivo experimental studies, narrative reviews[560] and opinion pieces.[561]

Two meta–analyses of the same two case–control studies[562, 563] reported null findings.[564, 565] Hardefeldt et al.[564] reported a summary odds ratio for use of deodorants and breast cancer of 0.81 (95% CI 0.51–1.28), while Allam[565] reported a summary odds ratio for use of antiperspirants and breast cancer of 0.40 (95% CI 0.35–0.46). Of the two case–control studies included in both meta–analyses, only one was population–based and adjusted for potential confounding factors, and found no effect modification according to underarm shaving with a razor.[563]

A systematic review of 19 studies included both biological or human data relevant to the association between antiperspirants containing aluminium and risk of breast cancer and concluded there was no evidence to support the hypothesis that aluminium–containing antiperspirants increases the incidence of breast cancer of the upper outer quadrant.[558]

An additional case–control study with major methodological limitations was identified in the literature.[566] The only exposure that showed an association with breast cancer was for women who reported using underarm cosmetic products several times daily under the age of 30 years (OR 3.88, 95% CI 1.03–14.66). However, the poor study design and wide confidence intervals means this estimate is not reliable.

Table D.71 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9.4 Dioxin

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to dioxin and risk of breast cancer is inconclusive. There are limited, poor–quality studies available. None of the available studies show any association.

Background

Dioxins are environmental contaminants produced by the incomplete combustion of materials containing chlorine. This combustion occurs in numerous industrial processes, including the production of pesticides and bleached paper.[542] The most toxic dioxin is 2,3,7,8–tetrachlorodibenzo–p–dioxin (TCDD).[542] It is fat soluble and accumulates in the food chain,[542] with a half–life in humans of 7–9 years.[567] One of the main sources of exposure in humans is dietary, through consumption of animal fats in dairy products, eggs, fish and meat.[568, 569] Dioxins are also present in human breast milk, although levels in children are similar regardless of method of infant feeding.[570]

The World Health Organization[571] indicated the omnipresence of dioxins means all people have background exposure and a certain level of dioxins in the body. Normal background exposure is not expected to affect human health on average.

Dioxins can mimic the activities of oestrogen, and exposure to these compounds has been suggested to increase the risk of some hormone–related diseases via 'endocrine disruption'.[572] TCDD is not 'genotoxic' and is thought to influence cancer risk via oxidative damage,[542] most likely related to an ability to bind to the aryl hydrocarbon receptor (AhR).[573] In vitro studies have demonstrated AhR plays an important role in the development of breast cancer via the suppression of apoptosis.[574, 575]

IARC

In 1997, the International Agency for Research on Cancer (IARC) classified TCDD as a Group 1 carcinogen on the basis of animal studies and mechanistic information focusing on the aryl hydrocarbon receptor (AhR), but noted there were limited human data from observational studies.[573] In 2012, IARC summarised the findings of observational studies in humans, noting sufficient evidence for all cancers combined and limited human evidence for lung cancer, soft tissue carcinoma and non–Hodgkin lymphoma.[573] Breast cancer was mentioned only briefly in relation to exposure at Seveso (see below).

Recent evidence

A meta–analysis, published in 2015, of the association between external exposure to TCDD and breast cancer risk included three studies with 3,768 breast cancer cases. A pooled RR for breast cancer of 0.99 (95% CI 0.93–1.06), with no evidence of significant heterogeneity, was reported.[576] It is not clear from the meta–analysis which three studies contributed to the summary estimate, although studies in the reference list were Warner et al.,[577] Reynolds et al.[578] and Viel et al.[579]

Warner et al.[577] examined the association between individual serum TCDD levels and breast cancer risk in women residing around Seveso, Italy, in 1976, when an industrial explosion resulted in the highest known population exposure (10–fold) to TCDD. The cohort comprised 981 females aged from infancy up to 40 years in 1976. At follow–up in 1996, there was a two–fold increased risk of premenopausal breast cancer (HR 2.1, 95% CI 1.0–4.6), proposed to be related to a window of susceptibility as a tumour promoter.[577] Follow–up of the cohort in 2008 revealed no increased risk of breast cancer (HR 1.44, 95% CI 0.89–2.33).[577]

Viel et al.[579] examined modelled ground–level air dioxin levels across census blocks in France, finding no association with risk of breast cancer. Reynolds et al.[578] conducted a hospital–based case–control study among 79 women diagnosed with invasive breast cancer and 52 controls diagnosed with benign breast conditions. Breast cancer risk was not associated with adipose levels of polychlorinated dibenzo–p–dioxins.

Additional studies include Dai et al.,[580] who examined breast cancer risk across 22 zip codes in the United States with dioxin contamination based on soil samples, and who found no evidence of an association. More recently, Danjou et al.[581] examined dietary exposure to dioxin among 63,830 women in the E3N cohort who completed dietary questionnaires in 1993 and were followed until 2008. Overall, no association was found between estimated dietary dioxin exposure—estimated by combining diet history information with food dioxin contamination data from the French national monitoring program—and breast cancer risk.

Table D.72 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9.5 Ethylene oxide

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between occupational exposure to ethylene oxide and risk of breast cancer is inconclusive. It is limited in amount and inconsistent. There is some evidence of a dose–response relationship.

Background

Ethylene oxide is an organic compound used primarily to produce other chemicals.[574] It is a flammable, colourless gas at room temperature.[574] Human exposure to ethylene oxide occurs predominantly when sterilising medical equipment.[582] The average concentration of ethylene oxide in hospitals in North America and Western Europe has been declining over time.[582]

Ethylene oxide is an alkylating agent that can cause direct damage to DNA.[582] Studies in animal models have shown that it can cause heritable mutations in germ cells.[582] It also causes chromosomal aberrations in the lymphocytes of exposed workers,[583] which can increase risk of cancer.[584]

IARC

The International Agency for Research on Cancer (IARC)[574, 582] has classified ethylene oxide as a Class 1 carcinogen, based on studies in animal models and in vitro studies demonstrating a genotoxic mechanism of carcinogenicity. Evidence from epidemiological studies was deemed limited, and the Working Group concluded that there was limited evidence in humans for a causal association of ethylene oxide with breast cancer.[574]

The IARC examined three studies relating to occupational exposure to ethylene oxide and risk of breast cancer.[585-587] Two studies observed no increased risk;[585, 586] the third study reported an excess risk of approximately 60%, which was of borderline significance[587] An internal analysis of data from the National Institute for Occupational Safety and Health study (NIOSH)[585] showed a significant increased risk in the highest compared with the lowest category of exposure to ethylene oxide among 7,576 women working in commercial sterilisation facilities (OR for >11620 parts per million–days, 15–year lag 1.87, 95% CI 1.12–3.10). A significant dose–response relationship after controlling for parity and family history of breast cancer was observed (p=0.002).

Recent evidence

Longer term follow–up data of the Swedish cohort of 1,309 exposed female workers reported on by Hagmar et al.[586] were published in 2011.[588] Compared with the general public, workers exposed for at least one year did not have an increased risk of breast cancer, with SIRs close to unity, and independent of lag period or follow–up time. However, compared with women in the first two quartiles of exposure, women in the third and fourth quartiles of exposure had a higher incidence of breast cancer (IRR 2.76, 95% CI 1.20–6.33 and 3.55, 95% CI 1.58–7.93, respectively); although these analyses were based on a small number of breast cancer cases overall (41 cases).

Table D.73 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9.6 Land contamination

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to land contamination and risk of breast cancer is inconclusive. There is limited evidence from mainly ecological studies.

Background

Land contamination can result from industrial activity and industrial and uncontrolled waste sites.[589] These sites can contain numerous hazardous substances, including known carcinogenic compounds such as organic pesticide residues, which can leach from the soil and contaminate groundwater and overland waterways. Human exposure to these compounds can arise from drinking contaminated water, consuming contaminated food or inhaling dust from contaminated sites.[433] Identifying and measuring exposure to diverse types of land contamination is complex, and an inherent limitation of epidemiological studies that evaluate associations between these environmental exposures and cancer risk.

Some compounds found in contaminated sites are reviewed as separate risk factors for breast cancer in this report, including polychlorinated biphenyl and dioxins.

IARC

An internal report from the International Agency for Research on Cancer (IARC)[433] listed contaminated land and groundwater as a low priority for review. IARC noted limited evidence from epidemiological studies in humans and experimental studies in animals, and on the contamination site–specific nature of exposure.

Recent evidence

Several ecological studies[589, 590] examined geographic variation in breast cancer incidence according to residential proximity to contaminated or potentially contaminated sites. Ecological studies are useful for hypothesis generation, but not for determining causal associations. Their findings should be interpreted accordingly.

Benedetti et al.[589] reported on the incidence of breast cancer in regions contiguous with Italian National Priority Contaminated Sites (NPCSs), at which compounds with known or suspected endocrine disrupting properties have been detected. The principal source of contamination was listed as polychlorinated biphenyls, dioxins, heavy metals and solvents.[589] Compared with the general population (northern central Italy or southern central Italy, depending on site location), excess incidence of breast cancer was reported for eight of the 14 sites, with SIRs ranging from 1.10 to 1.45 (Taranto site = SIR 1.45, 95% CI 1.34–1.56). No excess risk was observed in five sites, and a 10% lower incidence of breast cancer was reported for the remaining site (SIR 0.90, 95% CI 0.85–0.96). A separate report on the Taranto NPCS was published four years earlier.[590] A lower magnitude of increased risk of breast cancer among women at the Taranto NPCS relative to the population of the remainder of the Taranto province (SIR 1.24, 95% CI 1.13–1.36) was reported.

Guajardo & Oyana[591] assessed the spatial relationship between previously determined geographic clusters of breast cancer incidence among residents living near the two major river systems in Michigan in the United States. They reported an increased breast cancer risk in regions close to these major rivers (that is, on the floodplains). The spatial analysis confirmed a significant positive association between 'possible exposure to environmental pollution' and risk of breast cancer. The study could not determine the contribution of contamination from different industrial facilities.

Two studies reported specifically on exposure to dioxin in the soil and breast cancer risk.[592] Pesatori et al.[592] reported on breast cancer incidence in a cohort of women exposed to 2,3,7,8–tetrachlorodibenzo–p–dioxin (TCDD) through a 1976 industrial accident in Seveso, Italy. Levels of TCDD in the soil were recorded, and exposure zones were classified as low, medium and heavily contaminated. Although limited by a small number of breast cancer cases, an increased risk of breast cancer in the highly contaminated zone 15 years after the accident compared with a non–contaminated reference zone was observed (RR 2.57, 95% CI 1.07–6.20). There was no increased risk in the 'low' and 'medium' contamination zones. The other study[580] was conducted in the same Michigan area as the study by Guajardo & Oyana.[591] A spatial association between soil dioxin contamination and breast cancer incidence was reported, with a higher incidence of breast cancer in areas close to dioxin–contaminated areas.[591]

Table D.74 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9.7 Outdoor air pollution

Evidence summary

Evidence classification: Inconclusive.

The evidence of any association between exposure to outdoor air pollution and risk of breast cancer is inconclusive. There are inconsistent findings across studies. Interpretation of the evidence is hampered by differences in exposure definition across studies. Cohort studies show no evidence of an association between exposure to outdoor air pollutants, particularly nitrogen dioxide, and risk of breast cancer.

Background

Air pollution is when the air contains one or more substances at a concentration or for a duration above natural levels, and with the potential to produce an adverse effect.[593] It is caused by natural processes such as volcanic eruptions and wildfires, as well as human activities such as transportation, construction, mining and other industrial activities.

Air pollution is ubiquitous, and human exposure to outdoor air pollutants occurs continuously.[593] There is no standardised method to measure exposure to outdoor air pollution. Air pollutants are classified as being gaseous or particulate matter, which contains suspensions of very small particles that can be liquid or solid.[593] Gaseous compounds include nitrogen oxide (NO) and nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and volatile organic gases (for example, formaldehyde, ketones, alkanes and aromatics such as benzene).[593] Levels of air pollution are monitored using measures of $PM_{2.5}$ and PM_{10} (particulate matter of different sizes), and levels of NO_2 and SO_2.[593]

There is strong mechanistic evidence for the ability of air pollution (and many of its components) to induce genetic and related effects in humans.[593] Genotoxic effects are well documented, as well is oxidative stress and sustained inflammation.[593] There are no established mechanisms for a link between outdoor air pollution and breast cancer risk.[594] One proposed mechanism is the effect of NO_2 on DNA damage.[594]

IARC

The International Agency for Research on Cancer (IARC)[593] classified air pollution and particulate matter in outdoor air pollution as carcinogenic to humans (Group 1), citing sufficient evidence in humans and experimental animals that they cause lung cancer. The IARC[593] working group evaluated the evidence of an association between air pollution levels and breast cancer, reviewing seven studies (four cohort and three case–controls studies). Overall inconsistent findings were noted.

Recent evidence

The most recently published data on exposure to hazardous air pollutants and risk of breast cancer come from the Nurses' Health Study II.[595] Among 109,239 members of the cohort, no consistent pattern of association was found between exposure and risk of breast cancer.

Suggestive, non–significant increased risks of breast cancer were found only for the highest versus lowest exposures to 1, 2–dibromo–3–chloropropane.

A systematic review with meta–analysis on the association between NO_2 from outdoor air pollution and breast cancer risk included five studies: three ecological studies, one cohort study and one case–control study.[596] The two non–ecological studies were included in the IARCevaluation.[593] A pooled analysis of the three ecological studies reported a significant correlation between NO_2 exposure and breast cancer risk (RR 1.38, 95% CI 1.11–1.59).

Andersen et al.[597] examined the association between exposure to fine particulate matter and breast cancer incidence in the Danish Nurse Cohort Study (22,877 nurses). They reported null associations for exposure to $PM_{2.5}$ (HR 1.00, 95% CI 0.91–1.09), PM_{10} (HR 1.02, 95% CI 0.94–1.11) and NO_2 (HR 1.00, 95% CI 0.94–1.07), with no differences according to menopausal status or menopausal hormone therapy use.

Shmuel et al.[598] examined residential exposure to vehicular traffic–related air pollution during childhood and breast cancer risk in a large prospective cohort of 50,884 women from the United States and Puerto Rico. They found no associations between individual traffic–related characteristics and risk of breast cancer. They observed, however, modest and suggestive associations between a combined measure of higher potential exposure to traffic–related pollutants (close proximity, presence of median/barrier, multiple lanes and heavy traffic) and breast cancer risk overall, and for postmenopausal and oestrogen receptor negative (ER–) disease. An earlier report from the same cohort study reported null associations with $PM_{2.5}$ (HR 1.03, 95% CI 0.96–1.11), PM_{10} (HR 0.99, 95% CI 0.98–1.10) and NO_2 (HR 1.02, 95% CI 0.97–1.07).[599] In subgroup analyses according to hormone receptor status, a modest positive association between NO_2 exposure and ER+PR+ (but not ER–PR–) breast cancer was observed.

An earlier report from the Nurses' Health Study II cohort by Hart et al.[600] found no significant associations between PM exposures and incidence of breast cancer overall, or by menopausal status or hormone receptor subtype. A non–significant positive association with residential proximity to major roadways (for women living <50 m from the two largest road types compared with those living ≥200 m away, HR 1.60, 95% CI 0.80–3.21) was reported.[600]

Garcia et al.[601] examined the association between 24 different components of outdoor air pollution shown to be mammary gland carcinogens (MCGs, such as benzene, hydrazine and ethylene oxide) and breast cancer risk in the California Teachers Study cohort (112,378 women). Exposure was modelled using annual average ambient air concentrations of the various compounds, so any findings should be interpreted with caution. Most hazard ratios for the individual compounds were not statistically significant. The authors concluded that the results for propylene oxide and vinyl chloride were significant, but observed significantly increased risk for only the middle quintile of exposure versus the lowest quintile of exposure for both compounds, and not for higher levels of exposure. An aggregated variable for all 24 mammary gland carcinogens (MGCs) was not associated with breast cancer risk.

Table D.75 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9.8 Parabens

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to parabens and risk of breast cancer is inconclusive. There is no epidemiological evidence available in humans.

Background

Parabens are esters of p–hydroxybenzoic acid (PHBA), used since the 1920s as antimicrobial preservatives in pharmaceuticals, foods and cosmetics.[556] Most major brands of deodorants and antiperspirants do not contain parabens. They are also common environmental contaminants[602] Human exposure can result from ingestion, absorption through the skin or inhalation of products containing parabens.[556] Parabens have been found in a wide variety of human tissues[603] and are common in normal breast tissue.[604]

Concerns arose about a link between parabens and breast cancer risk largely as the result of findings from a small number of experimental studies that detected parabens in breast cancer cells,[605] and reported oestrogenic effects of parabens on breast cancer cell lines.[606]

Parabens are considered to be 'endocrine disrupting compounds'. However, a review of the endocrine activity of parabens concluded that only three parabens (butyl–, isobutyl–, and benzylparaben) have been shown to have oestrogenic activity in vivo. Further, they have a very low binding affinity to the oestrogen receptor, many orders of magnitude lower than for oestrogen.[557]

Recent evidence

There have been no epidemiological studies or quantitative reviews on the association between parabens and risk of breast cancer, with the literature consisting of in vitro and in vivo experimental studies, narrative reviews[556, 557, 560, 607] and opinion pieces (for example, Harvey et al.[561]).

4.9.9 Phthalates

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to phthalates and risk of breast cancer is inconclusive. There is a limited amount of available epidemiological evidence. Findings from a nested case–control study indicate no association between phthalates and risk of breast cancer.

Background

Phthalates, used to render plastics soft and flexible, are found in a wide variety of common products, including plastics (for example, children's toys), cosmetics and fragrances, pharmaceuticals, vinyl flooring, and food packaging.[7, 608] Food packaging, vinyl flooring, and plasticisers are major sources of higher molecular weight phthalates, like bis(2–ethylhexyl) phthalate (DEHP), while fragrances and cosmetics are important sources of lower molecular weight phthalates, like diethyl phthalate (DEP).[542]

Phthalates have been found in indoor air and dust, and in human urine and blood samples, amniotic fluid, human breast milk.[7] Phthalate metabolites are found in nearly all humans, though, as with bisphenol A (BPA), phthalates are rapidly metabolised and excreted so there can be substantial intra–individual variability in levels in humans.[542]

Some phthalates are considered to be 'endocrine disrupting compounds'. Rodgers et al.[542] report several animal studies showing endocrine disruption to oestrogen and progesterone. Some phthalates have been shown to bind weakly to the androgen receptor, and others have been shown to promote cancer stem cell growth through activation of the aryl hydrocarbon receptor (AhR). Non–hormonal pathways have also been suggested.[7]

Recent evidence

There has only been one prospective study on the association between phthalates and risk of breast cancer,[608] reported as a conference abstract. This was a nested case–control study within the Women's Health Initiative (WHI) prospective cohort involving 419 cases and 838 matched controls. Exposure to a panel of 13 phthalate metabolites (PMs) was measured in urine over a period of 1–3 years. No associations were found between individual PMs and risk of breast cancer. It was suggested that some phthalates may be associated with decreased risk, possibly through anti–oestrogenic actions.

Two hospital–based case–control studies were reported in the review by Rodgers et al.[542] but both studies—Lopez–Carrillo et al.[609] and Holmes et al.[610]—were of low methodological quality.

4.9.10 Polychlorinated biphenyls

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to polychlorinated biphenyls and risk of breast cancer is inconclusive. Meta–analyses of a large number of case–control studies show inconsistent findings.

Background

Polychlorinated biphenyls (PCBs) are a class of aromatic compounds with molecules that contain two benzene rings in which chlorine atoms replace hydrogen atoms.[611] They were commonly used in electrical equipment and other industrial applications from the 1920s until

the early 1980s.[611] PCBs are a common and highly persistent environmental contaminant found in the atmosphere in dust contaminated from PCB–containing building materials, and in water, sediments and soil.[542, 611] They are fat soluble and accumulate in the food chain, with a half–life in humans of three to 15 years.[542] The main sources of exposure to PCBs in humans are the consumption of fish from contaminated waterways and breathing contaminated air.[542]

Various mechanisms for how PCBs and metabolites of PCBs may influence cancer have been proposed. Less chlorinated PCBs may produce oxidative stress and genotoxicity. More highly chlorinated PCBs interact with various receptors that control steroid hormone metabolism and other processes that affect cell death and proliferation, the immune system and the inflammatory response.[611] They can act as oestrogen agonists or antagonists[612] and have been commonly found in breast adipose tissue and human breast milk.[611] There is evidence for gene–environment interactions, notably a modifying effect of a polymorphism in cytochrome P450 1A1 (CYP1A1) gene on the association between PCB levels and cancer risk.[611]

IARC

The International Agency for Research on Cancer (IARC)[611] classified PCBs as carcinogenic to humans (Group 1), based primarily on evidence supporting a positive association for melanoma and non–Hodgkin lymphoma. For breast cancer, the working group noted an increased risk associated with exposure to PCBs, which was higher in some subgroups of the population. Biological plausibility of the association was noted.

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR),[613] in its Second Expert Report, judged the evidence for an association between exposure to PCBs and breast cancer risk as 'Limited—no conclusion'. The evidence was not updated as part of the Continuous Update Project.[10]

Recent evidence

Two systematic reviews with meta–analyses examined the association between PCBs and risk of breast cancer.[612, 614] These studies measured and reported on PBC exposure differently, however. Leng et al.[614] examined individual PCBs from three groups: 'potentially oestrogenic' (PCB 187); 'potentially anti–oestrogenic, dioxin–like' (PCB 118, 138, 156, 170); and 'phenobarbital, CYP1 and CYP2B inducers' (PCB 99, 153, 180, 183). Zheng et al.[612] examined PCBs in total, and from the three groups defined above, but in aggregate, without distinguishing between individual PCBs.

The review by Leng et al.[614] included 16 case–control studies published to 2014. The pooled analysis showed an increase in the risk of breast cancer in women with higher plasma/fat levels of 'potentially oestrogenic' PCB 187 (OR 1.18, 95% CI 1.01–1.39) and two of the 'phenobarbital, CYP1 and CYP2B inducers' PCBs (PCB 99: OR 1.36, 95% CI 1.02–1.80; PCB 183: OR 1.56, 95% CI 1.25–1.95). No association was found for the 'potentially anti–oestrogenic, dioxin–like' PCBs or for PCBs 153, 180 from the 'phenobarbital, CYP1 and CYP2B inducers' group.

Zhang et al.[612] included 25 case–control studies, 10 of which were included by Leng et al.[614] and reported no association with total PCB exposure (OR 1.09, 95% CI 0.97–1.22; with evidence of significant heterogeneity). Zheng et al.[612] separately examined the same three groups of PCBs as studied by Leng et al.[614]:'potentially oestrogenic'; 'potentially anti–oestrogenic and immunotoxic, dioxin–like'; and, 'phenobarbital, CYP1 and CYP2B inducers'. The summary estimates supported an increased risk of breast cancer associated with PCBs from the latter two groups—'potentially anti–oestrogenic and immunotoxic, dioxin–like' (OR 1.23, 95% CI 1.08–1.40) and 'phenobarbital, CYP1 and CYP2B inducers' (OR 1.25, 95% CI 1.09–1.43)—but not for the 'potentially oestrogenic' group.

More recent data from a Swedish mammography cohort of 36,777 women reported no association between dietary exposure to PCBs and risk of breast cancer.[615] The study authors considered the estimates of dietary exposure to PCBs did not permit assessment of individual PCB exposure, so the overall null finding may mask significant associations with individual PCBs that have differential toxicities and effects.

Table D.76 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9.11 Occupation as a hairdresser

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between occupation as a hair dresser and risk of breast cancer is inconclusive. A substantial number of cohort studies show no association between occupation as a hairdresser and risk of breast cancer. However, there are limitations within the studies in measuring occupational exposure and potential confounders.

Background

Hairdressers are exposed to many chemicals contained in hair dyes, shampoos, conditioners and other hair products used occupationally on a daily basis. Several of these 5,000 or more chemicals (including aromatic amines, predominantly from hair dyes) are potentially carcinogenic overall.[616] Exposure can occur via skin contact, followed by dermal absorption, and, less commonly, though airborne exposure.[616]

Concerns about any cancer risk due to occupational exposures of hairdressers arose following the findings from in vitro experimental studies demonstrating genotoxic effects of hair dyes and carcinogenic effects in rats after oral, but not topical, administration.[616] The International Agency for Research on Cancer[616] also reported on studies that found chromosomal aberrations in the peripheral blood lymphocytes of professional hair colourists but indicated that other studies did not find an effect on sister chromatid exchange, DNA breakage in lymphocytes or mutagenicity in urine.

Regulatory authorities across the world have restricted the number and type of chemical components permitted for use in hair dyes in recent decades,[616] although exposure to carcinogenic or potentially carcinogenic aromatic amines is likely still occurring, at least in

some countries (for example, Johansson et al.[617]). Further, it is probable that hairdressers and allied occupations continue to be exposed to DNA–damaging agents other than those contained in hair dyes, such as formaldehyde, metacrylate and acetone.[618]

IARC

The International Agency for Research on Cancer (IARC)[616] concluded there is limited evidence in humans for the overall carcinogenicity of occupational exposures as a hairdresser or barber. Based on a consistent but modest increase in risk for urinary bladder cancer, especially in men, occupational exposures as a hairdresser or barber was classified as '*probably carcinogenic to humans*' (Group 2A).

For breast cancer specifically, IARC[616] concluded that many epidemiological studies, including the largest case–control studies and cohort studies, did not show any increased risk associated with professional use of hair colourants.

Recent evidence

A systematic review with meta–analysis examining incidence of breast cancer among hairdressers and related occupations compared with the general population included 12 studies (seven cohort studies and five case–control studies), 10 of which had been included in the IARC[616] review. No association with risk of breast cancer was observed among any of the individual studies or in the pooled analysis (pooled RR 1.03, 95% CI 0.98–1.08).[618] However, it was noted that the studies used information systems that may present incomplete information on confounders and occupational exposure.

An updated report from the Nordic Occupational Cancer (NOCCA) project[619] included data on cancer incidence between 1961 and 2005 and reported that, compared with all occupational categories, female hairdressers in Nordic countries did have a significantly elevated risk of breast cancer (SIR 1.06, 95% CI 1.01–1.10),[619] although this association was not observed in data from each individual country.

Data from the 'Sister Study' to NOCCA, which included 47,640 breast cancer–free sisters of women with breast cancer, found a borderline elevated risk of invasive cancer associated with workplace exposure to dyes and inks (HR 1.2, 95% CI 1.0–1.6) but null findings were reported for a link between workplace exposure to dyes or inks and risk of premenopausal breast cancer (HR 1.4, 95% CI 0.9–2.1) or postmenopausal breast cancer (1.0, 95% CI 0.80–1.30).[620] Further, there was no evidence of a linear dose–response relationship, although it was noted that a linear exposure–response model may not be the most appropriate approach for studying chemical exposures.

Table D.77 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.9.12 Personal use hair dyes/relaxers

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between personal exposure to chemical hair dyes or hair relaxers (straighteners) and risk of breast cancer is inconclusive. There are inconsistent findings across studies. Findings from the higher quality, cohort, studies do not support an association.

Background

Hair dyes and pigments are widely used in modern industrialised societies to change the appearance of hair. They can be classified as permanent (primarily aromatic amines and aminophenols with hydrogen peroxide), semi–permanent (nitro–substituted aromatic amines, aminophenols, aminoanthraquinones and azo dyes) and temporary (high–molecular–weight or insoluble complexes and metal salts, such as lead acetate).[616] Over the past 50 years, the number of chemical compounds approved by regulatory authorities for use in hair dyes has markedly decreased.[616] Personal exposure to hair dyes occurs predominantly via skin contact on the scalp, followed by dermal absorption, although airborne exposure is also possible.[616] Concerns about potential carcinogenic effects of hair dyes arose following the findings from *in–vitro* experimental studies demonstrating genotoxic effects of hair dyes, and carcinogenic effects in rats after oral administration (but not topical application).[616]

Hair relaxers/straighteners variously include sodium hydroxide, calcium hydroxide and/or thioglycolic acid salts, which are not known to be carcinogenic.[621] Some include formaldehyde or components that release formaldehyde, however,[542] which is a known carcinogen.[574]

IARC

The International Agency for Research on Cancer (IARC)[616] concluded there was inadequate evidence in humans and that personal use of hair dyes was '*not classifiable as to its carcinogenicity to humans (Group 3)*'. With respect to breast cancer, the Working Group considered the findings of a systematic review with a meta–analysis of 14 studies (two cohort and 10 case–control studies) evaluating the association between use of hair dyes and risk of breast cancer. A null finding overall, and for case–control and cohort studies separately, was reported and there was significant heterogeneity between included studies.[622] No association was evident with use of permanent dyes or with intense exposure.[622]

Recent evidence

A recent meta–analysis excluded data from various cohort studies and conducted a meta–analysis of eight case–control studies published between 1980 and 2017 of an association between never versus ever use of hair dyes, reporting an increased risk of 1.19 (95% CI 1.03–1.37).[623] Beyond the inherent problems associated with recall bias in case–control studies, there was significant heterogeneity between studies, no uniform adjustment for confounding factors (noting substantial confounding likely due to genetic, cultural and sociodemographic factors) and no analysis of a dose–response was possible.

One published cohort study was not included in the IARC review. Mendelsohn et al.[624] found no association with ever use of hair dyes compared with never use in the Shanghai Women's Health Study cohort of 70,366 Chinese women (RR 0.93, 95% CI 0.78–1.09), and no evidence of a dose–response relationship with increasing duration or intensity of use.

Rosenberg et al.[621] in a cohort of 48,167 African American women examined use of chemical hair relaxers in relation to risk of breast cancer and found no association with ever use, nor with increasing frequency or duration of use, of hair relaxers and risk of breast cancer. Two more recent case–control studies[625, 626] have reported inconsistent findings of an association between use of chemical hair relaxers and risk of breast cancer, with the latter showing no association among African American women.

Table D.78 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.10 Radiation exposure

4.10.1 Electromagnetic field radiation—low frequency

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to low frequency electromagnetic fields and risk of breast cancer is inconclusive. Exposure to extremely low frequency electromagnetic fields (ELF EMFs) is ubiquitous and difficult to quantify. There are methodological limitations to the mainly case–control studies in relation to exposure to ELF EMF and risk of breast cancer and high heterogeneity between studies. One cohort study and a nested case–control study show no association with occupational exposure to ELF EMF and risk of breast cancer. There was no evidence of a dose–response relationship in the cohort study.

Background

ELF EMFs occupy the lower part of the magnetic frequency range, 0–3000 Hertz (Hz), and are produced by both natural and artificial sources. Natural sources include the EMFs created by the earth and EMFs generated by thunderstorms, solar and cosmic activity.[627]

Artificial sources are the dominant sources of ELF EMFs and are usually associated with the generation, transmission and use of electricity at the frequency of 50 Hz in Australia or 60 Hz in some other countries.[628, 629] Powerlines, electrical wiring and common appliances such as electric blankets, televisions, hair dryers and computers all produce ELF EMFs.[629] Specifically, compared with background levels, readily measureable exposure to ELF EMFs occurs in the vicinity of overhead powerlines.

EMFs in the low and very low part of the electromagnetic spectrum are not able to cause direct damage to cells or DNA and there is no established carcinogenic mechanism[630]. One proposed mechanism for a link between ELF EMF and breast cancer risk is via the reduction of levels of melatonin, although there is no consistent evidence to support this hypothesis.[630]

IARC

The International Agency for Research on Cancer (IARC)[630] classified ELF magnetic fields as '*possibly carcinogenic to humans*' (Group 2B) based on evidence in relation to childhood leukaemia. ELF electrical fields (and static electrical and magnetic fields) were determined '*not classifiable as to their carcinogenicity in humans (Group 3)*'. Apart from the association with childhood leukemia, for which the evidence was evaluated as '*limited*' in humans, the IARC concluded that there was '*inadequate evidence in humans*' for the carcinogenicity of ELF magnetic fields in relation to all cancers, including breast cancer. They also concluded that there was '*inadequate evidence in humans*' for the carcinogenicity of static electric or magnetic fields and ELF electrical fields.

Recent evidence

Four systematic reviews with meta–analyses examined the association between ELF EMF exposure and risk of breast cancer.[631-634] All four meta–analyses included case–control studies only and there was substantial overlap in the included studies. Consequently, all four studies provided similar summary risk estimates for exposure to ELF EMF and risk of breast cancer: OR 1.07 (95% CI 1.00–1.15; 23 case-control studies); OR 1.10 (95% CI 1.01–1.20; 16 case-control studies); OR 1.07 (95% CI 1.02–1.13; 23 case-control studies); and, 0.99 (95% CI 0.90–1.09; 15 case-control studies), respectively. When stratified by menopausal status, an association was only observed between exposure to ELF EMF and risk of premenopausal but not postmenopausal breast cancer. One of the meta-analyses[633] stratified by hormonal subtypes, and reported an increased risk of ER–positive (OR 1.11, 95% CI 1.03–1.20) but not ER–negative (OR 0.96, 95% CI 0.84–1.10) breast cancer.

Substantial limitations to the findings of the meta–analyses were noted, due to methodological differences in quantifying exposure and heterogeneity between studies.

More recent data from a large Dutch occupational cohort of 62,573 postmenopausal women showed no association between occupational exposure to ELF EMFs and breast cancer risk, with no evidence of a dose–response trend with increasing duration of exposure or cumulative exposure.[635] Li et al.[636] similarly reported a null association in a case–control study nested in a cohort of Chinese textile workers, with no trend according to cumulative exposure to ELF EMFs.

Table D.79 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.10.2 Electromagnetic field radiation—radiofrequency

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to radiofrequency electromagnetic fields (RF–EMF) and risk of breast cancer is inconclusive. There are only a few available studies. Two large cohort studies have shown no association between use of mobile phones and risk of breast cancer.

Background

Radiofrequency electromagnetic fields (RF–EMF) are a form of non–ionising radiation that includes low frequency (LF), medium frequency (MF), high frequency (HF), very high frequency (VHF), ultra high frequency (UHF), microwave (MW) and millimeterwave, covering all frequencies between 30 kiloHertz (kHz) and 300 gigaHertz (GHz).[627] Exposure can come from both man–made and natural sources (earth and space) and is classified as personal, occupational or environmental. The strongest RF fields to which people are exposed come from induction heating, remote detection of objects and devices, telecommunications, medical diagnostics and medical therapy (for example, magnetic resonance imaging).[637] The most common exposure sources are via the use of mobile phones; lower levels of

exposure arise from high–power television and radio transmitters (up to several kilometres (km) away), mobile phone base station antennas (immediate vicinity only), microwave ovens, and magnetic resonance imaging.[627, 628]

RF–EMF radiation can heat human tissue, proportional to the rate of energy absorption, and the rate of energy absorption does not vary substantially according to frequency.[627] Ionising radiations such as X–rays are known to cause cancer in humans through enhancing cancer–causing carcinogens that cause DNA damage, but non–ionising radiations, such as the radiofrequency energy produced by cell phones, have not been found to be adequate for causing DNA damage.[638]

IARC

The International Agency for Research on Cancer (IARC)[637] evaluated the association between exposure to RF–EMF (personal, occupational and environmental exposures) and cancer, and classified them as '*possibly carcinogenic to humans (Group 2B)'*, based on an increased risk for glioma, a malignant type of brain cancer associated with wireless phone use.[637, 639] IARC noted there was limited evidence in humans for the carcinogenicity of RF–EMF radiation. The human epidemiological evidence was evaluated as being *limited* among users of wireless telephones for glioma and acoustic neuroma and *inadequate* to draw conclusions for other types of cancers, including breast cancer. IARC[637] noted that there was little information concerning mobile phone use and risk of breast cancer, but that no association was observed between mobile phone use and risk of breast cancer in a large national Danish cohort study (SIR 1.04, 95% CI 0.97–1.12; 711 cases).[640]

Recent evidence

One additional prospective study was identified examining exposure to ever versus never use of mobile phones and risk of brain neoplasms and other cancers.[641] After seven years' follow–up in a cohort of 791,710 middle–aged women in the United Kingdom, the Million Women Study of ever versus never use of mobile phones was not associated with any cancer type, including breast cancer (RR 0.99, 95% CI 0.96–1.02), nor was daily use or 10+ years of use associated with risk of breast cancer (RR 0.97, 95% CI 0.92–1.03; RR 1.02, 95% CI 0.96–1.08, respectively).

Two low quality studies examined the association between RF–EMF exposure from frequency modulation (FM) broadcasting transmitters and use of domestic electrical appliances, respectively, and risk of breast cancer.[642, 643] Hallberg et al.[642] reported the findings of an ecological study examining an association between density of FM broadcasting transmitters and incidence of breast cancer in 23 European countries and, separately, in Sweden. A significant correlation between average density of transmitters per 10,000 km^2 and risk of breast cancer was observed, although ecological studies are not suitable for examining causal associations. Davis et al.[643] conducted a population–based case–control study in Seattle (United States), examining the association between exposure to 60 Hertz (Hz) magnetic fields and breast cancer risk. Exposure was measured through self–reported use of domestic electrical appliances, 48 hour continuous measurements of magnetic field and light levels in the bedroom of the current residence, and quantification of electrical hardware and wiring from all residences occupied for at least six months. The study findings were null for all measures of exposure.

Table D.80 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.10.3 Occupation as a flight attendant (cosmic radiation)

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to cosmic radiation and risk of breast cancer among flight attendants is inconclusive. Although an increased risk of breast cancer has been observed among flight attendants/airline crew compared with the general population in several studies, the underlying reasons are uncertain as most studies did not adjust for known confounders. Any increased risk may be due to the disruption of circadian rhythms or to occupation–related lifestyle and reproductive factors. A cohort study found no association between estimated occupational cosmic radiation exposure and breast cancer risk among flight attendants.

Background

Flight attendants are exposed to higher levels of cosmic ionising radiation than the general population.[429] Exposure level depends on various factors such as flight route, altitude and type of aircraft. Median exposure levels of 2–9 millisieverts (mSv) per year are below the International Commission on Radiological Protection guideline limits of 20 mSv per year.[644]

Other possible environmental hazards that may play a role in cancer risk for flight crew include disruption of circadian rhythm (see section 4.7.24) due to irregular working hours and frequently crossing time zones.[429]

Flight attendants have been considered to be a highly selected group with many specific characteristics and exposures that might also influence cancers or other health conditions.[645]

IARC

The International Agency for Research on Cancer (IARC) classified 'neutron radiation' (a component of cosmic radiation) as '*carcinogenic to humans (Group 1)*' and 'shiftwork with circadian disruption' as a '*probable human carcinogen (Group 2A)*'. However no weight was accorded to studies involving 'occupation as a flight attendant' as providing evidence of an increased risk of cancer at any anatomical site, including breast cancer.

In the IARC monographs on neutron radiation and shift work involving circadian rhythm disruption,[333, 429] brief reference is made to studies on cancer risk among airline crew. These monographs noted nine cohort studies published between 1995 and 2003, which compared breast cancer incidence in flight attendants with that observed in the general population, with SIRs ranging between 1.0 and 2.0.

Recent evidence

A systematic review with meta–analysis that included data from 10 cohort studies was published in 2016, reporting a pooled SIR of 1.40 (95% CI 1.30–1.50).[646] This finding was consistent with two previous meta–analyses.[647, 648] The review by Liu et al.[646] has been criticised, however, for including overlapping study populations.[649] Moreover, most of the contributing studies were retrospective cohort studies with cancer diagnoses established through record linkage, without the ability to adjust for occupation–related lifestyle factors known to be associated with breast cancer risk, such as alcohol consumption and lower parity.

A cohort study examined exposure to cosmic radiation and circadian rhythm disruption in relation to breast cancer risk among 6,093 flight attendants.[650] After adjustment for age, age at menarche, height, alcohol consumption, parity, age at first birth, hormone therapy use and family history of breast cancer (first– and second–degree relatives), exposure to cumulative cosmic radiation dose was not associated with breast cancer incidence among these flight attendants. An earlier report of the same cohort, which was included in the meta–analysis by Liu et al.,[646] showed the increased incidence of breast cancer in flight attendants compared with the general population was due to differences in reproductive factors, including lower parity and later age at first birth.[651]

A large collaborative analysis of the joint Nordic study (8507 female flight attendants) reported a higher incidence of breast cancer in flight attendants compared with the general population after adjustment for reproductive factors (SIR 1.50, 95% CI 1.32–1.69).[652] The collaborative analysis included data from four national cohorts (Finland, Iceland, Norway, Sweden) which were individually reported previously and included in the meta–analysis by Liu et al.[646] as separate reports (albeit with shorter duration of follow–up).

Table D.81 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.10.4 Sun exposure

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between sun exposure and risk of breast cancer is inconclusive. There are a limited number of prospective studies available. Findings are inconsistent and limited by differences in exposure measurement. Some evidence suggests circulating levels of the bioactive form of vitamin D (25–hydihydroxyvitamin D, or 25(OH)D) may be associated with a decreased risk of breast cancer; however the evidence is mainly from case–control and nested case–control studies rather than prospective studies.

Background

Sunlight is the major source of human exposure to ultraviolet radiation (UVR), which includes wavelengths in the range of 100–400 nanometres (nm). It is further subdivided into UVA (315–

400 nm), UVB (280–315 nm) and UVC (100–280 nm).[653] Midday sun comprises approximately 95% UVA and 5% UVB.[653]

A proposed mechanism linking sunlight to breast cancer is vitamin D synthesis. The majority (80–90%) of vitamin D comes from endogenous production that requires skin exposure to UVB rays from sunlight.[653, 654] A large number of studies have measured serum levels of the biologically active form of vitamin D (that is, 25(OH)D). The link between sun exposure and 25(OH)D level is often not explicit, however.

The effects of vitamin D are mediated through the vitamin D receptor (VDR). The VDR is a steroid hormone receptor that is expressed in many cell types, including normal and malignant breast cells.[655] Vitamin D has been shown to play a role in regulating the proliferation, differentiation and survival of breast cancer cells.[656] Other hypothesised mechanisms include the influence of sunlight on immune function, on the production of melatonin, and on circadian rhythm. [655]

IARC

The International Agency for Research on Cancer (IARC) concluded '*solar radiation is carcinogenic to humans (Group 1)*', based on evidence relating to cutaneous melanoma and the keratinocyte skin cancers (basal cell carcinoma and squamous cell carcinoma), but not breast cancer. IARC examined three case–control and two cohort studies related to breast cancer. Three studies used location of residence as a measure of ambient sun exposure. Analyses of the Nurses' Health Study for women in California did not find a geographic gradient for increasing exposure to radiation and risk of postmenopausal breast cancer. A US death certificate–based case–control study observed a significant inverse association between residential and occupational sunlight and risk of breast cancer.[657] In the National Health and Nutrition Examination Survey I (NHANES I) prospective study, several measures of sunlight exposure were associated with decreased risk of breast cancer (RR 0.64–0.85).[658]

Recent evidence

Sun exposure

Three large cohort studies reported on different measures of sunlight in relation to breast cancer incidence.[659-661]

The US Radiologic Technologists (URST) study (36,725 women) reported ambient UVR (HR for lifetime fifth versus first quintile 1.22, 95% CI 0.95–1.56), time outdoors (HR for lifetime fifth versus first quintile 0.87, 95% CI 0.68–1.10) and combined UVR (HR for lifetime fifth versus first quintile 0.85, 95% CI 0.67–1.08) were unrelated to breast cancer risk.[659] Lin et al[660] also reported no association between cumulative ambient sun exposure and breast cancer risk in the National Institutes of Health–American Association of Retired Persons (NIH–AARP) Diet and Health study (178,138 women).

A large Swedish cohort study (42,559 women) found an association between some but not all measures of sun exposure and breast cancer risk.[661] Spending more than one week per year on sunbathing vacations when aged 10–29 years was inversely associated with breast cancer risk (HR 0.56, 95% CI 0.36–0.89). The annual number of sunburns or sunbathing vacations at other ages had no association with breast cancer risk.

Serum 25(OH)D

The most recent meta–analysis of the effects of serum 25(OH)D, serum 1,25(OH)2D and vitamin D intake on breast cancer risk[662] showed a protective effect between 25(OH)D and breast cancer in four cohort studies (RR 0.85, 95% CI 0.74–0.98) and 29 case–control studies (OR 0.65, 95% CI 0.56–0.76). This effect was not observed, however, in nested case–control studies (OR 0.92, 95% CI 0.83–1.01). A protective effect was observed for both premenopausal and postmenopausal breast cancer. This protective association persisted only in the premenopausal group (OR 0.67, 95% CI 0.49–0.92), however, when the analysis was restricted to nested case–control studies. Analysis by menopausal status was not possible for cohort studies.

Estébanez et al.[662] reported on the findings of eight meta–analyses (published between 2008 and 2014) that reported on 25(OH)D and risk of breast cancer. One of these meta–analyses, Gandini et al.,[663] provided evidence of a dose–response association with a decrease in the risk of breast cancer of 0.89 (95% CI 0.81−0.98) per 10 ng/mg increase in serum 25(OH)D. The significant protective effect was restricted to case–control studies which had many methodological limitations (RR 0.83, 95% CI 0.79–0.87) however, and was not evident for nested case–control and prospective cohort studies (RR 0.97, 95% CI 0.92–1.03).

Table D.82 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.10.5 Ionising radiation—diagnostic

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to diagnostic ionising radiation and risk of breast cancer is inconclusive. There were only two human epidemiological studies identified in the general population in relation to exposure to low dose diagnostic radiation. A record linkage study on computerised tomography (CT) scans during adolescence in Australia showed no association with breast cancer risk. An earlier study of monitoring radiaography for scoliosis did not show a significant excess risk for breast cancer.

No epidemiological studies of the radiation effects of mammographic screening on risk of breast cancer have been conducted.

Background

Diagnostic ionising radiation, or diagnostic radiation, refers to the clinical use of ionising radiation for diagnosis purposes, including X–rays, computed tomography (CT), fluoroscopy and angiography. Ultrasound and magnetic resonance imaging (MRI) do not use ionising radiation. Ionising radiation is measured in units of absorbed dose, which are Gray (Gy). Diagnostic examinations are the main source of radiation from medical use.[653, 664] The average dose of irradiation per medical diagnostic examination is between 0.1–20 mGy;[653] the average dose to the breast from a chest X–ray is 0.45 mGy[665] and from mammographic examination is 1.5 mGy.[653]

Radiation dose is also measured in units of Sieverts (Sv), which is a derived unit of ionising radiation dose and often the radiation dose is compared in Sieverts for exposures to x-rays including mammograms, and CT scans, compared to an equivalent period of exposure to background radiation for natural sources. Australian Radiation Protection and Nuclear Safety Agency (ARPANSA)[666] indicates that on average Australians are exposed to 1.5 mSv per year from natural sources. This is about the same amount of radiation received from 75 chest X–rays—one chest X-ray delivers approximately 0.02 mSv. Mammographic examination delviers 0.7 mSv. The average dose per CT procedure (1.5–25 mSv) is considerably higher than for most conventional X–ray procedures.[653]

Average levels of radiation exposure due to diagnostic use are increasing in developed countries worldwide, due to increasing use of CT, angiography, and interventional procedures;[653, 664] although amounts of radiation used in these procedures is decreasing.[667, 668]

Ionising radiation may increase risk of cancer through the energy transfer to cells, which can cause DNA damage either directly or indirectly through ionisation of water and the formation of free radicals.[628] Damaged DNA that is not repaired, or is misrepaired, can lead to carcinogenesis.[653] It has been proposed that exposure to radiation may be particularly carcinogenic when it occurs during sensitive periods in breast development, such as in utero, puberty and pregnancy, which are characterised by rapid proliferation of undifferentiated cells[669]. Proposed mechanisms include changes in tissue composition and stem cell regulation after exposure. Evidence from the study of atomic bomb survivors over more than 64 years shows increased breast sensitivity to ionising radiation in females during puberty[669]. Further, there is some concern that young *BRCA* (and other) mutation carriers are particularly at risk because of their impaired ability to repair the radiation induced double-strands DNA breaks.[670]

While the risk of cancer from exposure to high radiation doses is relatively well quantified and risk increases linearly with dose (e.g. Berrington de Gonzalez et al.,[671] Brenner et al.[669]), for low radiation exposures such as those received through medical imaging, the scientific evidence for increased health risk is more limited; and the linearity of association at doses below 100 mSv has been disputed.[666, 672] There is some evidence to suggest low doses of radiation might even benefit biological outcomes.[672]

IARC

The International Agency for Research on Cancer (IARC)[653] have evaluated the association between X–radiation and (gamma)γ–radiation and breast cancer risk and determined that there is sufficient evidence for a causal association. The evaluation was based on evidence from four studies, and, importantly, for three of these the exposure was *therapeutic radiation* rather than diagnostic radiation (section 4.10.6). The study examining exposure to diagnostic radiation was by Ronckers et al..[665] This retrospective cohort study was of 3010 women monitored by radiography for scoliosis between 1912 and 1965. The total breast dose received was 12 cGy and the average number of breast-exposed radiographs was 24. A non-significant excess relative risk (ERR) per Gy of exposure of 2.86 (95% CI -0.07–8.62) was observed during 118,905 woman-years of follow-up (median, 35.5 years) based on 78 cases of invasive breast cancer. A significantly larger dose-response relationship was observed for women with a family history of breast cancer in first or second-degree relatives (ERR/Gy 8.37,

95% CI 1.50-28.16) compared to women without affected relatives (ERR/Gy -0.16, 95% CI <0-4.41).

Recent evidence

Mathews et al.[673] examined the association between exposure to ionising radiation from diagnostic CT scans during adolescence and subsequent breast cancer risk in Australians using record linkage to administrative claims data for the time period 1985-2005. Mean follow-up was 9.5 years in the exposed group and 17.3 years in the unexposed group. The IRR for the exposed group compared with the unexposed group was not increased for breast cancer (among men and women)(IRR 0.99, 95% CI 0.83–1.17), and the absolute excess incidence rate was -0.03 per 100,000 person years (95% CI -0.39–0.34).

Several modelling studies have predicted the number of radiation-induced breast cancers from mammographic screening. These have been based on a linear association between ionising radiation exposure and risk of breast cancer observed among atomic bomb survivors.[674] One of these modelling studies has predicted that biennial mammographic screening among women aged around 50–75 years is associated with 27 (95% CI 19–38) radiation-induced breast cancers per 100,000 women screened [675]. In a similar type of modelling study, mammographic screening is estimated to induce 30–60 breast cancers per 100,000 women screened.[676]

Potential increased incidence of breast cancer through mammography screening is offset by the decreased breast cancer mortality associated with screening (e.g. Nelson et al.,[677] Miglioretti et al.[675]). In the modelling study by Miglioretti et al.,[675] it was estimated that 627 breast cancer deaths (determined from mortality rates from clinical trials and cohort studies) would be averted per 100,000 women screened; the ratio of predicted radiation-induced cancers to breast cancer deaths averted was 23 (95% CI 16−33). Similarly, Nelson et al.[677] estimated that women aged 50 to 69 years undergoing screening mammography have a 25% to 31% relative reduction in deaths from breast cancer. Mortality reduction has been estimated in two cohort studies in Australia[678] and New Zealand[679], to be 25%, 22% and 34% respectively.

Increased risk of breast cancer associated with mammographic screening has been shown in a dose-response relationship among women who are carriers of *BRCA1* or *BRCA2* gene mutations (e.g. Pijpe et al.[680], Colin et al.[681]), but no population estimates of risk could be determined for mammographic screening and the general population, except those derived by predictive modelling.[677] The systematic review by Colin et al.[681] showed an association between exposure to low cumulative X–ray doses before age 30 among *BRCA* mutation carriers and risk of breast cancer but no consistent data regarding the risk of breast cancer from radiological exposure after age 30. A review by Pauwels et al.[682] more cautiously recommends that individuals at high risk of breast cancer should avoid ionising radiation as much as possible.

Table D.83 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.10.6 Ionising radiation—radiotherapy

Evidence summary

Evidence classification: Convincing (for most exposures).

There is convincing evidence that exposure of women to therapeutic ionising radiation in the chest region for Hodgkin lymphoma (HL) and various childhood cancers, including HL in childhood, is associated with an increased risk of breast cancer. The evidence is consistent. There is a linear dose response relationship which is often expressed as excess relative risk per Sievert (Sv)or per Gray (Gy). A meta–analysis of four cohort studies by Doi et al.[683] reported an excess relative risk (ERR) of 0.31 (95% CI 0.16–0.59) for radiation therapy for childhood cancers and subsequent risk of breast cancer across study types. Most women do not know the dose of ionising radiation received. An overall increased relative risk for radiation (only) treatment for HL has been estimated as 4.70 (95% CI 3.28–6.75).[491] This risk is estimated to be higher among those treated at a younger age (<30 years; RR 14.08, 95% CI 9.93–19.98)[491] and particularly those treated close to menarche.

Background

Mantle field radiation, rarely used today, was used to treat HL in the 1960s. Radiation was delivered to a large area of the neck, chest and armpits. Other types of radiation treatment of the chest to treat childhood cancers include mediastonal irradiation, whole lung irradiation and total body irradiation. The mediastinum is the area of the chest that separates the lungs and is surrounded by the breastbone at the front, the spine at the back and the lungs on each side. Chemotherapy is now used in all patients and 'field radiation' is only delivered to a small area that initially has enlarged nodes.

Radiation exposure is measured in units of Gray (Gy). Linear dose–response and risk of breast cancer can also be given as excess relative risk per Gy (ERR/Gy); that is, increased risk is approximately proportional to the dose received.[684] In studies that included the radiation exposure levels for HL treatment, dose range was 10–50 Gy.[685-687] Within contemporary radiotherapy, chest radiation doses are generally in the range 10–19 Gy.[687] These doses are considerably higher than those used in diagnostic radiation (section 4.10.5).

Ionising radiation is a genotoxic carcinogen increasing risk of multiple tumour types. Ionising radiation may increase risk of cancer through the energy transfer to cells, which can cause DNA damage either directly or indirectly through ionisation of water and the formation of free radicals[628]. Damaged DNA that is not repaired, or is misrepaired, can lead to carcinogenesis[653]. It is this nonlethal cell modification that can eventually lead to malignant disease. Susceptibility is influenced by genetic factors.[628, 684, 688, 689]

It has been proposed that exposure to radiation may be particularly carcinogenic when it occurs during sensitive periods in breast development, such as in utero, puberty and pregnancy, which are characterised by rapid proliferation of undifferentiated cells.[669] Proposed mechanisms include changes in tissue composition and stem cell regulation after exposure. Evidence from the study of atomic bomb survivors over more than 64 years shows increased breast sensitivity to ionising radiation in females during puberty.[669]

IARC

The International Agency for Research on Cancer (IARC)[653] evaluated the epidemiological evidence for the carcinogenicity of X–radiation and γ(gamma)–radiation and breast cancer as '*sufficient*'.

Recent evidence

Much of the evidence relates to radiation treatment for HL and childhood cancers generally.

A meta–analysis of four cohort studies by Doi et al.[683] reported an excess relative risk (ERR) of 0.31 per Gy (95% CI 0.16–0.59) for radiation therapy for childhood cancers, including HL, and subsequent risk of breast cancer, across study types. Heterogeneity across studies was partly attributed to age at exposure.

A meta–analysis of 34 cohort studies examined the risk of breast cancer among female survivors of HL who developed HL at a median age of 23.7 years.[491] This study reported an increased risk of subsequent breast cancer among those treated with radiation as the sole therapeutic modality compared to all treatment modalities (with or without chemotherapy)(RR 4.70, 95% CI 3.28–6.75; 6 studies), and this risk was higher among those treated at a younger age (RR ≤30 years 14.08, 95% CI 9.93–19.98). There was no increased risk among women treated at age 40 years or older (RR 0.55, 95% CI 0.09–3.52). The risk was slightly higher for those treated with radiation plus chemotherapy or radiation therapy plus alkylating CT. A dose-response was not observed across all studies.

Sud et al.[690] have also reported no association with risk of breast cancer among women treated with radiation for HL at ages older than 35 years.

Ten cohort studies, including a nested case–control study, published 2009–2017 showed an increased risk of breast cancer following radiation treatment for HL or childhood cancers.[685, 686, 690-693] Three articles reported data from the Childhood Cancer Survivor Study (CCSS) in the United States/Canada.[687, 694, 695] For example, Inskip et al.[696] observed an excess risk of breast cancer of 0.27 per Gy (95% CI 0.10–0.67), equating to relative risks of 6.4 and 11.8 from radiation doses of 20 Gy and 40 Gy compared to no radiation, respectively among 5,797 female childhood cancer survivors. The slope increased to 0.34 per Gy (95% CI 0.10–0.67) when restricted to higher quality data. First cancers were mainly HL and bone cancer. Moskowitz et al.[695] showed that risk is increased after chest/absorbed doses of more than 10 Gy, with a dose-response relationship.

In particular, risk is increased with radiation treatment relative to age at menarche, with treatment closest to menarche associated with the highest risk.[691, 694]

Risk of breast cancer varies by treatment–related factors including the area of chest irradiated. The highest risk is associated with whole lung irradiation, followed by mantle irradiation and then mediastinal irradiation.[685, 687] Teepen et al.[692] reported treatment with total body irradiation for childhood cancers was associated with an increased risk of breast cancer of 10.6 (95% CI 3.7–30.2), compared with no RT. The same study reported an increased risk of breast cancer associated with chest irradiation of 2.5 (95% CI 1.3–4.9), compared with no RT.

Moskowitz et al.[695] reported no association with risk of breast cancer among women treated with spinal irradiation for leukaemia and central nervous system tumours during childhood compared to expected cases in the general population (SIR 2.4, 95% CI 0.8–7.5), although the risk was significant among those treated for childhood leukaemia (SIR 3.8, 95% CI 1.2–11.7). This study included 363 patients and only 3 cases of breast cancer.

Table D.84 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

4.10.7 Radioactive treatment for thyroid cancer

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between receiving radioactive iodine treatment (RAI) for thyroid cancer and risk of breast cancer is inconclusive. No studies showed any association. The studies evaluating the association generally had relatively short mean/median follow–up periods, however, which may not have sufficiently covered the latent period for breast cancer development.

Background

Radioactive iodine, also known as ^{131}I, is a radioisotope treatment that has been commonly used for radioactive ablation of benign overactive thyroid and of locally invasive or metastatic thyroid cancer for over 50 years.[333] When ingested, it is absorbed into the blood stream but concentrates only in thyroid cells because they express a sodium iodine transporter.[333] The radiation leads to cell death in thyroid cells that uptake the ^{131}I, with little damage to surrounding tissues.

There are concerns that women treated with radioactive iodine for thyroid disease may have a higher risk of breast cancer, although there is no clear biological mechanism to explain a possible link.[697]

IARC

The International Agency for Research on Cancer (IARC)[333] classified short–lived radioisotopes of iodine, including ^{131}I, as '*carcinogenic to humans (Group 1)*' and concluded that there is sufficient evidence in humans that exposure during childhood and adolescence to short–lived radioisotopes of iodine, including ^{131}I, causes cancer of the thyroid. Positive associations between exposure to ^{131}I and several other cancers were also noted, including cancer of the digestive tract and salivary gland, leukaemia, and bone and soft tissue sarcoma. The Working Group evaluated four case–control studies that examined breast cancer incidence following treatment for thyroid cancer. Two of the studies reported significantly increased risk of breast cancer, but it was noted that these increases were not related to ^{131}I exposure, and cited a lack of detail on levels of administered ^{131}I.[653]

Recent evidence

Two systematic reviews with meta–analyses have evaluated the association between RAI treatment for thyroid cancer and breast cancer risk.[698, 699]

The most recent review included data from six cohort studies. Among 17,914 women treated for thyroid cancer, those treated with RAI (9,000 RAI–treated patients) had a lower risk of breast cancer, compared with women with thyroid cancer not treated with RAI (pooled RR 0.61, 95% CI 0.7–0.79).[699] The mean follow–up time of the included studies ranged from 7.8 to 12 years. There was no evidence of significant heterogeneity across studies. The earlier review included two multi–centre studies, one of which[698] was also included in the meta–analysis by Zhang et al.[699] The pooled RR of breast cancer in women with thyroid cancer treated with RAI, compared with those not treated with RAI was 0.86 (95% CI 0.64–1.16). One of the contributing studies had a median follow–up period of 8.6 years, and the second had a mean of 13 years. These relatively short mean/median follow–up periods were a limitation of both studies.

Data from a national population–based cohort study conducted in Taiwan was published after the two meta–analyses.[503] The study included 10,361 women with thyroid cancer, of which 7,069 received RAI treatment. After a median follow–up period of 6.5 years, the risk of breast cancer was not significantly elevated in women with thyroid cancer treated with RAI, compared with those not treated with RAI. There was no evidence of a dose–response relationship.

Table D.85 contains detailed information about the studies discussed above, including sample size, exposures, outcomes, risk estimates, and any adjustments and limitations.

5 Summary

Overview

This review provides a detailed assessment of the body of evidence for each of a large number of factors which have been considered as potentially associated with an increased or decreased risk of breast cancer.

The evidence for each factor has been classified according to an explicit framework (section 2.4.1); specifically the evidence has been classified as 'Convincing', 'Probable', 'Suggestive', 'Inconclusive' or 'Evidence of no association'. Best estimates of increased or decreased risk are provided for those factors for which the evidence is classified as 'Convincing or 'Probable'.

There are a modest number of factors for which the evidence is 'Suggestive' of an association but for which more evidence is needed before they can be considered as risk or protective factors.

Further, there are a large number of factors for which the evidence is 'Inconclusive'. These factors are the most difficult for which to communicate the evidence as they may be classified as 'Inconclusive' for a number of reasons relating to the quality of evidence, or to the quantity of evidence, or to inconsistent findings across studies, or for any combination of these reasons. For some of the factors classified as 'Inconclusive' there is indicative but not sufficient evidence that they are not associated with risk of breast cancer. Where this is so, then this is indicated in the summary text for that factor. For some of these factors there is a lack of biological plausibility but the evidence is too limited, often in amount and quality, to be more certain that they are not associated with risk of breast cancer. For a small number of factors the evidence has been considered to be sufficient to indicate that there is no association with risk of breast cancer, or at least that an association is highly unlikely, and these are classified as 'Evidence of no association'.

The classifications are indicated below, as are the best estimates of risk for factors where the evidence has been classified as 'Convincing' or 'Probable'. A brief narrative summary of the findings of this review are also presented on a 'per factor' basis.

Evidence classifications

The classification for each factor is summarised in Table 5.1.

Table 5.1 Evidence classifications

Classification	Factor
Convincing	Age
	Geographic location and residence
	Urbanisation
	High socioeconomic status
	Height

Convincing	High mammographic breast density
	Family history of breast cancer
	Family history of other cancers
	ATM gene mutation
	BRCA1 gene mutation
	BRCA2 gene mutation
	CDH1 gene mutation (lobular breast cancer)
	CHEK2 gene mutation
	PALB2 gene mutation
	PTEN gene mutation
	Polygenic risk score (single nucleotide polymorphisms)
	STK11 gene mutation (with family history PJS)
	TP53 gene mutation
	Previous benign breast disease (proliferative)
	LCIS (lobular carcinoma in situ)
	DCIS (ductal carcinoma in situ)
	Previous primary invasive breast cancer
	Later age at menarche
	Nulliparity (risk)/parity (protective)
	Later age at first birth
	Later age at menopause
	Circulating hormones—oestrogen (postmenopausal), testosterone, insulin–like growth factor [IGF1])
	Current use combined hormonal contraception
	Current use combined menopausal hormone therapy
	Maternal exposure to Diethylstilboestrol
	Adiposity (e.g. BMI) in adulthood (postmenopausal)
	Weight gain (postmenopausal)
	Alcohol consumption
	Ionising radiation—radiotherapy

Probable	Birthweight (premenopausal)
	Breastfeeding (protective)
	High levels physical activity (protective)

Suggestive	Previous cancer other than breast cancer
	High levels vigorous physical activity (premenopausal) (protective)
	Diet—high in processed meat
	Tobacco smoking
	Shift work disrupting circadian rhythm
	Cardiac glycosides (digoxin)
	Diet—high in calcium (protective)
	Diet—high in vegetables (protective)
	Diet—high in foods containing carotenoids (protective)

Inconclusive	Birthweight (postmenopausal)
	Having been breastfed
	Breast size

Inconclusive	Bras
	Circulating hormones—oestrogen (premenopausal), sex hormone binding globulin [SHGB], luteal phase progesterone, prolactin
	Polycystic ovarian syndrome (PCOS)
	Hormonal contraception—progestogen only
	Menopausal hormone therapy—oestrogen only
	Hormonal infertility treatment
	DES in utero
	Adiposity—weight loss
	Coffee, tea, caffeine
	Diet—dietary fibre
	Diet—fruit
	Diet—Mediterranean diet
	Diet—phytoestrogens
	Diet—glycaemic index
	Diet—total energy
	Diet—sugar
	Diet—fat
	Diet—red meat
	Environmental tobacco smoke
	Aspirin
	Human papillomavirus (HPV)
	Hysterectomy
	Breast implants
	Stress
	Trauma to the breast
	Type 2 diabetes
	Bisphenol A (BPA)
	Deodorant/antiperspirant
	Dioxin
	Ethylene oxide
	Land contamination
	Outdoor air pollution
	Parabens
	Pthalates
	Polychlorinated biphenyls
	Occupation as a hairdresser
	Personal use hair dyes/relaxers
	Electromagnetic field radiation—low frequency
	Electromagnetic field radiation—radiofrequency
	Occupation as a flight attendant (cosmic radiation)
	Sun exposure
	Ionising radiation—diagnostic
	Radioactive treatment for thyroid cancer

Evidence of no association	Previous non-proliferative benign breast disease
	Pregnancy termination
	DDT exposure

Magnitude of risk

Estimated risks for those factors for which there is sufficiently strong evidence of an association with risk of breast cancer, i.e. those factors for which the body of evidence was classified as either 'Convincing' or 'Probable', are summarised in Table 5.2.

Table 5.2 Summary of risk estimates for factors where the body of evidence has been classified as either 'Convincing' or 'Probable'

Factor	Risk estimate	Reference
General & personal characteristics		
Age 50 years vs. 30 years old	10[xi]	AIHW (2017)[27]
Height per 10 cm increase in height	1.17 (95% CI 1.15–1.19)	Zhang et al. (2015)[47]
Mammographic breast density odds per standard deviation	1.53 (95% 1.44–1.64)	Pettersson et al. (2014)[56]
Family history & genetics		
Family history of breast cancer ≥ 1 second degree relatives 1 first degree relative 2 first degree relatives ≥ 3 first degree relatives	 1.5 (95% CI 1.4–1.6) 1.80 (95% CI 1.69–1.91) 2.93 (95% CI 2.36–3.64) 3.90 (95% CI 2.03–7.49)	 CGHFBC[xii] (2001)[76] CGHFBC (2001)[76] CGHFBC (2001)[76] Pharoah et al (1997)[77]
***ATM* gene mutation** mutation carrier vs. non-carrier	1.74 (95% CI 1.46–2.07)	Kurian et al. (2017)[93]
***BRCA1* gene mutation** mutation carrier vs. non-carrier	5.91(95% CI 5.25–6.67)	Kurian et al. (2017)[93]
***BRCA2* gene mutation** mutation carrier vs. non-carrier	3.31(95% CI 2.95–3.71)[xiii]	Kurian et al. (2017)[93]
***CHEK2* gene mutation** mutation carrier vs. non-carrier	1.99 (95% CI 1.70–2.33)	Southey et al. (2016)[128]
***PALB2* gene mutation** mutation carrier vs. non-carrier	3.39 (95% CI 2.79–4.12)	Kurian et al. (2017)[93]
***PTEN* gene mutation** mutation carrier vs. non-carrier	5.83 (95% CI 2.43–14.0)[xiv]	Kurian et al. (2017)[93]

[xi] Determined from age–specific incidence rates reported by AIHW in 2017
[xii] Collaborative Group for Hormonal Factors in Breast Cancer
[xiii] Cumulative risk among women with family history higher, comparable with that for *BRCA1* mutation
[xiv] Risk estimate uncertain (wide confidence intervals) due to low frequency of gene mutation

Single nucleotide polymorphisms (SNPs) highest 1% of PRS distribution[xv] vs. middle quintile PRS distribution lowest 1% of PRS distribution vs. middle quintile PRS distribution	3.36 (95% CI 2.95–3.83) 0.32 (95% CI 0.25–0.40)	Mavaddat et al. (2015)[141]
***TP53* gene mutation** mutation carrier vs. general population	5.37 (95% CI 2.78–10.4)[xiv]	Kurian et al. (2017)[93]
Breast pathology		
Proliferative benign breast disease atypical hyperplasia proliferative disease without atypia	3.93 (95% CI 3.24–4.76)[xvi] 1.76 (95% CI 1.58–1.95)[xvi]	Dyrstad et al. (2015)[168]
Lobular carcinoma in situ diagnosis of LCIS vs. general population	Uncertain: range 2 – 12	
Ductal carcinoma in situ diagnosis of DCIS vs. general population	3.9 (95% CI 3.6–4.2)	AIHW NBOCC (2010)[199]
Endogenous hormones		
Age at menarche per year younger at menarche	1.05 (95% CI 1.044–1.057)	CGHFBC (2012)[220]
Age at first birth per one year older ≥ 30 years vs. 25–29 years old	1.03 (95% CI 1.02–1.05) 1.20 (95% CI 1.02–1.42)	Sisti et al. (2016)[229] Nelson et al. (2012)[226]
Age at menopause per year older at menopause	1.029 (95% CI 1.025–1.034)	CGHFBC (2012)[220]
Breastfeeding per 5–month increase in duration	0.98 (95% CI 0.97–0.99)	WCRF/AICR (2018)[11]
Nulliparity nulliparous vs. parous women	1.16 (95% CI 1.04–1.26)	Nelson et al. (2012)[226]
Parity per birth	0.93 (95% CI 0.91–0.95)	CGHFBC (2002)[224]
Exogenous hormones		
Exposure to DES while pregnant exposed vs. unexposed women	1.27 (95% CI 1.07–1.52)	Titus–Ernstoff et al. (2001)[310]
Combined oral contraceptive pill per 5 years of current use	1.07 (95% CI 1.03–1.11)	Zhu et al. (2012)[257]

[xv] For 77-SNPs

[xvi] Risk estimate possibly inflated due to reference group mainly women with benign breast biopsy diagnosed with non-proliferative disease

Combined menopausal hormone therapy current use vs. never use	1.72 (95% CI 1.55–1.92)	Munsell et al. (2014)[276]
Lifestyle factors		
Body mass index (postmenopausal women) per 5–unit increase in BMI	1.12 (95 CI% 1.09–1.15)	WCRF/AICR (2018)[11]
Adult weight gain per 5 kg increase in weight	1.06 (95% CI 1.05–1.08)	WCRF/AICR (2018)[11]
Alcohol consumption per 1 standard drink (10 g) per day	1.07 (95% CI 1.05–1.09)	WCRF/AICR (2018)[11]
Physical Activity (postmenopausal women) highest vs. lowest levels	0.87(95% CI 0.79–0.96)	WCRF/AICR (2018)[11]
Vigorous physical activity (premenopausal women) highest vs. lowest levels	0.83 (95% CI 0.73–0.95)	WCRF/AICR (2018)[11]

General factors

Age is the main risk factor for breast cancer, with the majority of breast cancers occurring in women aged over 50 years. However, there are windows of susceptibility to other factors affecting long–term risk of breast cancer across the lifespan.

A number of general factors are associated indirectly with risk of breast cancer including place of birth, place of residence including geographic location and remoteness, Indigenous status, and socioeconomic status. These distal factors reflect exposures across a lifetime as well as current exposures. In Australia, interrelationships exist between socioeconomic status, remoteness and Indigenous status.

These general factors may act indirectly through differences in reproductive factors such as parity, and lifestyle factors such as alcohol consumption. These factors may be influenced by other factors, such as the physical attributes of an area that may promote or hinder exposure to breast cancer risk factors such as physical activity. Differences in breast cancer incidence across regions may also be due to differences in availability of and access to screening and diagnosis.

Personal characteristics

Birthweight is probably associated with a very small increased risk of premenopausal breast cance, but is unlikely to be directly causal. Rather, it is likely a marker for prenatal growth and a predictor of later growth and maturation, such as age at menarche—factors which are themselves determinants of breast cancer risk. The evidence for a positive association between adult-attained height and risk of breast cancer is convincing, although this factor is again unlikely to be directly causal and more likely to be a reflection of growth processes determined by genetic and environmental factors, including nutritional components.

The evidence for 'Having been breastfed' and risk of breast cancer is inconclusive and this may reflect the opposing potential mechanisms that may increase and decrease risk of breast cancer, or there may indeed be no association.

There is convincing evidence that mammographic breast density is associated with risk of breast cancer but the magnitude of risk has been frequently misreported. Several meta-analyses have reported on risk for women with higher breast density compared with women with the least dense breasts. Fewer than 10% of women have breasts in the lowest and highest quartiles of breast density; and breast cancer risk among women with dense breasts is more usefully compared to women with average breast density. Accordingly women with moderately dense breasts have approximately 1.5 times the risk of breast cancer and women with moderately non-dense breasts have approximately 0.6 times the risk of breast cancer compared with women with averagely dense breasts. Breasts become less dense as women age.

Breast size does not appear to be related to risk of breast cancer although studies are limited methodologically.

Family history & genetic factors

Most women who develop breast cancer do not have a family history ofbreast cancer and/or an inherited genetic mutation, or both. However, family history of breast and several other cancers, including particularly ovarian cancer, and being a carrier of a number of genetic mutations are convincing, and established, risk factors for breast cancer. Risk is higher if the familial breast cancer is in first-degree relatives, such as mother, sister or children, than in second-degree relatives such as a grandmother or aunt. Risk is higher for younger women and for women whose relatives were diagnosed at a younger age. The mechanisms for increased risk include inherited genetic mutations, and shared exposure to environmental, reproductive and lifestyle factors. A family history of other cancers, in particular ovarian cancer, but also prostate and pancreatic cancer, similarly reflect shared genetic mutations or shared lifestyle, reproductive or environmental factors. Inherited mutations in genes such as *BRCA1, BRCA2, TP53, PALB2, PTEN and STK11* may increase the risk of other cancers as well as breast cancer through similar biological mechanisms. Families may have similar dietary patterns, reproductive habits, physical activity or body size that may influence risk of different cancers.[84]

Although a family history of several other cancers is known to be associated with increased risk of carrying one or more of the genetic mutations associated with breast cancer; few studies have estimated the risk magnitude between familial history of these cancers and risk of breast cancer among those women with unknown inheritance of the various gene mutations.

There are a number of high-penetrance rare gene mutations associated with increased risk of breast cancer, namely *BRCA1*, *BRCA2*, *PTEN*, *PALB2*, and *TP53*. Other rare gene mutations convincingly associated with risk of breast cancer are *ATM*, *CHEK2*, *STK11* and *CDH1*. *CDH1* is associated only with increased risk of lobular breast cancer—lobular breast cancer constitutes about 10% of breast cancer. Mutations in *STK11* are very rare and generally only identified among women with familial or personal Peutz-Jeghers syndrome (PJS).

Many of the risk estimates included in the summary table (Table 5.2) for genetic risk factors are from a study by Kurian et al.[93] which determined risk estimates adjusted for family history

of cancer. These estimates therefore represent the magnitude of risk that is applicable to women with no family history of relevant cancers, potentially indicating the estimated risk determined from a combination of genetic and environmental and lifestyle factors. Many of the risk estimates, particularly those for *BRCA1* and *BRCA2* mutations, may be much higher among women that will be tested clinically after being assessed as 'high-risk' due to histories suggestive of hereditary breast cancer predisposition.

Breast pathology

Benign breast disease (BBD) is increasingly diagnosed as an incidental finding on mammography. BBD can be dichotomised as proliferative and non-proliferative, based upon the degree of cellular proliferation and atypia. The evidence indicates that non-prolfierative disease is not associated with an increased risk of breast cancer but proliferative disease, particularly atypical hyperplasia and less so proliferative disease without atypia, is associated with an increased risk of breast cancer. A higher number of atypical foci are associated with a higher breast cancer risk. Most risk estimates for proliferative BBD have been determined among women who have had benign breast biopsies, comparing breast cancer incidence among those with proliferative disease versus those women with non-proliferative disease, and therefore the indicated risk estimates may be inflated. Proliferative breast disease is generally regarded as a marker for breast cancer susceptibility due to common risk factors, although precursor cells may exist in benign breast disease that may progress into breast cancer.

Similarly, lobular carcinoma in situ (LCIS) was thought to be a marker of increased breast cancer, but there is accumulating evidence that it may also be a precursor lesion. Although there is convincing and consistent evidence that LCIS is associated with an increased risk of breast cancer, the magnitude of risk is uncertain as studies have provided widely different estimates, ranging from around 2 to around 12. There is similarly convincing and consistent evidence that ductal carcinoma in situ (DCIS) is associated with an increased risk of breast cancer. Partly because it is more common than LCIS, the risk estimates across studies have been within a narrower range. Studies which have examined both LCIS and DCIS and risk of breast cancer show no significant differences in risk estimates between the two diagnoses. DCIS is a heterogeneous disease however, and the breast cancer risk may differ greatly between high, intermediate and low grade DCIS.

There is convincing evidence that having had a previous breast cancer is associated with an increased risk of a second primary breast cancer by a modest amount.

Endogenous hormones

There is convincing evidence that levels of circulating steroid hormones including oestrogen, testosterone and insulin-like growth factor 1 (IGF–1), are associated with an increased risk of postmenopausal breast cancer and possibly breast cancer overall. The evidence is inconclusive regarding levels of progesterone and risk of breast cancer, possibly because progesterone has proliferative and anti-proliferative effects in the body.

There is convicning evidence that various reproductive factors are associated with an increased risk of breast cancer, including age at menarche, age at menopause and parity. These factors are related to extended exposure to oestrogen which may be the mechanism by which they affect breast cancer risk. However, other mechanisms are involved. A

younger age at menarche is more strongly associated, albeit still modestly so, with risk of breast cancer than a later age at menopause as it increases the period before first full-term pregnancy during which time the breast is mitotically active. In this way, and through earlier induction of terminal differentiation of breast cells at risk, a lower age at first birth is associated with a decreased risk of breast cancer. Parity is also associated with decreased risk of breast cancer, in a dose-response manner, as cells undergo differentiation during pregnancy which is thought to make them less vulnerable to DNA damage.

Breastfeeding probably has a small protective effect on risk of breast cancer, likely through the hormonal effects of amenorrhoea in reducing exposure to steroid hormones, as well as changes to the epithelial cells.

The evidence is inconclusive regarding polycystic ovarian syndrome (PCOS) and risk of breast cancer, despite PCOS being associated with high levels of circulating testosterone and testosterone being associated with an increased risk of breast cancer. The available evidence does not show an association but is limited in quality.

Exogenous hormones

Both the combined oestrogen-progestogen oral contraceptive pill (OCP) and combined oestrogen-progestogen menopausal hormone therapy (MHT) are associated with an increased risk of breast cancer—and risk increases with increasing duration of use. There is convincing evidence that the risk of breast cancer is only associated with current use of the OCP, with the risk attenuating after stopping use; and probably only with current use of combined MHT, although persistence in risk may be associated with some formulations of combined MHT. There is an indication that triphasic preparations of the OCP containing levonorgestrel as the progestin are associated with a higher breast cancer risk than other formulations. Risk is higher among combined MHT users when use is commenced close to menopause.

The evidence is inconclusive regarding an association between progestogen-only contraceptives and risk of breast cancer. Similarly the evidence for oestrogen-only MHT and risk of breast cancer is inconclusive and there is no evidence of a dose-response effect suggesting that an association is unlikely. No association was observed in a randomised controlled trial.

The evidence is inconclusive regarding hormonal infertility treatment and risk of breast cancer, however the body of evidence does not support a positive association.

The evidence is convincing between exposure to diethylstilboestrol (DES) during pregnancy and increased risk of breast cancer. Earlier analyses of several cohort studies showed that exposure to DES in utero may have also been associated with risk of breast cancer, however longer-term follow-up of the women in these cohorts has shown no association between exposure to DES in utero and risk of breast cancer.

Lifestyle factors

There is convincing evidence that higher adiposity across adulthood and during the postmenopausal period is associated with an increased risk of postmenopausal breast cancer, but body fatness in young adulthood and during the premenopausal period is

probably protective for premenopausal breast cancer. It is suggested that higher levels of oestrogen associated with adiposity act differentially before and after menopause. Measures of adiposity positively associated with postmenopausal breast cancer risk include body mass index (BMI), waist circumference and waist-to-hip ratio. Use of MHT may mitigate the effects of breast cancer risk associated with adiposity, although findings are inconsistent.

There are methodological limitations in studies regarding the effect of weight loss on breast cancer risk.

Higher levels of most types of physical activity, including walking, household activities, occupational activities and vigorous physical activities such as running or fast cycling, are probably associated with a decreased risk of breast cancer.

There is convincing evidence that alcohol consumption is associated with increased risk of breast cancer in a dose-response manner with no threshold for increased risk. That is, there are no safe levels of daily drinking with respect to risk of breast cancer. The association may only be for oestrogen–receptor positive (ER+) breast cancer.

A large range of dietary factors have been investigated with respect to increased or decreased risk of breast cancer. The evidence from the many possible exposures have been considered at length by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR),[10, 11] and a group of these exposures were considered within this review. Establishing an association between dietary factors and risk of cancer is challenging due to often self-reported measures of exposure, changing dietary intakes and patterns over time, time lags between exposure and outcome and the need to account for numerous confounders, including other aspects of diet and other lifestyle factors, such as physical activity and alcohol consumption. Nevertheless, there is suggestive evidence that dietary calcium [but not supplemental calcium], dairy, non-starchy vegetables (for oestrogen-receptor negative [ER–] breast cancer), and foods high in carotenoids, are protective factors and that processed meat is a risk factor, for breast cancer.

The evidence is inconclusive of an association between intakes of red meat, fat, glycaemic index, glycaemic load, total energy, or sugar, and risk of breast cancer, although most studies show no association. A recent large cohort study in Australia provides evidence of a suggestive positive association between intake of sugary drinks and risk of breast cancer. There are possible associations with dietary fibre and risk of postmenopausal breast cancer and for soluble but not insoluble fibre intake but the evidence is still inconclusive. Recent long-term follow-up of a large cohort showed that higher levels of fruit intake may be associated with decreased risk of ER– breast cancer, however the body of evidence is inconclusive.

As phytoestrogens, including soy and soy products, have structural similarities to oestrogens it has been suggested that they may be associated with an increased risk of breast cancer. However phytoestrogens have been shown to bind only weakly to oestrogen receptors and to also have anti-oestrogenic effects. The evidence is inconclusive, with studies generally showing a lack of effect, with risk estimates close to unity and no evidence of a dose-response.

There is suggestive evidence of a positive association between tobacco smoking and risk of breast cancer. The evidence is stronger for starting smoking at a younger age or before first

birth being associated with an increased risk. Inconsistent findings regarding a dose-response effect limit a stronger classification.

Studies examining an effect of environmental tobacco smoke, or 'passive smoking', on risk of breast cancer are limited methodologically, especially with respect to measuring exposure, therefore the evidence is inconclusive.

Various aspects of bra wearing have been considered in a number of poor quality studies which have shown no association with risk of breast cancer and there is a lack of biological plausibility to any association.

The evidence regarding shift work involving disruption to the circadian rhythm is suggestive and is limited by the measurement of different exposures and confounding variables. The evidence is strongest for a possible association between a long duration of night shift work over 20 years or more, or after shorter periods involving many consecutive shifts, and increased risk of breast cancer.

Medical factors

The evidence is inconclusive regarding regular use of aspirin and risk of breast cancer although stronger quality cohort studies do not show an association. There is suggestive evidence that use of cardiac glycosides from the plant genus *digitalis*, predominantly digoxin, is associated with an increased risk of breast cancer.

There is suggestive evidence that having had a previous cancer other than breast cancer is associated with an increased risk of breast cancer, as per familial history of other cancers, and this is related to common genetic factors, and environmental and lifestyle factors, as per familial history of other cancers.

The evidence for any association between Human Papillomavirus (HPV) and risk of breast cancer is inconclusive due to poor quality evidence. Having had an hysterectomy is possibly protective but the evidence is inconsistent and therefore classified as 'Inconclusive'. Having type 2 diabetes is unlikely to be associated with risk of breast cancer although the evidence is confounded by factors such as adiposity and diet, and is therefore also classidied as 'Inconclusive'.

Stress is unlikely to be associated with risk of breast cancer—higher quality studies have not shown an association, although studies are limited methodologically—as is 'trauma to the breast' for which there is a lack of biological plausibility, although the evidence is also methodologically poor. Both exposures are therefore classified as 'Inconclusive'.

There is good quality, consistent evidence indicating that pregnancy termination is not associated with risk of breast cancer. The evidence is inconclusive regarding an association between breast implants and risk of breast cancer. The evidence is methodologically limited and suggests a decreased rather than increased, if any, association with risk of breast cancer. There is convincing evidence, though, that textured breast implants are associated with a very small increased risk of a rare lymphoma—anaplastic large cell lymphoma.

Chemical exposures

There are only a small number of studies for exposure to Bisphenol A (BPA) and risk of breast cancer, and no studies in humans for risk of exposure to parabens and risk of breast cancer, therefore the evidence for these two factors is classified as inconclusive. For DDT exposure there are large numbers of studies which consistently show no association hence the classification of 'Evidence of no association', although exposure to DDT in early life is understudied. The evidence for occupational exposure to ethylene oxide is inconclusive.

The biological plausibility of an association between polychlorinated biphenyls (PCBs) and risk of breast cancer is higher than for BPA and parabens, and the epidemiologicl studies are indicative of a positive association but the evidence is still limited, and therefore the classification 'Inconclusive'.

Exposure to hair dyes and other hair chemicals such a chemical relaxers/straighteners has been considered in terms of personal use and in occupational use. Although the evidence is classified as 'Inconclusive' due to inconsistent findings and study methodoligcal limitations, any positive associations have been observed only in some case–control studies and no associations have been observed in more robust prospective cohort studies.

Radiation

The evidence is classified as inconclusive for any association between exposure to sources of electromagnetic radiation and risk of breast cancer as there are very few, if any, good quality studies. A limited number of studies have found no association between use of mobile phones and risk of breast cancer.

An observed higher incidence of breast cancer among air crew/flight attendants is unlikely to be due to higher exposure to cosmic radiation but there was only one study which specifically examined risk due to this exposure and the classification is inconclusive.

The evidence for an association between sun exposure and risk of breast cancer is inconclusive although no association has been observed in ecological studies. A hypothesised protective effect of sun exposure on risk of breast cancer through a vitamin D mechanism has been observed in some studies.

Although there is convincing evidence that exposure to high doses of ionising radiation through radiotherapy for cancers other than breast cancer is associated with an increased risk of breast cancer, the benefits outweigh any risks and risks are reduced by treating as small an area of the body as possible. There is no epidemiological evidence to show that exposure to low dose ionising radiation, including via mammography, is associated with risk of breast cancer, hence the evidence is classified as inconclusive.

Appendix A Acknowledgements

Cancer Australia wishes to acknowledge the many members of the Expert Reference Group and other External experts who have generously contributed their time and expertise to the development of this report.

Members of the Expert Reference Group

Professor David Whiteman (Chair)	Deputy Director and Group Leader, Cancer Control, QIMR Berghofer Medical Research Institute, QLD
Mrs Barbara Daniels	Consumer Health Forum representative, WA
Dr James G. Dowty	Senior Research Fellow, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, VIC
Professor Jon Emery	Herman Professor of Primary Care Cancer Research, Director of PC4, NHMRC Practitioner Fellow for Cancer Research, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, VIC
A/Professor Louise A. Keogh	Gender and Women's Health, Centre for Health Equity, Melbourne School of Population and Global Health, University of Melbourne, VIC
Dr Maarit Laaksonen	Senior Research Fellow, Cancer Epidemiology Research Unit, Centre for Big Data Research in Health, University of New South Wales, NSW
Dr Elizabeth Marles	Senior Staff Specialist, General Practice and Director, Hornsby–Brooklyn GP Unit, NSW
Ms Jebby Phillips	Health Consumers New South Wales representative, NSW
Professor Bernard W. Stewart	Head, Cancer Control Program, South Eastern Sydney Public Health Unit, NSW

Other External Experts

A/Professor Connie Johnson	Breast Cancer Research Laboratory, Garvan Institute of Medical Research. St Vincent's Clinical School, Faculty of Medicine, UNSW Australia
A/Professor Judy Kirk	Clinical geneticist, Familial Cancer Service, Crown Princess Mary Cancer Centre, Westmead Hospital, NSW
Dr Elgene Lim	Laboratory Head & Senior Medical Oncologist National Breast Cancer Foundation Endowed Chair
Professor David Roder	Cancer Epidemiologist; Chair of Cancer Epidemiology and Population Health,University of South Australia
A/Professor Kathy Tucker	Cancer Genetic Specialist, Hereditary Cancer Clinic, Nelune Comprehensive Cancer Centre, NSW

Appendix B IARC and WCRF/AICR classifications

International Agency for Research on Cancer

The International Agency for Research on Cancer (IARC) is an agency of the World Health Organization (WHO). The IARC classifies agents to which humans may be exposed, based on the strength of the scientific evidence of their potential as human cancer hazards. Each IARC monograph includes the following sections: exposure data, studies of cancer in humans, studies of cancer in experimental animals, mechanistic and other relevant data, summary, evaluation and rationale.

IARC uses standard terms to evaluate the strength of the evidence for carcinogenicity arising from human and experimental animal data. It also examines the strength of the mechanistic evidence. The evaluation categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). Importantly, risk may not be present at everyday levels of exposure. The IARC monographs identify cancer hazards even when risks are very low at current exposure levels, because new or unforeseen exposures could engender risks that are significantly higher.

IARC applies specific terms to the human and experimental animal evidence, and to the overall evaluation. See details of the methods and evaluation criteria that the IARC uses, at http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf. The various evaluation categories are summarised in Table C.1 (Appendix C).

For human epidemiologic evidence, in some instances, the categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues, such as breast tissue. In this report, although consideration is given to the overall carcinogenicity of an agent to humans if it has been considered in relation to breast cancer also, the classification as an overall carcinogen is of much less interest than the human epidemiological evidence specific to breast cancer.

In relation to breast cancer specifically, the 'List of classifications by cancer sites with sufficient or limited evidence in humans, volumes 1 to 122' indicates the following:

- Carcinogenic agents with sufficient evidence in humans:
  - Alcoholic beverages
  - Diethylstilboestrol
  - Oestrogen–progestogen contraceptives
  - Oestrogen–progestogen menopausal therapy
  - X–radiation, gamma–radiation
- Agents with limited evidence in humans:
  - Dieldrin
  - Digoxin
  - Oestrogen–only menopausal therapy
  - Ehtylene oxide
  - Polychlorinated biphenyls
  - Shift work that involves circadian disruption
  - Tobacco smoking.

IARC monographs can be found at https://monographs.iarc.fr/

World Cancer Research Fund/American Institute for Cancer Research

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project (CUP) is a rigorous, systematic and ongoing program to present, analyse and judge the global research on how diet, nutrition and physical activity affect cancer risk and survival, and to make cancer prevention recommendations. The first and second expert reports on cancers overall were published in 1997 and 2007. Specific reports on breast cancer were published in 2010 and 2017, with the latter updated in 2018 as part of the Third Expert Report.

The WCRF/AICR makes recommendations based on independently conducted systematic reviews of epidemiological evidence, supported by experimental evidence from human and animal studies. It also considers plausible biological mechanisms and dose–response relationships in making judgements about causality. An expert panel judges and classifies the evidence as convincing, probable, limited or unlikely to affect cancer risk. Details of the judgement process and criteria can be found at https://www.wcrf.org/dietandcancer/judging–evidence. The grading criteria are summarised in Appendix C, Table C.2.

The main reports in relation to diet, nutrition, physical activity and risk of breast cancer are:

- *Diet, nutrition, physical activity and cancer: a global perspective* (World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and breast cancer). Available at dietandcancerreport.org
- *The associations between food, nutrition and physical activity and the risk of breast cancer* (World Cancer Research Fund International Systematic Literature Review: the Associations between Food, Nutrition and Physical Activity and The Risk of Breast Cancer 2017). Available at https://www.wcrf.org/sites/default/files/breast–cancer–slr.pdf)
- *Food, nutrition, physical activity and the prevention of breast cancer* (World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report. *Food, Nutrition, Physical Activity and the Prevention of Breast Cancer*. 2010). Available at https://www.wcrf.org/sites/default/files/Breast–Cancer–2010–Report.pdf
- *Resources and toolkits* (World Cancer Research Fund/ American Institute for Cancer Research). Available at https://www.wcrf.org/dietandcancer/resources-and-toolkit

Appendix C IARC and WCRF/AICR categories of evidence and criteria for grading carcinogenicity

Table C.1 International Agency for Research on Cancer (2015): Categories of evidence of carcinogenicity

Overall carcinogenicity
IARC considers the body of evidence from studies in humans (across cancer sites) as well as in experimental animal studies and from mechanistic and other relevant data, to reach an overall evaluation of the carcinogenicity of the agent to humans.
Group 1—carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally: with less than sufficient evidence of carcinogenicity in humans but with sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans of a relevant mechanism of carcinogenicity.
Group 2A—probably carcinogenic to humans. Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases: inadequate evidence of carcinogenicity in humans, sufficient in animals, and strong evidence of mechanism in humans. Exceptionally: limited evidence of carcinogenicity in humans provides the sole basis for classification.
Group 2B—possibly carcinogenic to humans. Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. In some cases: inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some instances: inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals and supporting evidence from mechanistic and other relevant data. In some cases there may only be strong evidence from mechanistic and other relevant data.
Group 3—not classifiable as to its carcinogenicity to humans. Inadequate evidence of carcinogenicity in humans and inadequate or limited evidence of carcinogenicity in experimental animals. Exceptionally: inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental studies and strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents that do not fall into any other group are also placed in this category.
Group 4—probably not carcinogenic to humans. Evidence suggesting lack of carcinogenicity in humans and experimental animals. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

Evidence in humans
The evidence relevant to carcinogenicity of agents from studies in humans is classified into four categories by the IARC working group.[xvii] In some instances, the categories are used to classify the degree of evidence related to carcinogenicity in specific organs or tissues, such as breast cancer.
Sufficient evidence of carcinogenicity. The working group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is sufficient evidence is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.
Limited evidence of carcinogenicity. A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the working group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.
Inadequate evidence of carcinogenicity. The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.
Evidence suggesting lack of carcinogenicity. There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure.

Source: International Agency for Research on Cancer/World Health Organization. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Preamble. Lyon, France; 2015.[700]

[xvii] Note that IARC also uses the same labels (i.e. sufficient, limited, inadequate, lack of) for classifying the evidence from experimental animal studies.

Table C.2 World Cancer Research Fund/American Institute for Cancer Research (2018): Criteria for grading evidence for cancer prevention

Strong—Convincing	*Overall evidence strong enough to justify goals and recommendations to reduce cancer incidence* Causal relationship highly unlikely to be modified by new evidence in foreseeable future. Generally required: • Evidence from more than one study type and at least two independent cohort studies • No substantial unexplained heterogeneity within or between study types or in different populations regarding presence or absence of association, or direction of effect • Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias • Presence of a plausible biological gradient ('dose–response') in the association (gradient need not be linear or in same direction across different levels of exposure, so long as this can be explained plausibly) • Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes
Strong—Probable	*Overall evidence strong enough to justify goals and recommendations to reduce cancer incidence, but not as strong as convincing category* Generally required: • Evidence from at least two independent cohort studies/at least five case–control studies • No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect • Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias • Evidence for biological plausibility
Limited—Suggestive	*Overall evidence too limited for probable or convincing causal judgement, but suggesting direction of effect* • Evidence methodologically flawed or limited in amount, but generally showing a consistent direction of effect • Recommendations to reduce cancer incidence rarely justified Generally required: • Evidence from at least two independent cohort studies/at least five case–control studies • Direction of effect is generally consistent, although some unexplained heterogeneity may be present • Evidence for biological plausibility
Limited—No conclusion	*Evidence is so limited that no firm conclusion can be made* This category represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where

	insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. The evidence might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders), or by any combination of these factors.
Strong—Substantial effect on risk unlikely	Evidence is strong enough to support a judgement that a particular exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates. All of the following were generally required: • Evidence from more than one study type • Evidence from at least two independent cohort studies • Summary estimate close to 1.0 for comparison of high versus low exposure categories • No substantial unexplained heterogeneity within or between study types or in different populations • Good quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding, and selection bias • Absence of a demonstrable biological gradient ('dose–response') • Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes

Source: World Cancer Research Fund, American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Judging the evidence. Available at www.wcrf.org/sites/default/files/judging–the–evidence.pdf. 2018. (2018)[13]

Appendix D Data tables

Personal characteristics

Table D.1 Birthweight and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2014 Denmark, Europe, Sweden & USA	16 cohort studies 14 cohort studies	>3,135 cases >17,981 cases	Birthweight Dose response (per 500 g)	Premenopausal breast cancer Postmenopausal breast cancer	RR=1.05 (1.02–1.09); p<0.05; I^2=0%, p(heter)=0.846 RR=1.00 (0.98–1.02); I^2=0%, p(heter)=0.48	Model: NR Adjustments: Not all studies adjusted for age, alcohol intake, reproductive factors, and adult BMI Limitations: NR
Cohort studies						
Dartois et al., 2016[44] France	E3N–EPIC cohort Cohort dates: 1993–2008 Retrospective study Age at enrolment: 42–72 y Follow–up: 15 y	67,634 women 497 premenopausal cases 3,138 postmenopausal cases	Birthweight <2.5 kg 2.5–4 kg ≥4 kg <2.5 kg 2.5–4 kg ≥4 kg	Premenopausal breast cancer Postmenopausal breast cancer	 HR=1 (referent) HR=1.72 (1.01–2.95) HR=1.99 (1.05–3.76) HR=1 (referent) HR=1.13 (0.96–1.33) HR=1.03 (0.82–1.29)	Multivariate Cox proportional hazards regression model† Limitations: Low number of premenopausal breast cancer cases

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Sandvei et al., 2015[46] Norway	St. Olav's University Hospital & Central Person Registry Cohort dates: 1961–2012 Women born: 1920–1966 Prospective study Age at enrolment: NR Mean follow–up: 51 y	22,931 women 870 cases Median age at diagnosis: 54 y	Birthweight (per 500 g)	Breast cancer	HR=1.02 (0.95–1.10)	Cox regression model Adjustments: Age, length of gestation, socioeconomic status, maternal age and birth order Limitations: Imprecise information about gestational age in the birth records
		318 cases <50 y	Dose response (per 500 g)	Premenopausal breast cancer	HR=1.03 (0.91–1.16); p–trend=0.666	
			3–3.499 kg		HR=1 (referent)	
			<3 kg		HR=0.9 (0.6–1.4)	
			3.5–3.999 kg		HR=1.1 (0.9–1.4)	
			≥4 kg		HR=1.0 (0.7–1.4); p–trend=0.536	
		552 cases ≥50 y	Dose response (per 500 g)	Postmenopausal breast cancer	HR=1.02 (0.93–1.11); p–trend=0.738	
			3–3.499 kg		HR=1 (referent)	
			<3 kg		HR=1.2 (0.9–1.5)	
			3.5–3.999 kg		HR=1.2 (1.0–1.5)	
			≥4 kg		HR=1.0 (0.8–1.4); p–trend=0.948	
Xue et al., 2016[45] USA	Nurses' Health Study II Prospective study Cohort dates: 1991–2009 Age at baseline: 25–42 y Follow up: 1,133,893 person–y	116,430 premenopausal participants 1,574 incident premenopausal cases	Birthweight 3.9+ kg 3.2–3.8 kg 2.5–3.1 kg <2.5 kg	Premenopausal breast cancer	 HR=1 (referent) HR=0.83 (0.71–0.96) HR=0.75 (0.64–0.89) HR=0.74 (0.58–0.94) p–trend<0.001	Multivariate Cox regression models¶ Limitations: Restriction to premenopausal women Likely misclassification due to recall

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; E3N–EPIC cohort, Etude Epidémiologique auprès des femmes de la Mutuelle Generale de l'Education Nationale; FFTP, first full term pregnancy; g, grams; HR, hazard ratio; kg, kilograms; MET, metabolic equivalents; p, p–value; p–trend, p–value for trend; RR, relative risk or risk estimate; USA, United States of America; UVRd, ultraviolet radiation doses; WCRF, World Cancer Research Fund; y, year/s.

†Adjusted for age (as the time scale), first–degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at FFTP, physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and UVRd, oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).

¶Adjusted for age (continuous), premature birth (<38, >38 weeks) and birthweight (except in the analysis of birthweight), family history of breast cancer (yes, no), history of benign breast disease (yes, no), age at menarche (10, 11, 12, 13, 14, 15 y), interaction between parity (0, 1, 2, 3, 4, 5) and age at first birth (<24, 25–30, >30 y) with nulliparous women as reference, use of oral contraceptives (never, past and <5 y, past and >5 y, current and <5 y, current and 5–9 y, current and >10 y), alcohol consumption (never, <7.5, 7.5–14, 15–29, >30 g/day), physical activity (<3, 4–8, 9–17, 18–26, 27–41, 42 MET/day) and body fatness factors earlier in life (somatotype or BMI). Since somatotype at age 5 and somatotype at age 10 were highly correlated (Spearman correlation coefficient=0.81), these two factors were not adjusted for each other when one of the factors was assessed as the main exposure of interest.

Table D.2 Height and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2014 Asia, Europe & North America	26 studies for premenopausal breast cancer 33 studies for postmenopausal breast cancer	6,479 premenopausal cases Age: 15–81 y	Height Dose response (per 5 cm) Overall Adjusted studies Europe North America Asia	Premenopausal breast cancer	 RR=1.06 (1.02–1.11); I^2=45.8%, p(heter)=0.021 RR=1.07 (1.03–1.12) RR=1.04 (0.99–1.09); I^2=27% RR=1.08 (1.03–1.12); I^2=0% RR=1.20 (1.04–1.37); I^2=26%	Random effects model Adjustments: Age, alcohol intake & reproductive factors No publication bias (p=0.11) Limitations: NR
		24,975 postmenopausal cases Age: 15–81 y	Overall Adjusted studies Europe North America Asia	Postmenopausal breast cancer	RR=1.09 (1.07–1.11); I^2=32.8%, p(heter)=0.079 RR=1.08 (1.06–1.10) RR=1.10 (1.08–1.12); I^2=5% RR=1.06 (1.04–1.08); I^2=0% RR=1.13 (0.93–1.38); I^2=68%	
Zhang et al., 2015[47] Studies published to 2014 Australia, Canada, Denmark, Iceland, Netherlands, Norway, Sweden, UK & USA	159 prospective cohort studies from the BCAC, Discovery Biology & Risk of Inherited Variants in Breast Cancer Project	5,216,302 women 113,178 cases Ethnicity: European	Height Dose response (per 10 cm)	Breast cancer	RR=1.17 (1.15 –1.19); I^2=61%, p(heter)<0.001	Random effects model Adjustments: No adjustment for nutritional and social factors, such as energy intake and social status, and personal factors such as timing of puberty since they were not reported No publication bias (p=0.33)
		15,439 premenopausal cases		Premenopausal breast cancer	RR=1.16 (1.12–1.21); p<0.001	
		63,606 postmenopausal cases		Postmenopausal breast cancer	RR=1.17 (1.14–1.21); p<0.001	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		7,947 ER+ cases 1,845 ER– cases 5,176 PR+ cases 1,640 PR– cases 5,176 ER+PR+ cases 1,302 ER–PR– cases		ER+ ER– PR+ PR– ER+PR+ ER–PR–	RR=1.18 (1.13–1.23); p<0.001 RR=1.00 (0.87–1.14) RR=1.16 (1.10–1.22); p<0.001 RR=1.11 (1.02–1.20); p=0.01 RR=1.16 (1.10–1.22); p<0.001 RR=1.08 (0.99–1.18)	Limitations: Height information obtained after cancer diagnosis in case–control studies from BCAC, which may contribute to lower risk estimates for the association between adult height and breast cancer risk
Cohort studies						
Horn–Ross et al., 2016[50] USA	California Teachers study cohort Recruitment date: 1995–1996 End of follow–up: 31 December 2011 Age at enrolment: NR Follow–up: 10 y	46,822 premenopausal women 248 ER+ cases Median age: 41y	Height at age 18 <65 inches 65–66 inches	Premenopausal ER+ breast cancer	 HR=1 (referent) HR=1.10 (0.86–1.42)	Multivariable Cox proportional hazards model†‡§ Limitations: Collapsing subgroups based on small numbers of cases may have masked some associations and reduced over–interpretation of erroneous patterns Only 16 body–size phenotypes included in analysis. Available data limited evaluation at several specific points in time only Data on menopausal status and HT use were updated only at 5–year and 10–year follow–up and has some built–in imprecision Anthropometric data were self–reported and can result in measurement error
		36,977 postmenopausal women using HT 1,219 ER+ cases Median age: 57 y	Height at age 18 (current HT use) <65 inches ≥67 inches	Postmenopausal ER+ breast cancer	 HR=1 (referent) HR=1.19 (1.05–1.36)	
		21,788 postmenopausal women not using HT 1,056 ER+ cases Median age: 64 y	Height at age 18 (no HT use) <65 inches 65–66 inches		 HR=1 (referent) HR=1.20 (1.06–1.35)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Nitta et al., 2016[51] Japan	Japan Collaborative Cohort study Cohort dates: 1988–2009 Age at enrolment: 40–79 y Mean incidence survey follow–up: 13 y	9,367 premenopausal women 84 cases	Adult attained Height <149 cm 149–152.9 cm 153–156.9 cm ≥157 cm	Premenopausal breast cancer	 HR=1 (referent) HR=0.94 (0.37–2.36) HR=1.44 (0.61–3.36) HR=1.16 (0.48–2.80); p–trend=0.476	Multivariable–adjusted analysis with Cox model Adjustments: Age at baseline survey, age at menarche, number of live births and age at first delivery Limitations: Possible misclassification of menopausal status Self–reported information at baseline
		29,243 postmenopausal women 189 cases	<149 cm 149–152.9 cm 153–156.9 cm ≥157 cm	Postmenopausal breast cancer	HR=1 (referent) HR=1.13 (0.67–1.91) HR=1.27 (0.74–2.20) HR=1.51 (0.83–2.74); p–trend=0.165	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BCAC, Breast Cancer Association Consortium; cm, centimetre; ER+/–, oestrogen receptor positive/negative; HR, hazard ratio; HT, hormone therapy; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; PR+/–, progesterone receptor positive/negative; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; WCRF, World Cancer Research Fund; y, year/s.

†Premenopausal adjusted for history of benign breast disease and family history of breast cancer in a first–degree relative; age was the time metric and the model was stratified by age at baseline.

‡Postmenopausal with current HT use adjusted for nulliparity and age at first full–term pregnancy, history of benign breast disease, family history of breast cancer in a first–degree relative, average alcohol consumption in the year prior to baseline, and neighborhood socioeconomic status; age was the time metric and the model was stratified by age at baseline.

§Postmenopausal not using HT adjusted for age at menarche, nulliparity and age at first full term pregnancy, history of benign breast disease, family history of breast cancer in a first–degree relative, and consumption of a plant–based diet; age was the time metric and the model was stratified by age at baseline.

Table D.3 Having been breastfed and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Wise & Titus, 2013[52] Studies published to 2011 Countries: NR	15 studies 3 cohort studies 10 case–control studies 1 cross–sectional study 1 case series	Number of participants: NR	Ever breastfed as an infant	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=0.94 (0.89–0.99); I^2=37.6%, p=0.070 RR=0.88 (0.78–0.98); I^2= 53.9%, p=0.069 RR=0.98 (0.91–1.05); I^2=18.4%, p=0.298	Inverse–variance fixed effects model Adjustments: NR Publication bias: NR Limitations: NR
Cohort studies						
Cairns et al., 2014[701] Published as conference abstract UK	National breast screening programmes of England & Scotland cohort Prospective Cohort dates: 1996–2001 Mean age: 60y Follow–up: 9.3 y	560,879 women 48,610 incident invasive cancers	Having been breastfed	Overall cancer	RR=1.02 (0.99–1.05)	Cox regression model Adjustments: Age and 14 other known cancer risk factors Limitations: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Martin et al., 2005[53] Britain	Boyd Orr cohort Cohort dates: 1937–2003 Prospective study Age at enrolment: 0–19 y Follow-up: 1948–2003	3,844 participants: 1,883 males 1,961 females 74 cases	Ever breastfed	Breast cancer	HR=1.62 (0.89–2.94)	Cox proportional hazard model Adjustments: Current age, childhood socioeconomic factors and stratified by survey district Limitations: Participants were born between 1874 and 1939 No information on timing of breastfeeding initiation Confounding
Michels et al., 2001[54] USA	Nurses' Health Study cohort (1992–1997) Nurses' Health Study II cohort (1991–1997) Enrolment: 1976 (NHS) and 1989 (NHSII) Age at enrolment: 30–55 y (NHS), 25–42 y (NHS II) Prospective study Follow–up: 695,655 person–y	121,700 female registered nurses (NHS) 116,671 female registered nurses (NHS II) 1,073 cases	Having been breastfed	Premenopausal breast cancer Postmenopausal breast cancer	OR=0.97 (0.78–1.20) OR=1.12 (0.92–1.37)	Pooled logistic regression Adjustments: Age, year of birth, premature birth, birth weight, family history of breast cancer, history of benign breast disease, height, body mass index at age 18 years, weight change since age 18 years, age at menarche, parity, age at first child's birth, total caloric intake, and alcohol consumption Limitations: Misclassification of duration of breastfeeding Confounding from generational differences in infant feeding practices associated with socioeconomic status

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Case–control studies						
Wise et al., 2009[55] USA	Population–based Study duration: 1997–2001 Age at recruitment: 20–74 y	9,442 women 4,911 cases 4,531 controls	Breastfed All women Not breastfed Breastfed Not breastfed Breastfed Not breastfed Breastfed	Invasive & in situ breast cancer Premenopausal breast cancer Postmenopausal breast cancer	OR=1.0 (referent) OR=0.99 (0.90–1.08) OR=1.0 (referent) OR=0.96 (0.83–1.11) OR=1.0 (referent) OR=0.98 (0.87–1.10)	Unconditional logistic regression model† Limitations: Inability to validate breastfeeding reports Possible non–differential (random) misclassification Recall bias

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; NR, not reported; OR, odds ratio; p, p–value; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

*Adjusted for age, year of survey, referral base (from screening, others), area of residence, drinking, history of breast cancer in mother and sisters, occupation (professional or clerical), breastfeeding of subjects' own offspring, exogenous female hormone use, body mass index and menopausal status.

Table D.4 Mammographic breast density and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Bae & Kim., 2016[72] Publications up to 2015 Japan	6 studies 1 cohort study 5 case–control studies RR derived from 3 case–control studies	2,157 cases in total 26,944 controls in total RR derived from: 351 cases 882 controls Ethnicity: Asian	Increased mammographic breast density Dose response (per 25% increase in percent density)	Postmenopausal breast cancer	RR=1.73 (1.20–2.47); p(heter)=0.35	Random effects dose–response meta–regression model Adjustments: NR Publication bias: NR Limitations: An overall ES reflecting information from all 6 articles was not calculated due to breast density index variations The subgroup analysis was performed imperfectly The analysis of premenopausal women was insufficient for DRMR
Pettersson et al., 2014[56] Studies conducted 1980–2011 Australia, Canada, Netherlands, Singapore, Sweden, UK & USA	13 case–control studies 11 studies contributed to premenopausal breast cancer 12 studies contributed to postmenopausal breast cancer	1,776 cases 2,834 controls	Increased mammographic breast density (one standard deviation increases in the mammographic density phenotypes) Absolute NDA Absolute DA Absolute PDA	Premenopausal breast cancer	OR=0.78 (0.71–0.86); p(heter)=0.2 OR=1.37 (1.29–1.47); p(heter)=0.5 OR=1.52 (1.39–1.66); p(heter)=0.27	Random effects model Adjustments: Age, BMI & parity (in postmenopausal breast cancer summary estimates did not change after additional adjustment for MHT use) Publication bias: NR Limitations: Unable to determine the extent to which differences across studies in the associations
		6,643 cases 11,187 controls	Absolute NDA Absolute DA	Postmenopausal breast cancer	OR=0.79 (0.73–0.85); p(heter)=<0.01 OR=1.38 (1.31–1.44);	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
					p(heter)=0.15	between the mammographic density phenotypes and breast cancer risk were explained by study differences in exposure to other factors
			Absolute PDA		OR=1.53 (1.44–1.64); p(heter)=0.01	
McCormack & dos Santos Silva., 2006[71] Studies published 1976–2005 Canada, Finland, Israel, Italy, Japan, Netherlands, South Africa, Sweden, UK & USA	42 case–control & cohort studies: 17 prospective studies 17 case–control studies 9 symptomatic populations' studies 2 studies used for BI–RADS classification RR	14,134 cases in total 226,871 non–cases in total RR derived from: 4,508 cases 8,342 non–cases	Mammographic breast density <5% 5–24% 25–49% 50–74% ≥75%	Breast cancer	 RR=1 (referent) RR= 1.79 (1.48–2.16); p=0.22; I^2=27% RR= 2.11 (1.70–2.63); p=0.09; I^2=46% RR= 2.92 (2.49–3.42); p=0.63; I^2=0% RR= 4.64 (3.64–5.91); p=0.50; I^2=0%	Random effects model Adjustments: Individual studies adjusted for a range of factors – No effect modification by age No publication bias in studies of percentage density and breast cancer incidence (p>0.05) Limitations: Unable to cinder potential modifiers of the association other than report findings of individual studies
		1,572 cases 62,220 non–cases	Mammographic breast density (using BI–RADS classification Fatty parenchyma Scattered density Heterogeneously dense Extremely dense		 RR=1 (referent) RR=2.04 (1.56–2.67); p=0.34; I^2=0% RR=2.81 (2.13–3.71); p=0.46; I^2=0% RR=4.08 (2.96–5.63); p=0.81; I^2=0%	
Cohort studies						
Moshina et al., 2018[61] Norway	No cohort name Cohort dates: 2007–2015 Retrospective study Aged 50–69 y at time of screening	107,949 women 307,015 screening examinations in total Interval breast cancer analysis: 96,052 women 231,998 screening	Screen–detected Non–dense (VBD<7.5) Dense (VBD≥7.5) Interval Non–dense (VBD<7.5)	Breast cancer	 OR=1.00 (reference) OR=1.37 (1.19–1.59); p<0.0001 OR=1.00 (reference)	Model: NR Adjustments: Age at screening, screening location, and screening history Limitations: Missing values for tumour

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	(mean 58.3 y) Follow–up: 2 y	examinations Screen detected breast cancer: 1,791 cases 1,210 non–dense cases 581 dense cases Interval breast cancer: 384 cases 199 non–dense cases 185 dense cases	Dense(VBD≥7.5)		OR=2.93 (2.16–3.97); p<0.0001	characteristics and risk factors Women in non–dense group differed in some characteristics other than breast density from those in dense group VBD determined by using non–processed images
Chiu et al., 2010[73] Sweden	Cohort dates: 1977–2004 Prospective study Age at diagnosis: 45–59 y Follow–up: 25 y	15,658 women 873 cases	Dense breast tissue vs non–dense breast tissue	Breast cancer	RR=1.57 (1.23–2.01)†; p<0.01	Poisson regression model Adjustments: Age and BMI Limitations: Breast density was classified in a qualitative manner rather than a quantitative manner

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BI–RADS, Breast Imaging Reporting and Data System; BMI, body mass index; DA, dense area; DRMR, dose–response meta–regression; ES, effect size; MHT, menopausal hormone therapy; NDA, non–dense area; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; PDA, percent dense area; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; VBD, volumetric breast density; y, year/s. †A 95% confidence interval of 1.18–1.67 is noted in the abstract

Table D.5 Breast size and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Case–control studies						
Chen et al., 2014[75]	Population–based	Postmenopausal women	Bra cup size	IDC		Polytomous logistic regression model
			A		OR=1.9 (1.0–3.6)	
USA	Breast cancer diagnosed: 2000–2004	1,044 cases: 454 IDC & 590 ILC incident cases	B		OR=1 (referent)	Adjustments: Age at the reference date, reference year, county
			C		OR=1.0 (0.7–1.3)	
			D or above		OR=0.9 (0.7–1.3); p–trend=0.138	
	Age at recruitment: 55–74 y	469 controls	A	ILC	OR=1.8 (1.0–3.3)	Limitations: Self–reported data
			B		OR=1 (referent)	
			C		OR=0.8 (0.6–1.1)	
			D or above		OR=0.9 (0.7–1.3); p–trend=0.095	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BMI, body mass index; HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; OR, odds ratio; p–trend, p–value for trend; USA, United States of America; y, year/s.

Family history and genetics

Table D.6 Family history of breast cancer and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Collaborative Group on Hormonal Factors in Breast Cancer, 2001[76]	8 cohort studies (including NHS Iowa Women's Health, Million Women Study)	58,209 cases 101,986 women without BC	Number of first degree (FD) relatives affected	Breast cancer (age at diagnosis)		Conditional logistic regression model
		50,713 cases 94,548 controls	No relative affected		RR=1.00 (referent)	Publication bias: NR
Studies published: 1983–1999	27 case–control studies with population controls	6,810 cases 6,998 control	1 FD relative affected	All ages	RR=1.80 (1.70–1.91)	Adjustments: Stratified by study, age at diagnosis, menopausal status, number of sisters, parity and age at first birth
				<50 y	RR=2.14 (1.92–2.38)	
				≥50 y	RR=1.65 (1.53–1.78)	
Asia, Europe, North America, Costa Rica, Brazil, Australia, New Zealand	17 case–control studies with hospital controls		Relative's age at diagnosis			Limitations: Study could not account for *BRCA* mutations, family history of other cancers or attained ages of all first–degree relatives
			<40y	<40 y	RR=5.7 (2.7–11.8)	
			≥60y		RR=1.4 (0.9–2.1)	
			<40y	40–49 y	RR=2.9 (1.9–4.4)	
			≥60y		RR=1.4 (1.0–2.0)	
			<40y	50–59 y	RR=2.0 (1.2–3.4)	
			≥60y		RR=1.5 (1.2–2.0)	
			<40y	≥60 y	RR=1.4 (0.9–2.1)	
			≥60y		RR=1.4 (1.2–1.7)	
		603 cases 404 controls	2 FD relatives affected	All ages	RR=2.93 (2.37–3.63)	Separate analyses of mother and daughter could not be conducted
				<50 y	RR=3.84 (2.37–6.22)	
				≥50 y	RR=2·61 (2·03–3·34)	
			Relative's (≥1) age at diagnosis			
			<40 y	<50 y	RR=13.5 (3.4–53.9)	
			≥40 y		RR=7.8 (2.4–25.0)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		83 cases 36 controls	≥3 FD relatives affected	All ages	RR=3.90 (2.03–7.49)	
Pharoah et al., 1997[77] Studies published 1935–1996 Asia, Australia, Brazil, Costa Rica, Europe, Israel, New Zealand, North America & Russia	52 case–control studies 22 cohort studies	Participant details: NR	Number of FD relatives affected	Breast cancer		Model: NR Adjustments: NR
	38 studies		1 FD relatives affected	All ages	RR=2.1 (2.0–2.2)	Publication bias: NR
	5 studies		Relative's age at diagnosis	<50 y		Limitations: Confounding by other risk factors (e.g., age at menarche, parity, age at first birth, age at menopause) may bias results Differential bias in the risk estimates, in that recall of maternal history is likely to be less complete than for sister history
			<50 y		RR=3.3 (2.8–3.9)	
			≥50 y		RR=1.8 (1.5–2.2)	
	8 studies		Mother affected		RR=2.2 (1.9–2.6)	
	6 studies		Sister affected		RR=3.0 (2.5–3.5)	
	5 studies		2 FD relatives affected	All ages	RR=3.6 (2.5–5.0)	
	10 studies		1 SD relative affected		RR=1.5 (1.4–1.6)	
Cohort studies						
Beebe–Dimmer et al., 2015[82] USA	WHI study cohort Enrolment: 1993–1998 End of study: Aug 2009 Prospective Median age at enrolment: 64 y for cases & 63 y for non–cases	78,171 postmenopausal women 3,506 cases 636 cases with first–degree relative affected 83 cases with >1 first–degree relative affected	1 FD relative affected vs none affected	Postmenopausal breast cancer	HR=1.42 (1.30–1.55)	Multivariate Cox proportional hazards regression model
			>1 FD relative affected vs none affected		HR=1.66 (1.32–2.08)	Adjustments: Age, race, benign breast disease, hormone therapy usage & hysterectomy Limitations: Small number of African American women with breast cancer in the study The reliance on self–reporting

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						of the family history of cancer
	Median follow–up: 132 months					
Kharazmi et al., 2014[81]	Swedish Family Cancer Database	69,248 cases	1 FD relative affected vs none affected	Breast cancer		Cox proportional hazard model
		10,040 with first–degree relative affected	Mother/sister age at diagnosis			Adjustments‡
Sweden	Study duration: 1961–2008		Any age		HR=1.8 (1.8–1.9)	Limitations: NR
			<40 y		HR=2.3 (2.1–2.6)	
	Prospective	Mean birth y: 1972 (1932–2010)	>80 y		HR=1.5 (1.4–1.6)	
			Any age	<50 y	HR=2.13 (2.06–2.21)	
	Age at enrolment: 0–78 y			50–59 y	HR=1.8 (1.8–1.9)	
				60–78 y	HR=1.6 (1.5–1.7)	
	Follow–up: 34 y (mean); 36 y (median)					
Colditz et al., 2012[83]	The Nurses' Health Study cohort	69,805 women	Family history of breast cancer	Breast cancer		Log–incidence model
USA		4,327 cases				Adjustments†
	Study duration: 1980−2006	3,614 cases	No family history		RR=1.0 (referent)	Limitations: NR
			Mother history			
	Prospective	104 cases	<50 y		RR=1.69 (1.39−2.05)	
		331 cases	≥50 y		RR=1.37 (1.22−1.53); p=0.06	
	Age at enrolment: 30−55 y		Sister history			
		116 cases	<50 y		RR=1.66 (1.38−1.99)	
		167 cases	≥50 y		RR=1.52 (1.29−1.77); p=0.43	
	Follow–up: 26 y		Mother or sister history			

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		219 cases	<50 y		RR=1.70 (1.48–1.95)	
		467 cases	≥50 y		RR=1.40 (1.27–1.54); p=0.016	
Case–control studies						
Bevier et al., 2012[78]	Population–wide Swedish Family	56,498 cases	Family history of breast cancer	Breast cancer		Poisson regression model
Sweden	Cancer Database	2,116,421 controls				Adjustments¶
		7,861 cases	1 FD relative affected		RR=1.79	
	Breast cancer diagnosis: 1961–2008	543 cases	2 FD relatives affected		RR=2.84	Limitations: NR
		64 cases	≥2 second–degree relatives affected		RR=1.60 (1.24–2.07); p=sig.	
	Age at recruitment: ≥30 y	198 cases	Affected maternal grandmother		RR=1.27 (1.09–1.47); p=sig.	
		134 cases	Affected paternal grandmother		RR=1.26 (1.05–1.50); p=sig.	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: FD, first–degree; HR, hazard ratio; NHS, Nurses' Health Study; NR, not reported; p, p–value; RR, relative risk or risk estimate; SD, second–degree; WHI, Women's Health Initiative; UK, United Kingdom; USA, United States of America; y, year/s.

‡Adjusted for age, age at first pregnancy, number of children, calendar period, geographical region, socioeconomic status of the index case.

†Adjusted for age (grouped 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70?), calendar period (1961–1985, 1986–1990, 1991–1995, 1996–2000, and 2001–2008), region (big cities, northern Sweden, southern Sweden, and other), and socioeconomic status (agricultural worker, white–collar worker, and other worker, professional, private, and other) as well as the number of children and age at first birth.

¶Adjusted for age, duration of premenopause, menopause (type and duration), pregnancy history, benign breast disease, postmenopausal hormone therapy (type, duration and current or past use), body mass index, height, and alcohol use.

Table D.7 Family history of other cancers and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Pooled analyses						
Turati et al., 2013[80] Italy & Switzerland	Study dates: 1991–2009 13 network case–control studies	>12,000 incident cases >11,000 controls	Family history of a cancer other than breast cancer in cases vs family history in controls	Breast cancer		Unconditional multiple logistic regression model Adjustments‡
			Colorectal cancer		OR=1.5 (1.1–1.9); p=sig.	Limitations: Insufficient statistical power when the strength of the relation is modest or the cancer(s) is rare
			Prostate cancer		OR=1.6 (1.1–2.4)	
			Haemolymphopoietic cancers		OR=1.7 (1.2–2.4); p=sig.	
			Uterine cancer		OR=1.4 (1.0–1.9)	
			Stomach cancer		OR=1.2 (1.0–1.6)	
			Skin cancer		OR=3.0 (1.4–6.4)	
Cohort studies						
Beebe–Dimmer et al., 2015[82] USA	WHI study cohort End of study: Aug 2009 Prospective study Median age at baseline: 64 y for cases 63 y for non–cases Median follow–up: 11 y	78,171 women 3,506 cases 74,665 non–cases Median age at breast cancer diagnosis: 69 y	Family history of cancer among first–degree relatives vs no family history	Postmenopausal breast cancer		Cox proportional hazards regression model Adjustments†
			Prostate cancer			Limitations: Small number of African–American women with breast cancer in the study Family history of cancer was assessed only at the baseline Reliance on self–reporting of the family history of cancer
			≥1 first–degree relative		RR=1.14 (1.02–1.26)	
			Breast & prostate cancer			
			1 first–degree relative		RR=1.78 (1.45–2.19)	
			Colorectal cancer			
			>1 first–degree relative		RR=1.08 (0.99–1.19)	
			Breast & colorectal cancer			
			First–degree relatives		RR=1.47 (1.34–1.61)	
Sutcliffe et al., 2000[86]	UKCCCR Familial Ovarian Cancer	Families with at least 2 first–degree	Family history of ovarian cancer	Breast cancer		Risks were estimated by comparing the number of

UK	Register Prospective study First families enrolled from 1991	relatives with confirmed epithelial ovarian cancer 2,304 women from 319 families 11,936 person–y at risk 30 incident breast cancer cases	<50 y ≥50 y By 70 y Average *BRCA1* and *BRCA2* mutation–positive families		RR=3.74 (2.04–6.28); p=0.02 RR=1.79 (1.02–2.90); p=0.034 AR=15% RR=2.36 (1.59–3.37) RR=3.32 (1.52–6.31)	incident ovarian and breast cancer cases with the number expected, based on national–, age–, sex– and period–specific incidence rates for England and Wales Adjustments: NR Limitations: NR
Valeri et al., 2000[89] France	University Hospital of, Saint Louis–Paris, Brest & Nancy Retrospective study Prostate cancer patient selection: 1994−1997 Follow–up: NR	691 patients/ families 82 patients/families with prostate cancer history	Family history of prostate cancer Number of prostate cancer cases 1 ≥2 Age at diagnosis of prostate cancer <55 y ≥55−<65 y ≥65−<75 y ≥75 y	Breast cancer	 RR=1.0 (referent) RR=2.3 (1.3−4.3); p=0.007 OR=5.5 (1.9−15.3); p=0.002 OR=1.3 (0.6−2.8); p=NS OR=1.3 (0.7−2.6); p=NS OR=1.0 (referent)	Conditional logistic regression model Adjustments: NR Limitations: NR
Case–control studies						
Slattery & Kerber, 1993[87] USA	Population–based study (Utah population database) Breast cancer diagnosis: 1966−1989	4,083 incident cases 4,083 controls Controls selected from genealogy data	Family history of colon cancer Kinship order of colon cancer None ≥Fifth Fourth Third Second	Breast cancer	 OR=1.00 (referent) OR=1.05 (1.02−1.09) OR=1.10 (1.03−1.18) OR=1.15 (1.05−1.27) OR=1.21 (1.07−1.36)	Conditional likelihood logistic model Adjustments: NR Limitations: Database limited to Utah residents

	Age at enrolment: all ages		First		OR=1.26 (1.08−1.45)	
			Family history of ovarian cancer Kinship order of colon cancer			
			None		OR=1.00 (referent)	
			≥Fifth		OR=1.03 (0.98−1.08)	
			Fourth		OR=1.05 (0.96−1.15)	
			Third		OR=1.08 (0.95−1.23)	
			Second		OR=1.10 (0.93−1.31)	
			First		OR=1.13 (0.91−1.38)	
Claus et al., 1993[88] USA	Cancer and Steroid Hormone Study, population–based Recruitment dates: 1980–1992 Age of participants: 20–54 y	Woman with a first–degree family history of ovarian cancer 4,730 breast cancer cases 493 ovarian cancer cases 4,688 controls	First–degree family history of ovarian cancer	Breast cancer by 89 y		Autosomal dominant genetic model Adjustments: NR Limitations: Risks presented likely to underestimate the true risks
			1		Cumulative risk=13.5%	
			2		Cumulative risk=30.8%	
			First–degree family history of ovarian cancer & 1first–degree family history of BC diagnosed in her thirties	Breast cancer by 79 y	Cumulative risk=40%	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AR, absolute risk; NR, not reported; NS, not significant; OR, odds ratio; p, p–value; RR, relative risk or risk estimate; sig., significant; UK, United Kingdom; UKCCCR, Uniting Kingdom Coordinating Committee on Cancer Research; USA, United States of America; WHI, Women's Health Initiative; y, year/s.

†All models included age, race, benign breast disease, hormone replacement therapy usage, and hysterectomy. Breast or prostate cancer: models were also mutually adjusted for a family history of breast cancer and prostate cancer among first–degree relatives. Breast or colorectal cancer: mutually adjusted for a family history of breast cancer and colorectal cancer among first–degree relatives.

‡Adjusted for age, sex (when appropriate), study centre (when appropriate), year of interview, education, body mass index, alcohol drinking, tobacco smoking, and number of brothers and sisters. Reference category: no family history of the selected discordant cancer. Odds ratios for endometrial and ovarian cancers were further adjusted for menopausal status, age at menopause, oral contraceptive and hormone replacement therapy use, and parity; odds ratios for breast cancer were further adjusted for menopausal status, age at menopause, oral contraceptive and hormone replacement therapy use, parity and age at first birth.

Table D.8 ATM and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
van Os et al., 2016[94] studies published to 2014 France, Scandinavia, UK & USA	4 studies 4 cohort studies	974,710 women 28,572 cases 946,138 controls	*ATM* mutation heterozygotes carriers All female blood relatives Obligate heterozygous relative Younger women Older women	Breast cancer	 RR=1.7 (1.4–2.1) RR=3.0 (2.1–4.5) RR=7.0 (4.1–11.9) RR=2.1 (1.2–3.6)	Random effects model Adjustments: NR Publication bias: NR Limitations: Studies concerning polymorphisms in the *ATM* gene were disregarded Only a small number of studies were included Co–variables that may play a role in the association between certain diseases and the *ATM* mutation were excluded
Aloraifi et al., 2015[100] Studies published to 2014 Czech Republic, Finland, France, Netherlands, Spain, Switzerland, UK & USA	15 studies 15 case–control studies	9,832 women 4266 cases 67 heterozygous cases 5,566 controls 21 heterozygous cases	A–T heterozygotes carriers	Breast cancer	OR=3.20 (2.04–5.04); p–value; Heterogeneity chi–squared=13.46, p(heter)=0.413	Fixed and random effects model Adjustments: NR No publication bias, p > 0.05 Limitations: Ascertainment of families and potential confounding effects from variables such as environmental risk factors and population stratification
Easton et al., 2015[98] Studies published to: NR Denmark, France, Finland, Norway, Sweden, UK	Segregation analysis with estimates derived from BOADICEA model	Participant details: NR	Relatives with A–T *ATM p.Val2424Gly* mutation	Breast cancer	RR=2.8 (2.2–3.7); $p=4.7 \times 10^{-11}$ RR=8.0 (2.8–22.5); p= .0005	Model: NR Adjustment: NR Publication bias: NR Limitations: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Case–control studies						
Couch et al., 2017[101] USA	Population–based case–control study Study duration: 2012–2016 Age at diagnosis: 48.5 (11.1) y	41,154 cases 52,160 controls 29,229 cases 274 *ATM* mutations 26,644 controls 90 *ATM* mutations	*ATM* mutation All ethnicities European ancestry	Breast cancer	OR=2.91 (2.41–3.50); p=4.01 x 10^{-32} OR=2.78 (2.22–3.62); p=2.42 x 10^{-19}	Model: NR Adjustments: NR Limitations: Public reference data set Patients qualified for genetic testing included and not a population–based study Results from unmatched cases and controls that were sequenced on different platforms could cause inflation of ORs
Decker et al., 2017[102] UK	Population–based case–control Study duration: 1991–1996 Median age at enrolment: 48 y	13,087 cases 85 *ATM* carriers 5,488 controls 11 *ATM* carriers	*ATM* mutation	Breast cancer	OR=3.26 (1.82–6.46); p=2.1 x 10^{-5}	Model: NR Adjustments: NR Limitations: NR
Kurian et al., 2017[93] USA	Hospital–based case–control Study dates: 2013–2015 Age at enrolment: median 55 y; range 18–98 y	95,561 participants 26,384 cases 640 *ATM* mutations detected 244 women with breast cancer and	*ATM* mutation Multivariable logistic regression model	Breast cancer	OR=1.74 (1.46–2.07); p=6.5 x 10^{-10}	Multivariable logistic regression modelling and matched case–control analysis Adjustments: Age, race/ethnicity, family history

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		ATM mutation				Limitations: Eligibility criteria of clinically tested patients was not accrued Confirmation of family history was not feasible Potential bias of differential reporting of family history
		19,056 cases	Case–control test		OR=2.02 (1.49–2.75); p=2.3 x 10^{-06}	
		51,200 controls				
Goldgar et al., 2011[95] Australia, New Zealand & USA	Population–based & clinic–based study Study duration: NR Average age at diagnosis 47.9 y Average control reference age 48.4 y	2,570 cases 1,448 controls Ethnicity: Caucasian 27 families (129 family members): 15 families with *ATM c.7271T > G* variant	*ATM gene variants*	Breast cancer		A mixed model and likelihood ratio test Adjustments: NR Limitations: NR
			ATM c.7271T > G		RR=8.0 (2.3–27.4); p=0.0005	
			Other variants		RR=4.4 (0.70–28.1); p= 0.053	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: A–T, ataxia–telangiectasia; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

Table D.9 BRCA1 and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Easton et al., 2015[98] Studies published to: NR Denmark, France, Finland, Norway, Sweden, UK	Segregation analysis with estimates derived from BOADICEA model	Participant details: NR	Protein–truncating *BRCA1* gene mutations	Breast cancer	RR=11.4 AR by 80 y=75%	Model based on risks to age 80 years for a woman born in 1960 Limitations: Publication bias Potential ascertainment bias
Chen & Parmigiani, 2007[110] No search date Australia, Europe, Hong Kong, Israel, North America	10 studies Type of study NR	*BRCA1* participants Breast Cancer Linkage Consortium; AJ population; Australian Cancer Registry; hospital–based AJ cancer patients; kConFab; Italian cancer genetic clinics	*BRCA1* mutation By 20 y By 30 y By 40 y By 50 y By 60 y	Breast cancer By 70y	ACR =57% (47–66%) Mean risk=54% (46–63%) Mean risk=54% (45–63%) Mean risk=49% (41–58%) Mean risk=37% (30–44%) Mean risk=19% (15–24%)	Random effects model Adjustments: NR Publication bias: NR Limitations: There may be study characteristics that were not able to be examined
Pooled analyses						
Antoniou et al., 2003[109] Studies published to 2002 Australia, Europe, Hong Kong, Israel, North America	22 cohort studies Both population & hospital based participants	6,965 cases 289 *BRCA1* participants	*BRCA1* mutation 20–29 y 30–39 y 40–49 y 50–59 y 60–69 y	Breast cancer By 70 y	ACR=65% (44–78%) RR=17 (4.2–71) RR=33 (23–49) RR=32 (24–43) RR=18 (11–30) RR=14 (6.3–31)	Kaplan–Meier model Adjustments: NR Publication bias: NR Limitations: Confirmation of cancer diagnoses in relatives not always possible

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Kuchenbaecker et al., 2017[108] Australia, New Zealand, Europe, North America	EMBRACE, IBCCS, BCFR & kConFab Recruitment: 1997–2011 Prospective Follow–up: median 5 y Median age at follow–up: 37 y Median age at cancer diagnosis: 44 y	2,276 *BRCA1* women 269 cases	*BRCA1* mutation 21–30 y 31–40 y 41–50 y 51–60 y 61–70 y 71–80 y Family history of breast cancer No breast cancer 1 breast cancer ≥2 breast cancers	Breast cancer By 80 y	SIR=16.6 (14.7–18.7) ACR=72% (65–79%) SIR=73.7 (42.9–126.8) SIR=46.2 (37.3–57.1) SIR=17.2 (14.0–21.2) SIR=9.7 (7.2–12.9) SIR=7.0 (4.5–11.0) SIR=4.8 (1.8–12.8) HR=1 (referent) HR=1.51 (1.08–2.11); p=0.02 HR=1.99 (1.41–2.82); p<0.001	Cox regression model (HRs) Adjustments: multiple women from the same family Limitations: Data on tumour phenotypes of cancers were not available It was not possible to contrast the unaffected study participants to all other unaffected family members Number of events in some subgroups was small Lack of information about the use of preventative hormone therapies
Mavaddat et al., 2013[112] UK	EMBRACE study Study established: 1998 Prospective study Mean follow–up: 3.3 y	978 *BRCA1* women 365 cases 501 controls Mean age at diagnosis: 41.6 y	*BRCA1* mutation <20 y 20–29 y 30–39 y 40–49 y 50–59 y 60–69 y	Breast cancer By 70 y	ACR=60% (44–75%) IR=0 IR=8.7 (2.2–34.7) IR=16.9 (9.3–30.4) IR=19.9 (11.3–35.1) IR=36.1 (18.8–69.4) IR=7.4 (1.0–52.6)	Cox proportional hazards regression model (HRs) Adjustments: Stratified by birth cohort Limitations: Potential confounders and underreporting of prophylactic oophorectomy in women without cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Follow–up at 2, 5 & 10 y		≥70 y		IR=0	Therapies may reduce risk rather than oophorectomy Lack of data on therapies and surgical procedures used to treat unilateral breast cancer
Suthers, 2007[111] Australia & USA	Retrospective 2001 incidence in general population (Australia)—AIHW data 2006 incidence data among *BRCA1/2* carriers (USA)—Chen et al., 2006 data Age at enrolment & duration of follow–up: NR	Study sample details NR	*BRCA1* mutation Australian general population Age 20 y	Breast cancer By 70 y	ACR=almost 60%	Model: NR Adjustments: NR Limitations: NR
Case–control studies						
Kurian et al., 2017[93] USA	Hospital–based case–control Study dates: 2013–2015 Age range: 11–98 y	95,561 women enrolled 26,384 breast cancer cases 1,468 *BRCA1* mutations detected 739 *BRCA1* mutations detected in breast cancer cases	*BRCA1* gene mutation	Breast cancer	OR=5.91(5.25–6.67); p=2.2×10^{-186}	Multivariable logistic regression model Adjustments: Age, race/ethnicity & family history Limitations: Participants were not accrued according to the rigorous eligibility criteria of a clinical trial Potential bias may be

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		15,826 cases 15,826 controls	Exact McNemar's Case–Control Test		OR=5.89 (4.57–7.68); $p=7.4\times10^{-61}$	differential reporting of family history among cases versus controls

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AR, absolute risk; BCFR, Breast Cancer Family Registry; *BRCA1+*, *BRCA1* gene mutation carrier; BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; CR, cumulative risk; EMBRACE, Epidemiological Study of *BRCA1* and *BRCA2* mutation carriers; HR, hazard ratio; IBCCS, International *BRCA1/2* Carrier Cohort Study; kConFab, Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer; NR, not reported; OR, odds ratio; p, p–value; RR, relative risk or risk estimate; SIR, standard incidence ratio; UK, United Kingdom; USA, United States of America; y, year/s.

Table D.10 BRCA2 and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Easton et al., 2015[98] Study publication dates: NR Denmark, France, Finland, Norway, Sweden & UK	Segregation analysis with estimates derived from BOADICEA model	Participant details: NR	Protein–truncating *BRCA2* gene mutations	Breast cancer By 80 y	RR=11.7 AR=76%	Model based on risks to age 80 years for a woman born in 1960 Limitations: Publication bias Potential ascertainment bias
Chen & Parmigiani, 2007[110] Study publication dates: NR Australia, Europe, Hong Kong & North America	10 studies Type of study: NR	*BRCA2* population Breast Cancer Linkage Consortium; AJ population; Australian Cancer Registry; hospital–based AJ cancer patients; kConFab; Italian cancer genetic clinics	*BRCA2* carriers	Breast cancer After 70 y	ACR=49% (40–57%)	Random effects model Adjustments: NR Publication bias: NR Limitations: There may be study characteristics that were not able to be examined
Pooled analysis						
Antoniou et al., 2003[109] Studies published to 2002 Australia, Europe, Hong Kong, Israel, North America	22 cohort studies Both population– & hospital–based participants	6,965 breast cancer cases 221 *BRCA2* mutations	*BRCA2* carriers	Breast cancer By 70 y	ACR=45% (31%–56%)	Kaplan–Meier model Adjustments: NR Publication bias: NR Limitations: Confirmation of cancer diagnoses in relatives not always possible Variation in techniques used for mutation detection
				Breast cancer		
				20–29 y	RR=19 (4.5–81)	
				30–39 y	RR=16 (9.3–29)	
				40–49 y	RR=9.9 (6.1–16)	
				50–59 y	RR=12 (7.4–19)	
				60–69 y	RR=11 (6.3–20)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Kuchenbaeker et al., 2017[108] Australia, Canada, USA	EMBRACE, IBCCS, BCFR & kConFab Recruitment: 1997–2011 Prospective Follow–up: median 4 y Median age at start of follow–up: 39 y Median age at cancer diagnosis: 48 y	1,610 *BRCA2* mutations carriers 157 cases	BRCA 2 mutations Total 21–30y 31–40y 41–50y 51–60y 61–70y 71–80y 1 relatives affected vs no relatives affected ≥2 relatives affected vs no relatives affected	Breast cancer	SIR=12.9 (11.1–15.1) CR=69% (61–77%) SIR=60.8 (25.5–144.9) SIR=20.3 (13.5–30.5) SIR=16.4 (12.9–20.9) SIR=11.4 (8.4–15.5) SIR=6.4 (3.8–10.7) SIR=6.6 (3.0–14.7) HR=1.53(0.86–2.70); p=0.15 HR=1.91(1.08–3.37); p=0.02	Cox regression hazard model Adjustments: NR Limitations: Data on tumour phenotypes of cancers were not available Selection bias The number of events in some of the subgroups considered was small Lack of information about the use of hormone therapies
Mavaddat et al., 2013[112] UK	EMBRACE study Study established: 1998 Prospective study Mean follow–up: 3.3 y Follow–up at 2, 5 & 10 y	909 *BRCA2* mutation carriers 323 cases 485 controls Mean age at diagnosis: 45.2 y	*BRCA2* mutation 30–39 y 40–49 y 50–59 y 60–69 y	Breast cancer By 70 y IR=11.9 (5.0–28.6) IR=41.4 (26.1–65.8) IR=15.2 (5.7–40.6) IR=16.2 (4.1–64.8)	ACR=55% (41–70)	Kaplan–Meier model No adjustments Limitations: Results may have been confounded. Lack of data on tamoxifen, other therapies, & surgical procedures carried out for unilateral breast cancer. Underestimation of the effect of oophorectomy on cancer risks

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Case–control studies						
Kurian et al., 2017[93] USA	Hospital–based case–control Study dates: 2013–2015 Age range: 11–98 y	95,561 women enrolled 26,384 breast cancer cases 1,539 *BRCA2* mutation detected 703 *BRCA2* mutations detected in breast cancer cases	*BRCA2* gene mutation	Breast cancer	OR=3.31(2.95–3.71); p=2.7×10^{-95}	Multivariable logistic regression model Adjustments: Age, race/ethnicity & family history Limitations: Participants were not accrued according to the rigorous eligibility criteria of a clinical trial. Potential bias may be differential reporting of family history among cases versus controls
		15,826 cases 15,826 controls	Exact McNemar's Case–Control Test		OR=3.12 (2.56–3.83); p=1.7×10–34	
Suthers, 2007[111] Australia & USA	Retrospective study 2001 incidence in general population (Australia)—AIHW data 2006 incidence data among *BRCA1/2* carriers (USA)—Chen et al., 2006 data Follow–up: NR Age at baseline: NR	Population details: NR	*BRCA2* mutation vs Australian general population	Breast cancer	ACR=40%–60%	Model: NR Adjustment: NR Limitations: NR
			Age 20 y	By age 70 y		

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: ACR, average cumulative risk; AIHW, Australian Institute of Health and Welfare; AJ, Ashkenazi Jew; AR, absolute risk; *BRCA*, gene mutation carrier; CR, cumulative risk; EMBRACE , Epidemiological Study of *BRCA1* and *BRCA2* mutation carriers; HR, hazard ratio; IR, incident rate (per 1000 person–year); kConFab, Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer; NR, not reported; OR, odds ratio; RR, relative risk or risk estimate; SIR, standardised incident ratio; UK, United Kingdom; USA, United States of America; y, year/s.

Table D.11 CDH1 and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Case–control studies						
Kurian et al., 2017[93] USA	Hospital–based Study dates: 2013–2015 Median age at hereditary cancer testing: 55 y	95,561 participants 26,384 cases 42 mutations detected 13 breast cancer cases & detected *CDH1* mutation	*CDH1* gene mutation McNemar's Case–Control Test	Breast cancer Lobular breast cancer	OR=1.34 (0.66–2.68); p=0.42 OR=4.00 (0.80–38.7); p=0.11 OR=17.7 (7.68–40.1); p=1.4×10^{-11}	Multivariable logistic regression models Adjustments: Age, race/ethnicity & family history Limitations: Participants were not accrued according to the rigorous eligibility criteria of a clinical trial Potential bias may be differential reporting of family history among cases versus controls
Couch et al., 2017[101] USA	Exome Aggregation Consortium database Hospital–based Study dates: 2012–2016 Age at recruitment: NR	65, 057 women with breast cancer referred for hereditary cancer genetic testing 37,277 breast cancer cases 23 patients with *CDH1pathogenic variants*	*CDH1* variants vs no mutations	Breast cancer	OR=5.34 (1.60–20.94); p=2.09 x10^{-3}	Fisher exact test Adjustments: NR Limitations: Not a population–based study Use of results from unmatched cases & controls Ascertainment bias
Case–series						
Pharoah et al.,	Segregation	11 families	*CDH1* mutation	Breast cancer	RR=6.6 (SE: 0.67)	Mendel program

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
2001[119] UK	analysis Family samples were collected by members of IGCLC Age at recruitment: NR	(476 individuals) 7 cases Mean age at diagnosis: 53 y			Cumulative risk to 80 y: RR=39% (12–84)	Adjustments: NR Limitations: Ascertainment bias
Hansford et al., 2015[115] Italy & Portugal	Recruitment dates: 2006–2013 Age at recruitment: NR	75 *CDH1* mutation positive HDGC families 89 breast cancer cases	*CDH1* Age 10–49 y Age ≥50 y	Breast cancer	RR=7.7 RR=7.4 Cumulative risk to 80 y: 42% (23%–68%)	Mendel program Adjustments: NR Limitations: Assay cannot detect copy number alterations within targeted amplicons Lifestyle & environment factors are genetic modifiers Limited availability of additional materials from family members Inaccuracies in retrospective review
Kaurah et al., 2007[120] Canada	British Columbia Cancer Agency Study dates: 2004–2006 Age at recruitment: NR	4 families with *2398delC* mutation 16 cases of breast cancer	*CDH1* mutation	Breast cancer	Cumulative risk by 75 y: 52% (29%–94%)	Mendel program Adjustments: NR Limitations: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cross–sectional study						
Lowstuter et al., 2017[116] USA	Ambry Genetics & the University of Southern California Study dates: 2012–2014 Retrospective review	Laboratory cohort: 26,936 patients 16 patients with pathogenic *CDH1* mutations Clinic cohort: 318 patients 4 pathogenic *CDH1* mutation 14 breast cancer cases	*CDH1* mutation	Breast cancer	No risk estimate provided	Limitations: Limited or under–ascertained family history and incomplete appreciation of the histologic subtype of breast cancer

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: HDGC, Hereditary Diffuse Gastric Cancer; IGCLC, International Gastric Cancer Linkage Consortium; NR, not reported; NS, not significant; OR, odds ratio; p, p–value; RR, relative risk or risk estimate; SE, standard error; UK, United Kingdom; USA, United States of America; y, year/s.

Table D.12 CHEK2 and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Southey et al., 2016[128] Date of publication: NR Australia, Belarus, Belgium, Canada, Denmark, Finland, France, Ireland, Italy, Germany, Netherlands, Norway, Poland, Spain, Sweden, UK & USA	48 studies included in the BCAC were mostly population–based or hospital–based case–controls	42,671 incident cases 42,164 controls	*CHEK2* mutation (carriers vs non–carriers) *c349A>G* variant *c538C>T* variant *c715G>A* variant *c1036C>T* variant *c1312G>T* variant	Breast cancer	 OR=2.26 (1.29–3.95); p=0.003 OR=1.33 (1.05–1.67); p=0.016 OR=1.70 (0.73–3.93); p=0.210 OR=5.06 (1.09–23.5); p=0.017 OR=1.03 (0.62–1.71); p=0.910	Unconditional logistic regression model Adjustments: Study (categorical) Publication bias: NR Limitations: Limited set of variants with imprecise estimates, which may be limited to specific populations
Aloraifi et al., 2015[100] Studies published to 2014 Australia, Canada, Italy, Finland, France, Germany, Poland, UK & USA	9 case–control studies	7,263 incident cases 13,785 controls Women with a family history of breast cancer, onset at <50 y of age, or bilateral breast cancer	*CHEK2* mutation	Breast cancer	OR=3.25 (2.55–4.13); p(heter)=0.056	Fixed effects model (I^2<50%)/ Random effects model (I^2>50%) No adjustments No publication bias Limitations: Study limited to protein–truncating variants Uncertainties regarding modes of ascertainment of families and potential confounding effects Selection bias

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Yang et al., 2012[121] Studies published to 2012 Australia, Belgium, Brazil, Czech Republic, Canada, Denmark, Finland, Germany, Ireland, Pakistan, Philippines, Poland, Netherlands, Sweden, UK & USA	25 case–control studies 20 hospital–based studies 5 population–based studies	29,154 cases 37,064 controls Ethnicity: Caucasian	*CHEK2 1100delC* variant	Breast cancer	OR=2.75 (2.25−3.36); p<0.00001; I^2=0.0%, p(heter)=0.90	Fixed effects model (I^2<50%)/ Random effects model (I^2<50%) Adjustments: NR No publication bias Limitations: Controls were mostly hospital–based Controls and cases matched on few factors Unadjusted estimates No analysis on pathological classification of breast cancer or menstruation status
Liu et al., 2012[127] Studies published to 2011 Belarus, Czech Republic, Finland, Germany, Netherlands, Poland, North America & UK	13 studies	17,073 cases 26,501 controls	*CHEK2 I157T* variant vs non–carriers	Unselected breast cancer	OR=1.48 (1.31–1.66); p<0.0001; I^2=40.2%, p(heter)=0.081	Random effects model Adjustments: NR No publication bias (p>0.05) Limitations: Study heterogeneity Individual patient data or original data were unavailable

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Zhang et al., 2011[122] Studies published to 2010 Countries of origin: NR			*CHEK2* variant (carriers vs non–carriers)	Breast cancer		Random effects model Adjustments: NR Publication bias (p<0.10) Limitations: English–only studies included Publications without resolvable genotype counts not included Genotype counts and crude estimates of effect used Gene–gene or gene–environment interactions not evaluated Other sources of heterogeneity not examined
	5 case–control studies	9,970 cases 7,526 controls	*IVS2+1G>A* variant		OR=3.07 (2.03–4.63); p=9.82×10−8; I^2=0.0%, p(heter)=0.707	
	8 case–control studies	13,311 cases 10,817 controls	*rs17879961 (I157T)* variant		OR=1.52 (1.31–1.77); p=4.76×10−8; I^2=14%, p(heter)=0.324	
	5 case–control studies	10,543 cases 8,447 controls	1100delC variant		OR=2.53 (1.61–3.97); p=6.33×10−5; I^2=0.0%, p(heter)=0.419	
	47 case–control studies	41,791 cases 50,910 controls	*CHEK2* deletion		OR=3.10 (2.59–3.71); p<10−20; I^2=8%, p(heter)=0.315	
Weischer et al., 2008[123] Studies published to 2007 Australia, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Netherlands, Poland, Sweden, UK & USA	12 case–control studies	26,488 cases 27,402 controls	*CHEK2* deletion *CHEK2 1100delC* heterozygotes vs non–carriers	Unselected breast cancer	OR=2.4 (1.8–3.2); I^2=8%	Random effects model Adjustments: NR No publication bias Limitations: Potential for heterogeneity and publication bias
	9 case–control studies			Familial breast cancer	OR=4.6(3.1–6.8); I^2=0%	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Pooled analysis						
Easton et al., 2015[98] Date of publication: NR Finland & multinational	2 case–control studies	Number of participants: NR	*CHEK2 1100delC* mutation	Breast cancer	RR=3.02 (90% CI: 2.6–3.5); p<0.0001	Model: NR Adjustments: NR Limitations: Publication bias Potential ascertainment bias
Case–control studies						
Kurian et al., 2017[93] USA	Hospital–based Study dates: 2013–2015 Median age at hereditary cancer testing: 55 y	95,561 women 26,384 breast cancer cases	*CHEK2* mutation vs no cancer history at time of genetic testing	Breast cancer		Multivariate logistic regression model Adjustments: Family history of breast and ovarian cancer, age, and race/ethnicity Limitations: Eligibility criteria not rigorous Differential reporting of family history among cases versus controls
		319 incident cases 319 matched controls	Multivariate logistic regression model		OR=1.99 (1.70–2.33); p<0.0001	
		19,056 incident cases 15,826 controls	Exact McNemar's case–control test		OR=2.12 (1.63–2.77); p<0.0001	
Couch et al., 2017[101] USA	Exome Aggregation Consortium database Hospital–based Cohort dates: 2012−2016	29,090 incident cases: 424 *CHEK2* mutations 25,215 controls: 163 *CHEK2* mutations Mean age at	*CHEK2* mutation Pathogenic variant *1100delC* variant Missense variants	Breast cancer	OR=2.26 (1.89–2.72) OR=2.31 (1.88–2.85) OR=1.48 (1.31–1.67)	Model: NR Adjustments: NR Limitations: Not a population based study Use of unmatched cases and controls sequenced on different platforms

Authors	Study details	Study sample	Exposures	Outcomes		Risk estimates	Author comments
	Age at recruitment: NR	diagnosis: 48.5 y					
Decker et al., 2017[102] UK	Population–based Start of study: 1996 Age at recruitment: NR	13,087 incident cases 5,488 controls Breast cancer diagnosed <55 y from 1991 and <70 y from 1996	*CHEK2* truncating mutations (carriers vs non–carriers)	Breast cancer		OR=3.11 (2.15–4.69); p<0.0001	Unconditional logistic regression model Adjustments: Gene length & multiple testing Limitations: No analysis on very rare variant classes and less common breast cancer subtypes
					ER+	OR=3.42 (2.33–5.21); p<0.0001	
					ER–	OR=1.59 (0.80–3.00); p=0.18	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AR, absolute risk; BCAC, Breast Cancer Association Consortium; CI, confidence interval; ER, oestrogen receptor; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s

Table D.13 PALB2 and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Southey et al., 2016[128] Date of publication: NR Australia, Belarus, Belgium, Canada, Denmark, Finland, France, Ireland, Italy, Germany, Netherlands, Norway, Poland, Spain, Sweden, UK & USA	48 studies included in the BCAC were mostly population–based or hospital–based case–controls	34,488 cases 34,059 controls Referent: non carriers	*PALB2 c1592delT (p.Leu531Cysfs)* *PALB2 c3113G>A (p.Trp1038)* *PALB2 c2816T>G (p.Leu939Trp)*	Breast cancer	OR=3.44 (1.39–8.52); LRT p=0.003 OR=4.21 (1.84–9.60); LRT p=1.2x10^{-4} OR=1.03 (0.80–1.32); LRT p=0.82	Unconditional logistic regression Publication bias: NR Adjustments: Study (categorical) Limitations Limited set of variants with imprecise estimates, which may be limited to specific populations
Aloraifi et al., 2015[100] Studies published to 2014 China, Canada, Czech Republic, Finland, Germany, Italy, Malaysia, Poland, UK, USA	13 case–control studies	5,862 cases 17,453 controls Women with a family history of breast cancer, onset at <50 y of age, or bilateral breast cancer	*PALB2* mutation	Breast cancer	OR=21.4 (10.10–45.32); p(heter)=0.947	Fixed and random effects models No adjustments No publication bias (funnel plot and Egger's test) Limitations: Study limited to protein–truncating variants Uncertainties regarding modes of ascertainment of families and potential confounding effects

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						Selection bias
Pooled analyses						
Easton et al., 2015[98] Finland & multinational	1 family–based case–control study 2 case–control studies	Number of participants: NR	*PALB c1529delT*	Breast cancer	RR=5.3 (90% CI 3.0–9.4)	Model: NR Adjustments: NR Limitations: Publication bias Potential ascertainment bias
Case–control studies						
Couch et al., 2017[101] North America	Exome Aggregation Consortium database Hospital–based Study dates: 2012–2016 Age at recruitment: NR	Mean age at diagnosis: 48.5 y 42,435 incident cases: 352 mutations of *PALB2* 52,529 controls: 70 mutations of *PALB2*	*PALB2* mutation All ethnicities	Breast cancer	OR=6.25 (4.82–8.14); p=1.00 x 10^{-60}	Model: NR Adjustments: NR Limitations: Not a population based study Unmatched cases and controls sequenced on different platforms
		30,025 incident cases: 241 *PALB2 mutations* 26,869 controls: 29 *PALB2* mutationa	European ancestry		OR=7.46 (5.12–11.19); p=4.31x10^{-38}	
Decker et al.,	Population–based	13,087 incident	*PALB2* gene variants	Breast cancer		Unconditional logistic regression

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
2017[102] UK	case–control Start of study: 1996 Breast cancer diagnosed: ≥1991 Age at recruitment: NR	cases Breast cancer diagnosed <55 y from 1991 and <70 y from 1996 12,998 *PALB2* mutation non–carriers 89 *PALB2* mutation carriers 5,488 controls: 8 carriers 5,480 non–carriers	Overall		OR=4.69 (2.27−9.68); p=6.9×10−6	model Adjustments: NR Limitations: NR
Kurian et al., 2017[93] USA	Hospital–based case–control Study dates: 2013–2015 Median age at hereditary cancer testing: 55 y	95,651 women 484 *PALB2* mutations detected in all patients 257 cases with *PALB2* mutation Matched case–control 19,056 incident cases 15,826 controls	*PALB2* mutation	Breast cancer	OR=3.39 (2.79–4.12); p=2.0 x 10^{-34} OR=4.13 (2.88–6.05); p=2.2 x 10^{-18}	Multivariate logistic regression model Adjustments Age, race/ethnicity & family history Limitations: Eligibility criteria not rigorous Differential reporting of family history among cases versus controls
Cybulski et al.,2015[131] Poland	Hospital–based Recruitment dates: 1996–2012 7 centres recruited patients with breast	12,529 cases 4,702 controls *PALB2* mutation present in 116 cases and 10 controls	*PALB2* mutation	Breast cancer	OR=4.39 (2.30–8.37)	Two–by–two table with Wald chi–squared test Adjustments: NR Limitations: Not able to confirm causes of death

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	cancer 18–92 y 11 centres included patients 21–50 y Follow–up: until 2014 Mean age at recruitment: 53.5 y					Studied two founder mutations in one country(Poland), possible misclassification of women who carry other non–founder *PALB2* mutations Estimates based on small numbers of patients and deaths
Antoniou et al., 2014[130] Australia, Belgium, Canada, Finland, Greece, Italy, UK & USA	Family–based Study duration: NR Age at enrolment: NR	362 individuals from 154 families	*PALB2* mutation carrier vs UK general population (1993–97) Family history to 70 y No family history ≥ 2 first–degree relatives	Breast cancer	RR=9.47 (7.16–12.57) CR=33% (25%–44%) CR=58% (50%–66%)	Most parsimonious model Adjustments: Method of ascertainment Limitations: NR
			Age group 20–24 y 25–29 y 30–34 y 35–39 y 40–44 y 45–49 y 50–54 y 55–59 y 60–64 y 65–69 y 70–74 y 75–79 y		Mean RR=9.01 (5.70–14.16) Mean RR=8.97 (5.68–14.08) Mean RR=8.85 (5.63–13.78) Mean RR=8.54 (5.51–13.08) Mean RR=8.02 (5.29–11.95) Mean RR=7.31 (4.98–10.55) Mean RR=6.55 (4.60–9.18) Mean RR=5.92 (4.27–8.10) Mean RR=5.45 (4.00–7.33) Mean RR=5.10 (3.80–6.76) Mean RR=4.82 (3.63–6.33) Mean RR=4.56 (3.48–5.95)	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BCAC, Breast Cancer Association Consortium; CI, confidence interval; CR, cumulative risk; LRT, likelihood ratio test; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

Table D.14 PTEN and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Case–control studies						
Couch et al., 2017[101] USA	Hospital–based Study duration: 2012–2016 Mean age at recruitment: 48.5 y	38,179 cases 20 *PTEN* mutations detected 24,166 controls 1 *PTEN* mutation detected	*PTEN* variants vs no mutation	Breast cancer	OR=12.66 (2.01–258.89); $p=5.79\times10^{-04}$	Fisher exact test Adjustments: NR Limitations: Not a population–based study Use of results from unmatched cases and controls Ascertainment bias
Kurian et al., 2017[93] USA	Hospital–based Study dates: 2013–2015 Median age at hereditary cancer testing: 55 y	95,561 women 26,384 cases 24 *PTEN* mutation detected 15 cases with detected *PTEN* mutation Median age at genetic testing: 55 y for cases	*PTEN* gene mutation vs no mutation	Breast cancer	OR=5.83 (2.43–14.0); $p=7.7\times10^{-05}$	Multivariable logistic regression model Adjustments: Family history of breast & ovarian cancer Limitations: Participants were not accrued according to the rigorous eligibility criteria of a clinical trial Potential bias may be differential reporting of family history among cases versus controls
Case series						
Nieuwenhuis et al., 2014[134] Australia, Denmark, France, Germany,	Laboratory–based Patients born between 1928–2008	99 women 24 cases	*PTEN* mutation	Breast cancer by 60 y	Cumulative RR=67.3%	Kaplan–Meier model Adjustments: NR Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Norway, Switzerland, Netherlands, UK & USA	Prospective study Mean age at last contact: 32 y (men & women)					Ascertainment bias Detailed information on *PTEN* mutations missing in some cases
Bubien et al., 2013[139] France	Laboratory–based Prospective study Study dates: 1997–2008 Median age at enrolment: 36 y (men & women)	146 patients 70 women 23 cases	*PTEN* mutation	Breast cancer Breast cancer at 70 y	SIR=39.1 (24.8–58.6) RR=77% (59–91)	Kaplan–Meier model Adjustments: Age & sex Limitations: Recruitment & ascertainment bias
Tan et al., 2012[138] Asia, Europe & North–America	Community & medical centre–based Prospective study Study dates: 2000−2010 Median age at enrolment: 39 y (men & women)	205 women 67 cases	*PTEN* mutation Lifetime risk	Breast cancer	SIR=25.4 (19.8–32.0) Penetrance=85.2% (71.4–99.1)	Kaplan Meier model Adjustments: Age Limitations: Ascertainment bias

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: NR, not reported; OR, odds ratio; p, p–value; RR, relative risk or risk estimate; SIR, standardized incident rate; UK, United Kingdom; USA, United States of America; y, year/s.

Table D.15 Single nucleotide polymorphisms and susceptibility loci studies and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Michailidou et al., 2017[140] Dates of publication search: NR Australia, Belarus, Belgium, Canada, China, Denmark, Finland, France, Germany, Greece, Israel, Italy, Japan, Korea, Macedonia, Malaysia, Netherlands, Norway, Poland, Russia, Singapore, Spain, Sweden, Taiwan, Thailand, UK & USA	68 studies from BCAC and DRIVE Majority of studies were population based case–control studies, or case–control studies nested within population based cohorts	67 European ancestry studies: 122,977 cases 105,974 controls 12 East Asian ancestry: 14,068 cases 13,104 controls cases	Common susceptibility variants identified through GWAS, including 65 newly identified susceptibility loci	Breast cancer	FRR=18%	Logistic regression Adjustments: Principal components, country and study Publication bias: NR Limitations : NR
Milne et al., 2017[143] Dates of publication search:	68 BCAC studies Majority of studies were case–control	21,468 ER– cases 18,908 *BRCA1* mutation carriers:	125 SNPs	ER– breast cancer	FRR=14%	Logistic regression Adjustments: Principal components, country

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
NR Australia, Belarus, Belgium, Canada, Denmark, France, Finland, Germany, Greece, Ireland, Israel, Italy, Macedonia, Netherlands, New Zealand , Norway, Poland, Russia, Spain, Sweden, UK & USA	studies	9,414 breast cancer cases 100,594 controls Ethnicity: European				and study Publication bias: NR Limitations: NR
Pooled–analyses						
Li et al., 2017[146] Data collected from 1995 & 1997 onwards Australia, Canada, New Zealand & USA	2 pooled cohort studies BCFR & kConFab cohorts Prospective analysis	4,365 women analysed 2,869 unaffected women 1,496 women with breast cancer Mean age: 53.6 y Mean follow–up: 7.4 y	24 SNPs Continuous PRS combined (per SD) PRS combined Q1 Q2 Q3 Q4 Q5	Breast cancer	HR=1.38 (1.22–1.56); p=2.9x10^{-7} HR=1.00 (referent) HR=1.71 (1.00–2.95) HR=2.34 (1.40–3.90) HR=2.46(1.47–4.13) HR=3.18 (1.84–5.23); p=4.7x10^{-6}	Cox proportional hazard model Adjustments: NR Publication bias: NR Limitations: Ascertainment bias
Mavaddat et al., 2015[141] Dates of publication search:	Breast Cancer Association Consortium	33,673 cases 33,381 controls Age at diagnosis:	77–SNP PRS <1% 1–5% 5–10% 10–20%	Breast cancer	OR=0.31 (0.24– 0.39) OR=0.42 (0.37–0.46) OR=0.49 (0.45–0.54) OR=0.61 (0.57–0.66)	Logistic regression model Adjustments: Study and seven principal components

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
NR Australia, Belarus, Belgium Canada, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden, UK & USA		57 y Age at interview (controls): 56 y Ethnicity: European	20–40% 40–60% 60–80% 80–90% 90–95% 95–99% >99%		OR=0.79 (0.75–0.83) OR=1.00 (referent) OR=1.27 (1.21–1.33) OR=1.44 (1.36–1.52) OR=1.85 (1.72–1.99) OR=2.34 (2.17–2.52) OR=3.36 (2.95–3.83)	Publication bias: NR Limitations: Limited sample number Estimates less precise for ER–negative disease Oversampling for family history Lifestyle/environmental risk factors not included in the model
					ER+ OR=2.80 (2.26–3.46) ER– OR=3.73 (3.24–4.30)	
			First–degree family history of breast cancer Yes Lowest quintile Highest quintile	Breast cancer	 Cumulative AR=8.6% Cumulative AR=24.4%	
			No Lowest quintile Highest quintile		 Cumulative AR=5.2% Cumulative AR=16.6%	
Vachon et al., 2015[151] Data collected in 1997, 2003−2006, 2001−2008 & 2002−2010 USA	3 case–control studies	1,643 cases 2,397 controls Mean age: 60.1 y	76–SNP PRS PRS and BI–RADS density vs BI–RADS density	Breast cancer	OR=1.48 (1.38–1.58)	Logistic regression model Adjustments: Case–control design, age and 1/BMI Publication bias: NR Limitations: Lack of independent cohort data
Cohort studies						
Kuchenbaecker et al., 2017[147]	CIMBA study	15,252 *BRCA1* mutation carriers	*BRCA1/2* pathogenic mutation polygenic	Breast cancer		Weighted cohort Cox regression with time to diagnosis model

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
26 countries	Prospective study Study duration: NR Age at enrolment: >18 y Follow–up: NR	8,211 *BRCA2* mutation carriers 94 SNPs Ethnicity: European	risk scores *BRCA1* (per unit SD) *BRCA2* (per unit SD)	ER+ ER– ER+ ER–	HR=1.11 (1.08–1.15); p=3.5x10^{-13} HR=1.27 (1.23−1.31); p=8.2x10^{-53} HR=1.22 (1.16–1.27); p=4.0x10^{-19} HR=1.15 (1.10–1.20); p=6.8x10^{-10}	Adjustments: NR Limitations: Information on family history unavailable
Case–control studies						
Cuzick et al., 2017[148] UK	Nested case–control Cohort dates for Data from IBIS–I: 1992−2001 Median follow–up: 16.5 y Cohort dates for data from Marsden trial: 1986−1996 Median follow–up: 18.4 y Median age at recruitment: 50 y	995 women 359 cases 636 controls	88 SNPs	Breast cancer	OR=1.37 (1.14–1.66); p<0.001	Model: NR Adjustments: NR Limitations: Could not assess performance of SNPs in conjunction with mammographic breast density
Dite et al., 2016[149] Australia	Population–based Australian Breast Cancer Family Registry Study duration: 1992−1999	750 cases 405 controls Caucasian women not carrier of *BRCA1* & *BRCA2*	77–SNP PRS	Breast cancer	OR=1.46 (1.29–1.64); p=2x10^{-16}; c^2=11.4, p=0.2	Logistic regression model Adjustments: Age group Limitations: Missing values for model's risk

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						score calculations
	Age at baseline: 20–49 y					
Shieh et al., 2016[150]	Nested case–control	981 women	83 polygenic risk score	Breast cancer		Fitted BCSC logistic regression model
USA	California Pacific Medical Center Research Institute Cohort	486 cases	<0.57		OR=1 (referent)	Adjustments:
			0.57–0.84		OR=1.41 (0.92–2.16); p=0.12	First degree relative with breast cancer, history of breast biopsy, BMI and breast density
		495 controls	0.84–1.26		OR=1.86 (1.22–2.84); p=0.004	
	Study duration: 2004–2011		>1.26		OR=2.51 (1.63–3.86); p<0.001	Limitations:
		Ethnicity: 80% Caucasian descent				Single centre study
	First diagnosis of invasive breast cancer: 1998–2013					Baseline risk of participants may differ from general population
	Mean age: 56 y					

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AR, absolute risk; BCAC, Breast Cancer Association Consortium; BCFR, Breast Cancer Family Registry; BCSC, Breast Cancer Surveillance Consortium; BI–RADS, breast imagining reporting and data system; BMI, body mass index; BRCA, BRCA gene mutation; c^2, Hosmer–Lemeshow goodness–of–fit test; CIMBA, Consortium of Investigators of Modifiers of *BRCA1/2*; DRIVE; Discover, Biology and Risk of Inherited Variants in Breast Cancer Consortium; ER, oestrogen receptor; FRR, familial relative risk; GWAS, genome–wide association study; HR, hazard ratio; IBIS–1, International Breast Intervention Study; kConFab, Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer; NR, not reported; OR, odds ratio; p, p–value; p(heter), p value for heterogeneity; PRS, polygenic risk score; Q[1–5], quintiles 1–5; SD, standard deviation; SNP, single–nucleotide polymorphisms; UK, United Kingdom; USA, United States of America; y, years.

Table D.16 STK11 and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Giardiello et al., 2000[152] Studies published 1966–1998 Netherlands, UK & USA	6 cohort studies Peutz–Jeghers Syndrome families	104 females with PJS 11 cases Ethnicity: white Age at enrolment: 15–64 y	PJS vs general population	Breast cancer	RR=15.2 (7.6–27); p<0.001	Poisson regression model Adjustments: NR Publication bias: NR Limitations: Small number of families analysed Familial PJS may not be applicable to sporadic case Ascertainment bias
Cohort studies						
Resta et al., 2013[154] Italy	Cohort dates: 1997–2009 End of follow–up: 2009 Retrospective study Age at enrolment: NR Duration of follow–up: NR	119 participants (58 men & 61 females) with PJS 99 with STK11 mutation 6 female breast cancer cases Median age at end of follow–up: 36.5 y	PJS vs general population	Breast cancer	RR=12.5 (5.1–26.0)	Model: NR Adjustments: NR Limitations: Ascertainment bias
Case–control studies						
Kurian et al., 2017[93] USA	Clinic–based Study dates:	19,056 incident cases 15,826 matched	*STK11* gene mutation	Breast cancer	OR=4.41 (0.66–29.6); p=0.13	Multivariate logistic regression model

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	2013–2015 Median age at hereditary cancer testing: 55 y	controls				Adjustments: Age, race/ethnicity and family cancer history Limitations: Eligibility criteria lacked rigour of a clinical trial Potential differential reporting of family history among cases versus controls Family history did not include number of unaffected relatives
Case series						
Hearle et al., 2006[153] Australia, Europe & USA	Study dates: NR Age at recruitment: NR	419 individuals with PJS 297 males and females with *STK11* mutation 16 cases Age at diagnosis: 35–61 y	PJS	Breast cancer By age 40 y 50 y 60 y 70 y	CR=8% (4–17%) CR=13% (7–24%) CR=31% (18–50%) CR=45% (27–68%)	Cox proportional hazards regression model Adjustments: NR Limitations: Ascertainment bias

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: CR, cumulative risk; NR, not reported; OR, odds ratio; p, p–value; PJS, Peutz–Jeghers polyposis and cancer syndrome; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

Table D.17 TP53 and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Easton et al., 2015[98] USA Study published in 2003	1 segregation analysis	Population: based on families ascertained through sarcoma probands	*TP53* gene mutation vs no *TP53* gene mutation	Breast cancer	RR=105 (90% CI: 62–165)	Model: NR Adjustments: NR Publication bias: NR Limitations: Potential ascertainment bias
Cohort studies						
Mai et al., 2016[166] USA	NCI LFS study Start of recruitment: Aug 2011 Prospective study Age at enrolment: NR Follow–up duration: NR	186 *TP53*+ participants 76 cases Median age at time of death or last follow–up: 35 y	*TP53* gene mutation & LFS syndrome	Breast cancer by age 60 y	CIR=approximately 85%	Model: NR Adjustments: NR Limitations: Referral/selection bias due to identification of families with cancer diagnosis among family members Inclusion of only *TP53*+ family members Potential inflation of survival estimates Limited data on treatments and data collected retrospectively
Bougeard et al., 2015[167] France	Prospective study Cohort tested for TP53 mutations:	257 female *TP53* carriers 127 cases	*TP53* mutation	Breast cancer CBC	127 out of 160 (79%) of affected mutation carriers 40 out of 127 (31%) with CBC	Model: NR Adjustments: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	1993–2013 Age at enrolment: NR Follow–up duration: NR	Mean age of tumour onset: 35 y				Limitations: NR
Hwang et al., 2003[165] USA	Prospective study End of study: 2001 Childhood soft tissue sarcoma diagnosed: 1944–1975 Follow–up: >20 y	107 kindreds from patients with childhood soft tissue sarcoma: 56 germline *TP53* mutation carriers 13 cases (out of 56 carriers) 48 non–carriers	*TP53* mutation & familial childhood sarcoma Mutation carriers	Breast cancer	SIR=105.1 (55.9–179.8)	Monsoon program Cohort Analysis for Genetic Epidemiology Adjustments: Birth year, race and familial correlation Limitations: NR
Case–control studies						
Couch et al., 2017[101] USA	Laboratory–based Controls from Exome Aggregation Consortium Genetic testing: Mar 2012–Jun 2016 Age at enrolment: NR	38,305 incident cases 26,789 controls Ethnicity: multi–ethnic	*TP53*	Breast cancer	OR=2.58 (1.39–4.90); $p=1.53x10^{-3}$	Model: NR Adjustments: NR Limitations: Not a population–based study
		8,009 incident cases 26,789 controls Ethnicity: multi–ethnic		Breast cancer at ≤40 y	OR=8.25 (4.27–15.84); $p=1.04x10^{-11}$	Association analysis limited to sequencing results from breast cancer cases and the database of Exome Aggregation Consortium reference samples

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						Cases and controls were not matched and were sequenced on different platforms, which may inflate ORs
Kurian et al., 2017[93] USA	Laboratory–based Genetic testing: Sep 2013–Sep 2015 Median age at hereditary cancer testing: 55 y	19,056 incident cases 51,200 cancer–free controls 15,826 cases with matched controls	*TP53* Overall Matched case–control analysis	Breast cancer	OR=5.37 (2.78–10.4); p=5.7 x 10^{-7}† OR=5.00 (1.07–46.9); p=0.039‡	Multivariable logistic regression model Adjustments§ Limitations: Eligibility criteria was not rigorous Family history obtained from requisition forms completed by ordering physicians and genetic counsellors Differential reporting of family history Family history did not include number of unaffected relatives
McCuaig et al., 2012[164] Canada	Retrospective case–only study, clinic–based Genetic testing: 1992−2011 Age at enrolment: NR	28 incident cases diagnosed <30 y 15 cases from families suggestive of LFS	*TP53* pathogenic mutation Did not meet current criteria for LFS	Breast cancer	Prevalence of mutation in those who did not meet current criteria for LFS=7.7%	Model: NR Adjustments: NR Limitations: Retrospective study, with limited ability to collect clinical information Small sample size

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Mouchawar et al., 2010[163] Australia	Australian Breast Cancer Family Study, population–based Breast cancer diagnosed: 1992–1999 Age at enrolment: >18 y	52 prevalent cases	*TP53* germline mutation	Very early onset breast cancer (before age 30 y)	Prevalence of mutation=4% (n=2)	Model: NR Adjustments: NR Limitations: NR
		42 prevalent cases	2 or more first– or second–degree relatives with breast or ovarian cancer	Early onset breast cancer (aged 30–39 y)	Prevalence of mutation=7% (n=3)	

Note: Risk estimates are presented with 95% confidence intervals (except for Easton et al., 2015, which presented a 90% confidence interval).

Abbreviations: CBC, contralateral breast cancer; CIR, cumulative incidence rate; LFS, Li–Fraumeni syndrome; n, number; NCI LSF, National Cancer Institute Li–Fraumani Syndrome; NR, not reported; OR, odds ration; RR, relative risk or risk estimate; SIR, standard incidence ratio; TP53+, TP53 mutation carriers; USA, United States of America; y, year/s.

†Multivariable logistic regression model.

‡Matched case–control analyses, exact McNemar's test.

§Adjusted for age, ancestry, personal and family cancer histories associated with HBOC, and Lynch and adenomatous polyposis colon cancer syndromes.

Breast pathology

Table D.18 Previous benign breast disease and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Dyrstad et al., 2015[168] Studies published 1972–2010 Canada, China, Italy, Japan, UK & USA	32 retrospective & prospective case–control studies Mean follow–up: 12.8 y	Participant information: NR Referent group: reported as either 'designated reference population' or 'BBD' Mean age at biopsy: 46.6 y Median age at breast cancer diagnosis: 55.9 y	BBD Non–proliferative PDWA Not otherwise specified AH not otherwise specified	Breast cancer	RR=1.17 (0.94–1.47); I^2=79.7%, p(heter)<0.0001 RR=1.76 (1.58–1.95); I^2=40.1%, p(heter)=0.0542 RR=2.07 (1.64–2.61); I^2=97.8%, p(heter)<0.0001 RR=3.93 (3.24–4.76); I^2=33.2%, p(heter)=0.1166	Random effects model Publication bias assessed by Funnel plot & rank correlation method of Begg. Significant heterogeneity in studies for: benign breast disease not otherwise specified & non–proliferative disease Adjustments: NR Limitations: Lack of uniform reporting on specific BBD pathologies Each risk estimate adjusted for factors that varied for each study & may affect statistical analysis
Zhou et al., 2011[169] Studies published 1992– 2010 Canada, Italy, UK & USA	7 nested case–control studies 2 case–control studies	2,340 cases 4,422 controls Participants information: NR	BBD Non–proliferative (referent) PDWA AH ADH	Breast cancer	OR=1 (referent) OR=1.44 (1.28–1.63); p(heter)=0.80 OR=2.81 (1.91–4.12); p(heter)<0.01 OR=2.93 (2.16–3.97); p(heter)=0.479	Random effects model No significant publication bias (Egger's test 0.05) Adjustments: NR Limitations: Both very old & relatively new

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			ALH		OR=5.14 (3.52–7.52); p(heter)=0.975	studies were included in this study Most subjects were Caucasian & not Asian ORs were unadjusted
Cohort studies						
Visscher et al., 2017[174]	Mayo clinical BBD cohort Benign breast biopsies: 1967–2001 Retrospective study Age categories: <45, 45–55 & >55 y Median follow–up: 20.3 y	1,414 women 140 cases	BBD vs non–proliferative First biopsy PDWA AH Second biopsy PDWA AH First to second biopsy NP to NP NP to PDWA/AH PDWA to NP PDWA to PDWA PDWA to AH AH to NP/PDWA AH to AH	Breast cancer	HR=1.79 (1.20–2.66) HR=4.60 (2.41–8.79); p–trend<0.001 HR=1.77 (1.22–2.57) HR=3.40 (2.08–5.55); p–trend<0.001 HR=1 (referent) HR=1.69 (1.01–2.82) HR=1.12 (0.54–2.34) HR=2.32 (1.38–3.88) HR=3.23 (1.53–6.85) HR=3.36 (1.34–8.45) HR=7.30 (2.68–19.86); p–trend<0.001	Proportional subdistribution hazards model† Limitations: Biopsies provide a small sample of total breast tissue, & small proliferative or atypical lesions may not be present in the biopsy Findings were from clinically distinct subset of BBD women who underwent more than one benign biopsy for clinical reasons MBC differed significantly by age, family history of breast cancer & clinical presentation from other subsets in cohort
Radisky et al., 2016[175]	Mayo clinical BBD cohort	106 cases 1,009 controls	BBD vs non–proliferative PDWA	Breast cancer	HR=2.10 (1.31–3.35)	Cox proportional hazards regression model

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Multiple breast biopsy cohort only Benign breast biopsies: 1967–2001 Retrospective study Ages: 18–85 y Median follow–up: 21.9 y		AH		HR=5.49 (2.56–11.81); p–trend<0.001	Adjustments: Time from first biopsy to second biopsy & histologic impression Limitations: Significant differences in average age between the MBC & overall BBD cohort; & limited power of statistical comparisons
Degnim et al., 2016[178]	Mayo clinical BBD & Nashville AH cohort Retrospective study	1,174 AH cases Mayo cohort: 708 AH cases & 143 breast cancer cases Ages: 18–85 y Median follow–up: 13.5 y Nashville cohort: 466 AH cases & 115 breast cancer cases Women aged 20–91 y Median follow–	Benign breast disease ADH (overall) ADH (number of atypical foci) 1 2 ≥3 ALH (overall) ALH (number of atypical foci) 1 2 ≥3 ADH (overall) ADH (number of atypical foci) 1	Breast cancer Invasive breast cancer	SIR=3.49 (2.88–4.22) SIR=2.65 (2.06 –3.41) SIR=5.19 (3.59–7.52) SIR=8.94 (5.48–14.59); p–trend<0.001 SIR=3.41 (2.87–4.04) SIR=2.58 (1.95–3.42) SIR=3.49 (2.51–4.86) SIR=4.97 (3.74–6.62); p–trend=0.001 SIR=3.46 (2.77–4.31) SIR=2.88 (2.19–3.80)	SIR calculation: Observed breast cancer incidence divided by population–based expected counts Adjustments: The analyses account for the effects of age & calendar period Limitations: There may be variability in how number of foci were identified AH is only detected via tissue biopsy, which limits analyses in regard to breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		up: 17 y	2		SIR=4.61 (2.94–7.23)	
			≥3		SIR=7.14 (3.84–13.28); p–trend=0.007	
			ALH (overall)		SIR=3.71 (3.08–4.48)	
			ALH (number of atypical foci)			
			1		SIR=2.90 (2.14–3.92)	
			2		SIR=3.51 (2.40–5.11)	
			≥3		SIR=5.58 (4.09–7.61); p–trend=0.004	
Said et al., 2015[176]	Mayo clinical BBD cohort Benign breast biopsies: 1967–2001 Retrospective study Age categories: <45, 45–55 & >55 y Median follow–up: 16.8 y	11,591 women with excisional breast biopsy 282 FEA cases: 48 FEA + breast cancer cases 1,044 no FEA + breast cancer cases	Benign breast disease NP PDWA AH	Breast cancer	 HR=1 (referent) HR=1.61 (1.40–1.85) HR=3.80 (3.04–4.74); p<0.0001	Cox proportional hazards regression analysis Adjustments: FEA absent/present, age at biopsy, year of biopsy, extent of lobular involution & family history of breast cancer
Hartmann et al., 2014[177]	Mayo clinical BBD cohort Benign breast biopsies: 1967–2001 Retrospective study	13,652 women AH cases: 698 ADH cases: 330 ALH cases: 327 ADH + ALH cases: 32 Breast cancer cases: 143	Benign breast disease AH (overall) Age at AH <45 y 45–55 y >55 y	Breast cancer	 SIR=4.34 (3.66–5.12) SIR=5.45 (3.17–8.73) SIR=5.43 (4.13–7.01) SIR=3.54 (2.74–4.49); p=0.04	Limitations: Single institute, which could reflect bias in findings Study included women who had histologic findings of atypical hyperplasia on breast biopsy between 1/1/1967 & 12/31/2001 at Mayo clinic,

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Age categories: <45, 45–55 & >55 y Mean follow–up: 12.5 y		Type of AH			women referred to Mayo because of a finding of atypia on an outside biopsy were not included
			ADH		SIR=3.93 (3.00–5.06)	
			ALH		SIR=4.76 (3.74–5.97)	
			ADH + ALH		SIR=4.36 (1.75 –8.96); p=0.54	
			Number of atypical loci			
			1		SIR=3.19 (2.46–4.07)	
			2		SIR=5.53 (3.95–7.53)	
			≥3		SIR=7.61 (5.36–10.49); p<0.001	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; AH; atypical hyperplasia; BBD, benign breast disease; FEA, flat epithelial atypia; HR, hazard ratio; MBC, multiple biopsy cohort; NP, non–proliferative disease; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for linear trend; PDWA, proliferative disease with atypia; RR, relative risk or risk estimate; SIR, standardised incidence ratio.; UK, United Kingdom; USA, United States of America; y, year/s.

†Adjusted for age at index biopsy, year of index biopsy, extent of lobular involution, family history of breast cancer, and time between index and second biopsy. Time was modelled as time from index biopsy to cancer for index biopsy characteristics and time from second biopsy to cancer for secondary biopsy characteristics. Age at index biopsy was used as an adjustment term for the characteristics at index biopsy, and age at second biopsy was used for characteristics at second biopsy.

‡Observed breast cancer incidence divided by expected counts. The expected number was determined by dividing the patient's follow–up into 5–year periods according to the patient's age and according to the calendar period; this accounted for differences related to the variables. Potential heterogeneity in SIRs across subgroups was assessed with Poisson regression analysis.

Table D.19 LCIS and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Mao et al., 2017[186] USA	SEER Prospective study Cohort dates: 1998–2007 Women aged 20–84 y (diagnosed with LCIS within last 6 months) Median follow–up: 109 months	10,304 women HR+: 9,949 cases Median age at diagnosis: 62 y HR–: 355 cases Median age at diagnosis: 63 y 9,179 white women 588 black women 509 other	LCIS HR– HR+ Treatment No surgery BCS Radiation No Yes HR– HR+ Treatment No surgery BCS Mastectomy	Invasive IBC Invasive CBC	 HR=1 (referent) HR=0.356 (0.141–0.899); p=0.029 HR=1 (referent) HR=0.074 (0.026–0.210); p<0.001 HR=1 (referent) HR=0.490 (0.263–0.912); p=0.024 HR=1 (referent) HR=0.172 (0.108–0.274); p<0.001 HR=1 (referent) HR=0.181 (0.064–0.509); p=0.001 HR=0.225 (0.080–0.632); p=0.005	Multivariable Cox proportional model Adjustments: Demographic, clinico–pathologic, & treatment factors Limitations: Lack of information on family history, lifestyle factors, clinical pathological characteristics, genetic mutations & use of chemo–preventatives The pathology & HR reporting may not be accurate The incidences of second breast cancers are generally underestimated
King et al., 2015[180] USA	Patients participating in surveillance for LCIS at Memorial Sloan Kettering Cancer Center Cohort dates: 1980–2009 Prospective study	1,060 women with LCIS 173 women taking chemoprevention 168 cases	LCIS Use of chemoprevention	Breast cancer Ipsilateral breast cancer Contralateral Breast cancer	HR=0.269 (0.15–0.50); p<0.001 63% 25%	Cox regression model Adjustments: NR Limitations: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Median follow up: 81 months Median age at baseline: 50 y			Bilateral breast cancer	12%	
Li et al., 2006[184] USA	SEER Prospective study Cohort date: 1988–2002 Follow–up: up to 14 y	4,270 women 282 cases Mean age at diagnosis: 54.3 y 3,606 Non–Hispanic white 328 Black 153 Asian/Pacific Islander 175 Hispanic white 9 American Indian/Alaska Native	LCIS Initial DCIS Initial LCIS Initial DCIS Initial LCIS	Invasive LBC Invasive DBC	 HR=1 (referent) HR=5.3 (4.1–6.9); p=sig. HR=1 (referent) HR=0.8 (0.7–1.0); p=sig.	Cox proportional hazard model Adjustments: Age, year, registry, race/ethnicity, & surgery Limitations: Misclassification errors Possible confounders
Rawal et al., 2005[189] Sweden	Swedish Family–Cancer Database Prospective study Cohort dates: 1993–2000 Age at baseline: ≥21 y Follow–up: up to 7 y	In situ breast cancer: 3,802 women 15 cases: 6 CBC cases; 9 IBC cases 34,803 without in situ breast cancer Population covered by national mammographic screening	LCIS	Invasive CBC No Yes Invasive IBC No Yes	 RR=1.00 (referent) RR=3.16 (1.42–7.03); p=sig. RR=1.00 (referent) RR=4.74 (2.46–9.11); p=sig.	Poisson regression model Adjustments: Age, family history, parity & age at first birth Limitations: Small number of cases A higher incidence of DCIS/LCIS due to screening Possible confounders (treatment, contraceptives, stage of cancer & tumour size)

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Chuba et al., 2005[181] USA	SEER database Prospective study Cohort dates: 1973–1998 Age at baseline: NR Follow–up: 25 y	4,853 women 350 cases	LCIS All ages <40 y 40–49 y 50–59 y 60–69 y >70 y Partial mastectomy Mastectomy	Breast cancer	 SIR=2.4 (2.1–2.6) SIR=3.3 (1.9–5.4) SIR=2.2 (1.8–2.7) SIR=2.1 (1.7–2.6) SIR=2.7 (2.1–4.0) SIR=2.9 (2.0–4.0) CIR=24.3% CIR=12.8%	Model: NR Adjustments: Age & year of diagnosis Limitations: Under reporting or imperfect ascertainment Pathological definitions of LCIS changed during the study period Data on treatment factors & personal history was lacking
Levi et al., 2005)[187] Switzerland	Vaud Cancer Registry Prospective Cohort dates: 1977–2002 Follow–up: up to 25 y, 4,025 person–y Age range: 27–91 y	88 LCIS patients 11 cases	LCIS Overall Histological subtype Ductal Lobular Other	Invasive breast cancer	SIR=4.2 (2.1–7.5) SIR=2.6 (0.8–6.1) SIR=11.5 (3.7–26.8) SIR=3.6 (0.0–20.1)	Model: NR Adjustments: NR Limitations: Lack of treatment information, family history, histology & other confounding factors
Wärnberg et al., 2000[191] Sweden	Swedish Cancer Registry Cohort dates: 1980–1992 Mean follow–up: 4.3 y	55 LCIS patients 14 cases Age at diagnosis NR	LCIS	Invasive breast cancer	SIR=4.0 (2.1–7.5)	Model: NR Adjustments: NR Limitations: Small incidence number

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Page et al., 1991[195] USA	Hospital cohort Cohort dates: 1950–1968 Follow–up: 19 y	39 LCIS patients Women who underwent breast biopsies in Nashville hospitals	LCIS	Invasive carcinoma of the breast	RR=8.2 (3.6–18)	Cox hazard regression model Adjustments: age Limitations: NR
Lo et al., 2018[185] Australia	Victorian Cancer Registry Cohort dates: 1982−2015 Prospective study Median age at LCIS diagnosis: 50 y Mean follow-up: 9.8 y	732 LCIS cases 73 invasive breast cancer cases within 10 y of LCIS diagnosis 356 women without invasive breast cancer at <10 y follow-up LCIS cases excluded previous or synchronous DCIS or invasive breast cancer in either breast (including within 6 months after LCIS diagnosis) Women with other invasive cancer diagnoses (except non-melanotic skin cancer) prior to their pure LCIS diagnosis were also excluded	LCIS	Invasive breast cancer	Mean observed risk at 10 y=14.1% (11.3−17.5%) Mean assigned risk at 10 y=20.9%	Chi-squared goodness-of-fit statistic comparison Adjustments: NR Limitations: Information lacking on uptake of bilateral mastectomy or risk-reducing medication after LCIS diagnosis Potential misclassification of LCIS as atypical hyperplasia Overestimation and poorer calibration of data for women diagnosed with LCIS at age ≥50 years Overdiagnoses from mammographic screening Patient migration out of Victoria after LCIS diagnosis

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Wong et al., 2017[197] USA	SEER database Cohort dates: 1983–2014 Retrospective study Age at enrolment: NR Median follow-up: 8.1 y	19,462 women with histological diagnosis of LCIS 1,837 breast cancer cases Median age at LCIS diagnosis: 53.7 y†† LCIS diagnosed between 1983 and 2013 Ethnicity: majority were Caucasian & non-Hispanic Inclusion of women aged ≥18 y with histologically confirmed LCIS Exclusion of women with a history of prior malignancy, as well as those with a synchronous malignancy diagnosed within 6 months of LCIS diagnosis Breast cancers were diagnosed >6 months following the index LCIS	LCIS	DCIS or invasive breast cancer, including IDC and ILC	10-year cumulative risk=11.3% (10.7–11.9%) 20-y cumulative risk=19.8% (18.8–20.9%)	Kaplan–Meier method No adjustments Limitations: Pure pleomorphic LCIS not treated with radiation may exist within the cohort and increase the incidence of ipsilateral malignancies Lack of information on chemoprevention or reasons for surgical treatment selection, as well as LCIS grade, extent of disease, and multifocality Potential patient migration out of SEER registry catchment areas Progressive incorporation of additional SEER registries in 1992 and 2000 confounds the surgical trend observation. 11.1% (n=2159) of women with LCIS underwent mastectomy

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Robinson et al., 2008[193] Southeast England	Thames Cancer Registry Cohort dates: 1971−2004 Retrospective study Age at enrolment: NR Follow-up duration: NR	12,836 women with BCIS 512 invasive breast cancer cases Mean age at initial BCIS diagnosis: 57 y Women were diagnosed with BCIS 1971-2003 Women with BCIS were excluded if recorded date of diagnosis was the same as the date of death, if prior or synchronous cancer was present and if patients were wrongly classified as having received chemotherapy	LCIS First year post-diagnosis BCIS	Ipsilateral breast cancer Breast cancer	SIR=8.06 (2.62−18.8) SIR=1.96 (1.79-2.14)	Model: NR Adjustments: NR Limitations: Cancer registry data contains limited and incomplete treatment information Underreporting of second cancers in those who leave the registry catchment area Cancer incidence until the end of 2004 may be incomplete
Soerjomataram et al., 2006[192] The Netherlands	Eindhoven Cancer Registry Cohort dates: 1972−2003 Prospective study End of follow-up:	1,223 women with BCIS§§, including 66 cases LCIS 143 cancer cases; 3 cases of second breast among 66 initial cases of LCIS	LCIS vs general population	Second breast cancer	SIR=2.5, AER: 42	Poisson probability for 95% CI of SIR Adjustments: age (in 5-year categories) and calendar year of BCIS diagnosis. Limitations: Most women had less than 10

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Dec 2003 Age at enrolment: >25 y Mean follow-up: 6.3 y	Mean age at initial BCIS diagnosis: 57.1 y Women were diagnosed with BCIS 1972-2002 Patients with <1-year of follow-up time and with unknown morphological code were excluded				years of follow-up The absolute numbers are relatively small Increased medical surveillance of women with BCIS may have increased detection of second cancers AER should be interpreted with caution since BCIS accounts for only approximately 13% of all breast cancer diagnoses 57% of all secondary cancers were diagnosed in 1−4 y of follow-up
Franceschi et al., 1998[194] Switzerland	Vaud Cancer Registry Cohort dates: 1977−94 End of follow-up: 1994 Retrospective study Median age at entry: 50 y for LCIS patients	249 incident cases diagnosed with histologically confirmed CIS 59 incident LCIS cases 4 secondary invasive breast cancer cases Exclusion of women with a history of previous malignant neoplasm, with the	LCIS CIS	Invasive breast cancer	SIR=4.2 (1.1−10.7) SIR=7.2 (4.6-10.6	Poisson distribution Adjustments: NR Limitations: Information on selected clinicopathological characteristics, such as site and margin status was lacking No meaningful pattern was

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Follow-up duration: NR	exception of non-melanomatous skin cancer and concurrent cancer of the breast or other sites				observed for breast cancer after LCIS due to limited number of cases diagnosed
Bodian et al., 1996[190] USA	Last patient contact: 1993−94 Prospective study Median age at enrolment: 47 y Median age at last-known diagnosis of LCISpreceding CA: 50 y Median follow-up: 18 y	236 patients with LCIS 62 carcinoma cases (intraductal and invasive carcinoma) LCIS diagnosed by biopsy	Lobular neoplasia vs general population All patients Multivariate analysis † By years after initial diagnosis of LCIS 1−4 y 5−9 y 10−14 y 15−19 y 20−29 y 30−39 y	Invasive or intraductal carcinoma	RR=5.4 (4.2−7.0) RR=5.3; p=0.001 RR=5.8 (2.8−10.7) RR=8.9 (5.3−13.8) RR=5.1 (2.5−9.1) RR=7.3 (4.0−12.2) RR=2.0 (0.7−4.8) RR=3.5 (0.7−10.2)	Standardised morbidity ratios Adjustments: NR Limitations: NR Patients had at least one year of follow-up, at least one biopsy specimen with LCIS, and no previous or concurrent CA, with at least one breast intact after their first diagnosis of LN
Rosen et al.,1978[188] USA	Cohort dates: LCIS cases diagnosed 1940−1950 Retrospective study Mean age at LCIS diagnosis: 45 y Mean follow-up: 24	99 LCIS cases who underwent breast biopsy 32 invasive breast cancer cases 77 LCIS patients with 28 cases of breast cancer included in risk analysis	LCIS vs general population	Breast cancer	9-fold increased risk (observed vs expected p<0.001)	Expected number of cancers calculated by calendar year & 5-y age intervals using incidence data from the Connecticut Tumor Registry Adjustments: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	y	(Inclusion criteria for analysis: patients whose only lesion was untreated unilateral LCIS; patients with no prior or simultaneous contralateral breast carcinoma; known age and year of diagnosis of LCIS; known age at diagnosis of subsequent carcinoma if it occurred; and known age at last follow-up or death) Exclusion of women treated by mastectomy; exclusion of women with LCIS and intraductal carcinoma in same breast; and exclusion of patients with simultaneous LCIS and infiltrating carcinoma				Limitations: NR Intervals between diagnosis of LCIS and carcinoma of the breast varied 2 to 31 years in cancer of the ipsilateral breast to from 3 to 30 years in the contralateral breast About 38% of patients developed breast cancer at least 20 years after a diagnosis of LCIS
Andersen, 1977[196]	Cohort dates: 1942–1961	3,299 cases of benign breast	LCIS	Invasive breast cancer		Model: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Denmark	Retrospective study Age at enrolment: NR Mean follow-up: 15.9 y	lesions 44 LCIS cases 11 invasive breast cancer cases Mean age at time of operation (biopsy): 46 y The figures are based on biopsy-treated patients only Excluded those with previous invasive cancer and those who had LCIS treated with mastectomy				Adjustments: NR Limitations: NR Review of 5,278 newly prepared slides from 3,299 cases of benign breast lesions The National Registry provided further patient data
Case-control studies						
To et al., 2014[198] Canada	The CNBSS study Nested case control study within an RCT Recruitment: 1980–1985 Follow-up by surgeon: 1980–1996	35 women with LCIS 7 invasive breast cancer cases Controls‡ Mode of LCIS detection: 77.1% screen detected (70.4%	LCIS Case-control analysis‡ DCIS LCIS	Breast cancer	5-year CIP=5.71% 10-year CIP=11.52% 15-year CIP=17.52% 20-year CIP=21.26% OR=2.69 (1.07–6.75); p=0.0346 RR=1 (referent) RR=1.03 (0.43–2.46); p=0.9494	Models and methods§¶ Adjustments§¶ Limitations: NR Mean time from diagnosis of LCIS to diagnosis of invasive breast cancer was 8.62±6.26 years compared to 5.45±5.22 years for DCIS Case-control analysis: potential controls were excluded if they

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	End of passive follow-up through record linkage: Dec 2005 Age at entry: 40–59 y	mammography alone, 18.5% physical examination alone & 11.1% for both) 5.7% Interval (<12 months after screening) 17.1% Incident (>12 months after screening)				had died or been diagnosed with invasive breast cancer prior to the case's diagnosis of CIS Histological verification required a review of the slides from all breast biopsies performed during the period of screening, regardless of the diagnosis made by the community pathologist

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AER, absolute excess risk; BCS, breast conserving surgery; CA, invasive or intraductal carcinoma; CBC, contralateral breast cancer; CIP, cumulative incidence probability; CIR, cumulative incidence rate; CIS, carcinoma in situ; CNBSS, Canadian National Breast Screening Study; DBC, ductal breast cancer; DCIS, ductal carcinoma in situ; HR, hazard ratio; HR+/–, hormone receptor status positive/negative; IBC, ipsilateral breast cancer; IBIS-RET, International Breast Cancer Intervention Study Risk Evaluation Tool; LBC, lobular breast cancer; LCIS, lobular carcinoma in situ; NA, not applicable; NR, not reported; p, p–value; p(heter), p-value for the measure of heterogeneity; RR, relative risk or risk estimate; SEER, Surveillance, Epidemiology & End Results; SIR, standardised incidence ratio; USA, United States of America; y, year/s.

†Multivariate "baseline group" patients had an initial LN diagnosis between the ages 40 and 54 years, had no family history of CA, no personal history of BBD preceding their LN, and their initial LCIS had at least 90% of the acini in the lobule of maximum involvement showing the characteristic features of LCIS.

‡Conditional logistic regression with 1:5 matching used. Cases and controls were matched by age at entry, allocation group and centre of recruitment. Number of reference controls=175 women.

§Actuarial life table method for cumulative incidence probability. Adjusted for the 1:5 matching and stratified by CIS type.

¶Cox proportional hazards regression model for RR estimates. Adjusted for histological type, age at entry into the CNBSS and surgical treatment received.

†† Median age of diagosis of LCIS was stated as 52 y in the text and 53.7y in the abstract

§§Of the 1276 women diagnosed with BCIS, only 1223 were retained in the analyses

Table D.20 DCIS and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Zhang et al., 2016[207] Studies published to 2014 Asia, Europe & North America	13 observational studies 5 RCTs	Age of DCIS patients: 20–80 y 10,021 cases 10,866 cases	DCIS By tumour characteristics Positive vs negative margins Non– screening vs screening detection	Local invasive recurrence following DCIS	HR=1.36 (1.04–1.69); I^2=39.7%, p(heter)=0.127 HR=1.38 (1.12–1.63); I^2=48.2%, p(heter)=0.086	Fixed effects model (no heterogeneity/ random effects model (heterogeneity) Adjustments: Type of treatment Publication bias: Sig. for PR & HER2 studies only Limitations: The number of eligible studies was relatively small Different definitions of tumour predictors
Cohort studies						
Elshof et al., 2017[702] Netherlands	Surgical treatment: 1989–2004 Retrospective study Median follow–up: 10.5 y	7,042 women surgically treated for DCIS Screen–detected DCIS: 4,814 Interval–detected DCIS: 651 Non–screen related DCIS: 1,577 363 IBC cases 378 CBC cases	DCIS Non–screening–related Screen–detected Interval Non–screening–related Screen–detected Interval	Invasive IBC Invasive CBC	 HR=1 (referent) HR=0.75 (0.59–0.96) HR=1.02 (0.68–1.51) HR=1 (referent) HR=0.86 (0.67–1.10) HR=0.83 (0.54–1.26)	Multivariable–adjusted Cox proportional hazards analysis Adjustments: DCIS treatment (time–varying), DCIS grade & period of diagnosis Limitations: Non–screening group was heterogeneous including women not invited to screening program & women refusing to participate

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		Age at DCIS diagnosis: 49–75 y				May not reflect current screening methods (screen–film vs full–field digital mammography)
Elshof et al., 2016[205] Netherlands	Netherlands Cancer Registry & nation–wide network & registry of histology & cytopathology DCIS diagnosis: 1989–2004 Retrospective study Median follow–up: 10.7 y Age at enrolment: NR	10,090 women BCS + RT: 2,612 BCS alone: 2,658 Mastectomy: 4,820 Median age at DCIS diagnosis: 57.6 y 79% of women aged ≥50 y at DCIS diagnosis	DCIS Age at DCIS diagnosis <50 y ≥50 y Treatment <50 y of age 0–5 y follow–up BCS & RT BCS alone Mastectomy 5–10 y follow–up BCS & RT BCS alone Mastectomy >10 y follow–up BCS & RT BCS alone Mastectomy Treatment ≥50 y of age 0–5 y follow–up BCS & RT BCS alone Mastectomy 5–10 y follow–up BCS & RT	Invasive IBC	HR=1 (referent) HR=0.38 (0.25–0.59); p<0.001 HR=1 (referent) HR=2.11 (1.35–3.29); p=0.001 HR=0.35 (0.20–0.61); p<0.001 HR=1 (referent) HR=1.01 (0.66–1.55); p=0.95 HR=0.13 (0.07–0.23); p<0.001 HR=1 (referent) HR=0.78 (0.46–1.33); p=0.37 HR=0.20 (0.11–0.37); p<0.001 HR=1 (referent) HR=4.44 (3.11–6.36); p<0.001 HR=0.27 (0.16–0.46); p<0.001 HR=1 (referent)	Cox proportional hazards analysis Adjustments: Treatment & period Limitations: Potential of confounding by indication Bias due to non–randomisation of DCIS treatment & potential relationship between indication & risk of ipsilateral breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			BCS alone Mastectomy >10 y follow–up BCS & RT BCS alone Mastectomy		HR=2.13 (1.54–2.96); p<0.001 HR=0.10 (0.06–0.17); p<0.001 HR=1 (referent) HR=1.64 (1.01–2.69); p=0.05 HR=0.15 (0.08–0.29); p<0.001	
Buckley et al., 2016[202] Australia	Sample source: population–based, from the BSSA Cohort dates: 1989–2010 Retrospective cohort study Median follow–up: 12.2 y Age at enrolment (eligible for screening): 40–69 y	272,047 women DCIS screen–detected: 1,277 women 121 breast cancer cases Median age at DCIS diagnosis: 54 y Median age at first screen: 52 y Non–screen detected DCIS: 270,770 women 9,433 breast cancer cases Median age at first screen: 51 y	Screen–detected DCIS ≤5 y since diagnosis By treatment BCS +/– RT Mastectomy Mastectomy + BCS	Invasive breast cancer	HR=4.0 (3.4–4.8) HR=1 (referent) HR=0.54 (0.30–0.96) HR=6.31 (0.86–46.04)	Univariate Cox regression model Adjustments: Socio–economic status, area of residence (metropolitan or rural), age at initiation of screening & year of the woman's first breast screen Limitations: No data on DCIS margins & nuclear grade No natural history of DCIS. Most DCIS cases were surgically treated, affecting breast cancer risk & risk factor detection Risk also affected by radiotherapy, tamoxifen & other systemic therapies not recorded in the administrative data
Liu et al., 2015[208] USA	Sample source: SEER DCIS diagnosis:	40,749 women receiving BCS & radiation therapy	DCIS Treatment (by propensity score matching)	IBC		Multivariable logistic regression analysis Adjustments:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	2002–2011 Retrospective study Median follow–up: 46 months Age at enrolment: NR	WBI: 38,537 women APBIb: 2,212 women Median age at diagnosis: 58 y (range 18–100 y) 22.1% of patient population were from ethnic minority groups	WBI APBIb APBIb by propensity score adjustment		OR=1 (referent) OR=1.74 (1.06–2.85); p=0.03 OR=1.68 (1.13–2.49); p=0.01	Patients were nested within counties to account for the non–independence of treatment selection among patients from the same county Limitations: Potential confounders were unavailable, including surgical margins, multifocality, endocrine therapy & comorbidities Lack of the information on surgical margins & endocrine therapy may have resulted in the underestimation of DCIS outcomes in APBIb patients Short follow–up time & incomplete capture of second breast tumours
			WBI APBIb APBIb by propensity score adjustment	CBC	OR=1 (referent) OR=0.91 (0.59–1.41); p=0.68 OR=0.87 (0.65–1.15); p=0.32	
Rakovitch et al., 2015[703] Canada	Sample source: Ontario population–based DCIS cohort Diagnosis 1994–2003 End date: 2010 Retrospective study Median age at diagnosis†: 61 y	3,320 women BCS alone: 1,658 BCS & RT: 1,662	DCIS (treated by BCS & negative resection margins) DCIS Oncotype DX® score	Breast cancer (local recurrence)	HR=1.68 (1.08–2.62); p=0.02	Cox proportional hazards model Adjustments: Margin status & year of diagnosis for DCIS score Limitations: Patients were not randomised, but were selected for treatment by BCS alone based on clinico–pathologic features & patient preference Margin width & tumour size data were incomplete
			Adjusting for margin status DCIS score		HR=2.11 (1.43–3.09); p<0.001	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Median follow–up: 9.6 y Age at enrolment: NR					Data on clinical presentation or family history were not available
Cheung et al., 2014[206] UK	Sample source: West Midlands cancer registry database DCIS diagnosis: 1988–2008 Retrospective study Follow–up: to 2011 Age at enrolment: NR	3,930 patients Age at DCIS diagnosis: 23–95 y	DCIS Radiotherapy No Yes Surgical treatment BCS Mastectomy Unknown/no Tx Mode of detection Non–screening–detected Screening detected Cytonuclear grade Low Intermediate High Unknown	IBC	 HR=1 (referent) HR=0.455; p<0.0001 HR=1 (referent) HR=0.264; p<0.0001 HR=1.046; p=0.783 HR=1 (referent) HR=0.318; p<0.0001 HR=1 (referent) HR=0.985; p=0.913 HR=1.609; p=0.0001 HR=1.379; p=0.032	Cox proportional hazard model Adjustments: Patients aged 50–70 y for screening status Other adjustments not stated Limitations: Lack of information on tumour size
Rakovitch et al., 2013[704] Canada	Sample source: population–based cohort identified via the Ontario Cancer Registry DCIS diagnosis: 1994–2003	3,762 women BCS alone: 1,867 women 363 cases BCS & RT: 1,895 women 233 cases	DCIS (Treated by BCS) Margin status Negative Positive DCIS (Treated by BCS & RT) Margin status Negative	Breast cancer (local recurrence)	 HR=1 (referent) HR=1.4 (1.0–1.9); p=0.025 HR=1 (referent)	Cox proportional hazard model Adjustments: Time of initial treatment adjusted for year of diagnosis Other adjustments not stated Limitations: Tumour size & margin width

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	End of follow–up: 31 Mar 2010 Retrospective study Mean age at time of treatment: 61.03 y (BCS alone) 58.66 y (BCS & RT) Median follow–up: 10 y Age at enrolment: NR		Positive		HR=1.7 (1.2–2.4); p=0.002	were not consistently reported Data on clinical presentation were not available
Yi et al., 2012[209] USA	Sample source: clinic–based – MDACC & MSKCC Surgery: 1990–2007 Retrospective study Median age at diagnosis of DCIS: 57 y Median follow–up 5.6 y (MDACC) 7.1 y (MSKCC) Age at enrolment: NR	2,662 women from MDACC & MSKCC cohorts Multi–ethnic cohort	DCIS Adjuvant endocrine therapy Yes No MDACC MSKCC Adjuvant radiation therapy Yes No MDACC MSKCC Initial presentation Radiologic Clinical MDACC MSKCC	IBC (recurrences)	 HR=1 (referent) HR=2.45 (1.15–5.24); p=0.02 HR=2.11 (1.29–3.46); p=0.003 HR=1 (referent) HR=1.59 (0.88–2.89); p=0.1 HR=2.67 (1.91–3.75); p<0.001 HR=1 (referent) HR=1.87 (1.03–3.37); p=0.039 HR=1.39 (0.95–2.03); p=0.09	Multivariate Cox proportional hazard model Adjustments: No other adjustments apart from those listed under exposure column Limitations: Small sample size & only pathological features were used to determine risk estimates

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Falk et al., 2011[203] Norway	Sample source: Cancer Registry of Norway—population–based DCIS diagnosed: 1993–2007 End of follow–up: 31 Dec 2007 Retrospective study Follow–up: 10 y (4 months–>10 y) Age at enrolment: NR	3,046 women with DCIS 192 cases Age at DCIS diagnosis: 0–>85 y	DCIS (compared with general population)	All malignancies	SIR=4.8 (4.1–5.5)	Multivariate Cox proportional hazards regression model Adjustment: NR Limitations: Limited details on the patient's risk factors, tumour characteristics & treatment procedures
			Age at diagnosis	Invasive IBC		
			≤49 y		HR=1 (referent)	
			50–69 y		HR=0.9 (0.5–1.5)	
			>70 y		HR=1.0 (0.5–1.8)	
			Treatment			
			Mastectomy		HR=1 (referent)	
			BCS only		HR=3.3 (1.4–7.8)	
			BCS & RT		HR=2.1 (1.1–4.1)	
			Detection method			
			Non–screen detected		HR=1 (referent)	
			Screen–detected		HR=0.7 (0.4–1.1)	
			Age at diagnosis	Invasive CBC		
			≤49 y		HR=1 (referent)	
			50–69 y		HR=1.2 (0.6–2.3)	
			>70 y		HR=1.4 (0.6–3.1)	
			Treatment			
			Mastectomy		HR=1 (referent)	
			BCS only		HR=0.6 (0.1–2.5)	
			BCS & RT		HR=0.6 (0.3–1.4)	
			Detection method			
			Non–screen detected		HR=1 (referent)	
			Screen–detected		HR=0.8 (0.4–1.5)	
AIHW & NBOCC, 2010[199] Australia	DCIS diagnosed: 1995–2005 (1997 onwards for South Australia & 1996 onwards for	13,749 women diagnosed with DCIS 706 cases	DCIS vs all Australian women (<11 months follow–up)	Invasive breast cancer		Model: Kaplan–Meier product limit technique Adjustments: NR
			Overall		RR=3.9 (3.6–4.2)	
			Follow–up			

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Northern Territory)	Age at DCIS diagnosis: <40–≥80 y Sample source: derived from state & territory cancer registries	<5 y 5–11 y <11 y Age at diagnosis <40 y 40–49 y 50–59 y 60–69 y 70–79 y ≥80 y		RR=3.6 (3.3–3.9) RR=5.3 (4.5–6.0) RR=3.9 (3.6–4.2) RR=19.8 (14.2–25.4) RR=5.6 (4.7–6.5) RR=3.0 (2.5–3.4) RR=3.4 (2.9–3.9) RR=4.1 (3.3–4.8) RR=4.2 (2.4–5.9)	Limitations: Women who were diagnosed with invasive breast cancer within 4 months of their DCIS diagnosis had their DCIS diagnosis deleted from their record In Queensland, the DCIS diagnosis was deleted if a diagnosis of invasive breast cancer was within 6 months of DCIS being diagnoses
Innos et al., 2008[204] USA	DCIS diagnosis: 1988–1999 End date: 31 Dec 1999 Retrospective study Mean follow–up: 55 months (3 months–≥5 y) Age at enrolment: NR	23,547 women 23,411 women analysed for CBC; 14,664 women analysed for ipsilateral DCIS Invasive CBC: 502 cases Invasive IBC: 108 cases Age at diagnosis: <40–≥65 y Sample source: population–based, California Cancer Registry Multi–ethnic, including White,	DCIS vs general population Overall Age at diagnosis of first DCIS <40 y 40–49 y 50–64 y ≥65 y Treatment Partial mastectomy & RT Partial mastectomy only Overall Age at diagnosis of first DCIS <40 y 40–49 y 50–64 y	Invasive IBC Invasive CBC	 SIR=1.7 (1.4–2.1) SIR=23.9 (12.9–44.4) SIR=5.4 (3.9–7.4) SIR=1.3 (0.9–1.9) SIR=1.0 (0.7–1.4) IRR=1 (referent) IRR=3.07 (1.91–4.93) SIR=1.4 (1.2–1.5) SIR=5.3 (3.7–7.5) SIR=1.8 (1.4–2.2) SIR=1.2 (1.0–1.4)	Poisson regression model Adjustments: Race/ethnicity, age at diagnosis of first DCIS, histological subtype of first DCIS, & treatment for first DCIS Limitations: Possible misclassification of the primary diagnosis—distinguishing between DCIS & ADH Short follow–up for invasive IBC

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		African Americans, Hispanic & Asian–Pacific Islander	≥65 y		SIR=1.2 (1.1–1.4)	
Rawal et al., 2005[189] Sweden	DCIS diagnosis: 1993–2000 Retrospective study Follow–up: from latter of age 21 y/diagnosis/immigration/Jan 1993 until diagnosis of breast cancer/death/emigration/31 Dec 2000 Age at enrolment: NR	5,000,000 women 3,802 in situ breast cancer patients 35,480 invasive breast cancer cases Sample source: Swedish Family Cancer Database	In situ vs general population	Invasive IBC Invasive CBC	RR=3.80 (2.98–4.84); p=sig. RR=1.96 (1.40–2.74); p=sig.	Poisson regression model Adjustments: Age, family history, parity & age at first birth Limitations: Number of cases was small Information on treatment received, contraceptives, stage of cancer & tumour size, was not available
Levi et al., 2005[187] Switzerland	CIS diagnosis: 1977–2002 Median age: 55 y (range 27–91 y) at enrolment Follow–up: until Dec 2002 Age at enrolment: NR	579 in situ patients 482 DCIS patients 55 invasive breast cancer cases Sample source: Vaud Cancer Registry file	CIS	Invasive breast cancer	SIR=4.6 (3.4–6.2)	Limitations: Lack of treatment information, family history, histology & other confounding factors

Note: Risk estimates are presented with 95% confidence intervals. Cases refer to breast cancer cases unless specified otherwise.

Abbreviations: ADH, atypical ductal hyperplasia; AIHW, Australian Institute of Health and Welfare; APBIb, accelerated partial breast irradiation through brachytherapy; BCS, breast conserving surgery; BSSA, South Australian breast cancer screening programme; CBC, contralateral breast cancer; CIS, carcinoma in situ; DCIS, ductal carcinoma in situ; EORTC, European Organisation for Research and Treatment Centre; HER2, human epidermal growth factor receptor 2; HPHC, Harvard Pilgrim Health Care; HR, hazard ratio; IBC, ipsilateral breast cancer; IRR, incident rate ratio; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California; MDACC, MD Anderson Cancer Centre; MSKCC, Memorial Sloan–Kettering Cancer Centre; NBOCC, National Breast and Ovarian Cancer Centre; NR, not reported; NSABP, National Surgical Adjuvant Breast Project randomised trials for DCIS; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; PR, progesterone receptor; RR, risk estimate or relative risk; RT, radiation therapy; SEER, Surveillance, Epidemiology, and End Results program; sig., significant; SIR, standardised incidence ratio; SweDCIS, Swedish randomised DCIS trial; UK, United Kingdom; UKCCCR/ANZ DCIS trial, UK Coordinating Committee on Cancer Research Ductal Carcinoma in situ Working Party; USA, United States of America; WBI, whole body irradiation; y, year/s.

†When initial breast surgery associated with DCIS diagnosis occurred.

Table D.21 Previous primary invasive breast cancer and risk of secondary breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Bazire et al., 2017[211] France	Cohort name: NR Cohort dates for first breast cancer diagnosis: 1981–2000 Retrospective study Age at enrolment: NR Median follow–up: 13.4 y	17,745 women 1,503 CBC cases 14,709 women not using hormonal therapy 3,036 women using hormonal therapy	Non–metastatic breast cancer Overall vs general population No hormonal therapy Hormonal therapy	CBC	SIR=2.96 (2.82–3.12); p<0.0001 RR=1 (referent) RR=0.70 (0.60–0.82); p<0.001	Poisson regression model Adjustments: Radiation–, chemo– and hormonal therapy Limitations: Data on personal history of smoking status and alcohol intake was lacking
Ricceri et al., 2015[212] Denmark, France, Netherlands, Norway, Sweden & UK	EPIC cohort Cohort dates: 1992–1998 Prospective study Age at enrolment: 35–70 y Follow–up: 11 y	10,045 women 139 cases Analyses performed only on subjects from France, UK, Netherlands, Sweden, Denmark & Norway.	First primary breast cancer (no history of other cancers) Overall	CBC	Age–standardised SIR=1.15 (1.02–1.29)	Cox proportional hazards regression model† Limitations: Lack of information on therapies, surgeries, and hormonal subtypes of breast cancer Dates of diagnosis for the cases were from 1993 onwards Study limited to invasive cancers
Rusner et al., 2014[213] Germany	EPIC cohort Cohort dates for first breast cancer	49,804 women 594 CBC cases Median age at	Any first primary invasive breast cancer	CBC	SIR=1.2 (1.1–1.3)	Poisson regression model Adjustments: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	diagnosis: 1998–2007 Prospective study Age at enrolment: NR Median follow–up: 3 y	diagnosis of first primary breast cancer: 63 y				Limitations: Small number of CBC cases Short follow–up Lack of stage and treatment information
Vichapat et al., 2012[218] Sweden	Cohort name: NR Cohort dates: 1992–2008 Prospective study Age at enrolment: NR Median follow–up: 9.9 y	35,897 women 894 CBC cases 442 CBC cases in women who did not use endocrine treatment 438 CBC cases in women who used endocrine treatment Median age at CBC diagnosis: 64 y	First primary invasive breast cancer Endocrine treatment No Yes	Metachronous CBC	HR=1 (referent) HR=0.78 (0.68–0.90)	Cox proportional hazards regression model‡ Limitations: Histologic grade and histologic type were only available for a limited number of patients
Bouchardy et al. 2011[219] Switzerland	Cohort name: NR Cohort dates for first breast cancer diagnosis: 1995–2007 Prospective study	4,152 women 63 cases 620 first –ER– women; 19 breast cancer cases 3,335 first ER+	First primary invasive breast cancer ER status of first tumour ER– ER+ Anti–oestrogen use	Second primary invasive breast cancer	SIR=1.98 (1.19–3.09); p<0.05 SIR=0.67 (0.48–0.90); p<0.05	Poisson regression model/Multivariate Cox proportional hazards regression model§ Limitations: Central pathological reviews of the breast tumours were lacking

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Mean age at enrolment: 60.4 y for ER+ 56.8 y for ER– 65.9 y for unknown Median follow–up: 5.16 y	women; 43 breast cancer cases 2,983 women with anti–oestrogen use and 1,169 women without anti–oestrogen use	All secondary Yes No		HR=0.51 (0.26–0.99); p<0.05. HR=1 (referent)	Small number of second breast cancers Limited information on duration of anti–oestrogen treatment
Youlden & Baade 2011[210] Australia	Cohort name: NR Cohort dates for first breast cancer diagnosis: 1982–2001 Retrospective study Age at enrolment: NR Median follow–up: 5.5 y	26,725 women 2,962 cases Age at first diagnosis: ≥15 y	Primary invasive breast cancer	Secondary invasive breast cancer (vs general population)	SIR=1.55 (1.45–1.66)	Poisson regression model Adjustments: NR Limitations: NR
Cluze et al., 2009[214] France	Cohort name: NR Cohort dates for first breast cancer diagnosis: 1989–1997	5,663 women 98 cases Mean age at diagnosis: 59.9 y	Primary invasive breast cancer vs general population Overall	Second primary invasive breast cancer	SIR=1.74 (1.41–2.12); p=sig.	Poisson regression model Adjustments: NR Limitations: Adverse events analysed quickly after diagnosis

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	End of study period: Jan 2002 Retrospective study Age at enrolment: NR Mean follow–up: 4.1 y					(maximum 5 years) Small number of people lost to follow–up (<5%)
Kurian et al., 2009[215] USA	SEER population based cohort Cohort dates for first breast cancer diagnosis: 1992–2004 Retrospective study Age at enrolment: NR End of follow–up: Dec 2005	4,927 cases	First primary invasive breast cancer Overall vs general population	CBC	SIR=2.46 (2.40–2.52)	Model: NR Adjustments: Age, race and calendar year Limitations: No analysis for additional tumour markers or by family history, inherited mutations, or treatment details including tamoxifen use
Schaapveld et al., 2008[216] Netherlands	Cohort name: NR Cohort dates for first breast cancer diagnosis: 1989–2002 Retrospective study	45,229 women 1,477 CBC cases	Primary invasive breast cancer CBC vs non–CBC Overall Treatment Hormone therapy Chemotherapy RT	Metachronous CBC	SIR=1.9 (1.8–2.1) HR=0.58 (0.48–0.69); p=sig. HR=0.73 (0.60–0.90); p=sig. HR=0.96 (0.92–1.01)	Poisson regression model (SIR)/Cox proportional hazards model¶ Limitations: Information on treatment for secondary cancer not recorded Underestimation of hormone

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Age at enrolment: NR Median follow–up: 5.8 y					treatment may have occurred
Soerjomataram et al., 2005[217] Netherlands	Cohort name: NR First breast cancer diagnosis: 1972–2000 End of follow–up: 2001 Retrospective study Age at enrolment: >25 y Mean follow–up: 6.6 y	9,919 women 588 cases Mean age at first breast cancer diagnosis: 58.8 y	Invasive primary breast cancer vs general population Overall	Second primary invasive breast cancer	SIR=3.5 (3.2–3.8); p=sig.	Poisson regression model Adjustments: NR Limitations: Family history and genetic factors not included Increased incidence may be related to RT

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: CBC, contralateral breast cancer; EPIC, European Prospective Investigation into Cancer and Nutrition; ER, oestrogen receptor; HR, hazard ratio; p, p–value; RR, relative risk or risk estimate; RT, radiation therapy; SEER, Surveillance, Epidemiology, and End Results; SIR, standardised incidence rate; UK, United Kingdom; USA, United States of America; sig., significant; y, year/s.

†Adjusted for age at first tumour, body mass index, smoking status, education, menopausal status, history of full–term pregnancy, and nutrients.

‡Adjusted for age, calendar period, clinical tumour stage, pathologic nodal stage, and endocrine treatment of the initial breast cancer in categories.

§SIRs adjusted for age, using as standard the 5–year age distribution of the Geneva female resident population; rates are per 100,000 person–years. HRs adjusted for ER status of the first tumour, age (years), period, family history and anti–oestrogen use.

¶SIRs adjusted for age, stage, treatment and follow–up period. HRs adjusted for age (continuous variable), morphology, stage, and treatment at index cancer diagnosis.

Endogenous hormones

Table D.22 Age at menarche and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Collaborative Group on Hormonal Factors in Breast Cancer, 2012[220] Studies published to 2011 35 countries mostly from Europe & North America	117 studies 35 cohort studies 56 population–based case–control studies 26 hospital–based case–control studies	118,964 cases 306,091 controls Median birth y: 1939 Median age at diagnosis: 54 y Mean age at menarche: Cases 13.0 y Controls 13.1y	Age at menarche Per year younger Age group <11 11 12 13 14 15 ≥16	Breast cancer	RR=1.050 (1.044–1.057); p<0.0001 RR=1.19 (1.13–1.25) RR=1.09 (1.06–1.12) RR=1.07 (1.05–1.09) RR=1.00 (0.98–1.02) RR=0.98 (0.96–1.00) RR=0.92 (0.89–0.95) RR=0.82 (0.79–0.85)	Conditional logistic regression model Adjustments† Publication bias: NR Advantages: Meta–analysis includes almost all available epidemiological evidence for the association between menarche and breast cancer risk Reviews both published and unpublished findings Limitations: Possible misclassification of age at menarche
			Per year younger	Ductal carcinoma, ER+	RR=1.034 (1.026–1.052)	
				Ductal carcinoma, ER–	RR=1.024 (1.004–1.044)	
				Lobular carcinoma, ER+	RR=1.083 (1.052–1.115)	
				Lobular carcinoma, ER–	RR=1.076 (0.999–1.159)	
Cohort studies						
Dartois et al., 2016[44] France	E3N–EPIC cohort 1998–2008 Prospective study	67,634 women 497 premenopausal cases	Age at menarche ≥14 y <10 y 10–12 y 12–14 y	Premenopausal breast cancer	HR=1 (referent) HR=1.43 (0.35–5.81) HR=1.26 (0.95–1.66) HR=1.36 (1.09–1.70)	Multivariable adjusted model Adjustments‡ Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Mean age at enrolment: 52.8y (range 42–72 y) Follow–up period: 15 y; 876,468 person–y	3,138 postmenopausal cases	≥14 y <10 y 10–12 y 12–14 y	Postmenopausal breast cancer	HR=1 (referent) HR=1.58 (0.91–2.74) HR=1.19 (1.07–1.32) HR=1.13 (1.04–1.23)	Possible menarche measurement error Limited number of premenopausal breast cancer cases was observed due to restriction of women over 40 years
Bodicoat et al., 2014[223] UK	BGS Recruitment: 2003–2013 Retrospective study Mean age at recruitment: 46.7 y Mean follow–up: 4.1 person–y	104,931 women 1,095 cases	Age at menarche 13–14 y ≤12 y ≥15 y	Breast cancer	HR=1(referent) HR=1.06 (0.93–1.21) HR=0.78 (0.62–0.99); p <0.05 HR for trend=0.89 (0.81–0.99) ; p <0.05	Multivariable adjusted model Adjustments§ Limitations: Average follow–up was only 4 y Retrospective analysis may compromise accuracy Confounders such as benign breast disease were not adjusted for

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BGS, Breakthrough Generations Study; E3N–EPIC, Etude Epidémiologique auprès des femmes de la MGEN – European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; p, p–value; p–trend, p–value for trend; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

†Stratifications by study, year of birth, age, parity and age at first birth, height, current BMI, smoking, alcohol consumption, height and current body mass index.

‡Adjusted for age (as the time scale), first–degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at first full term pregnancy, physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and mean daily ultraviolet radiation doses (UVRd), oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).

§Adjusted for attained age, menopausal status, family history of breast cancer in a first degree relative, adult height, age at first full term pregnancy and hormone therapy status.

Table D.23 Parity and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta−analyses						
Lambertini et al., 2016[227] Studies published to 2014 Asia, Europe & USA	14 studies 3 cohort studies 9 case–control studies 1 pooled analysis of cohort studies 1 pooled analysis of case–control studies	21,941 cases 864,177 controls	≥1 pregnancies vs nulliparity	Breast cancer subtype Luminal HER2+ TNBC	 pOR=0.75 (0.70–0.81); I^2=46.2%, p(heter)=0.04 pOR=0.90 (0.69–1.16);I^2=33.2%, p(heter)=0.13 pOR=1.01 (0.87–1.17); I^2=30.3%, p(heter)=0.13	Random effects model Adjustments: Correlation within studies and heterogeneity between studies No publication bias (Macaskill et al method) Limitations: Methodological limits Data were retrieved from published articles; Confounding factors HER2+/HR+ breast cancer could not be evaluated
Nelson et al., 2012[226] Studies published to 2011 Countries: NR	17 studies† 4 cohort studies 13 case–control studies 13 studies for number of birth 2 cohort studies 11 case–control studies	Women aged 40−49 y	Nulliparity Overall Number of births 0 1 2 ≥3	Breast cancer	 RR=1.16 (1.04−1.26); I^2=80.3%, p(heter)<0.001 RR=1.00 (referent) RR=0.95 (0.81−1.11); I^2=48.3%, p(heter)=0.026 RR= 0.93 (0.77−1.12); I^2=73.2%, p(heter)<0.001 RR=0.73 (0.61−0.87); I^2=82.4%, p(heter)<0.001	Random effects model Adjustments: NR Publication bias: NR Limitations: Potential bias in the combined estimates of RRs Inclusion of women outside the targeted age group

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Collaborative Group on Hormonal Factors in Breast Cancer, 2002[224] Studies published from 1983 30 countries	47 case–control & cohort studies 42 case–control studies 5 cohort studies	50,302 incident cases, average number of birth: 2.2 96,973 controls, average number of births: 2.6	Parity Reduction in risk per birth	Breast cancer	7.0% (5.0%–9.0%); p<0.0001	Mantel−Haenszel stratification model Adjustments: Stratified by study, age, parity, age at first birth, and menopausal status Limitations: Confounders, as well as measurement errors and limited numbers with substantial exposures Limited statistical power
Cohort studies						
Dartois et al., 2016[44] France	E3N–EPIC cohort Cohort dates: NR Age at enrolment: 42–72 y; mean 52.8 y (SD 6.6 y) Follow–up: 15 y (876,468 person–y)	67,634 women 497 premenopausal cases 3,138 postmenopausal cases 63,999 non–cases	Number of children and age at FFTP 1 child before 30 y 1 child after 30 y ≥1 child, the first† before 30 y ≥1 child, the first after 30 y Nulliparous 1 child before 30 y 1 child after 30 y ≥1 child, the first before 30 y ≥1 child, the first after 30 y	Premenopausal breast cancer HR=0.99 (0.73–1.34) HR=1.64 (1.16–2.31); p=sig. HR=1 (referent) HR=1.44 (1.04–1.98); p=sig. HR=0.97 (0.69–1.35) HR=0.99 (0.88–1.12) Postmenopausal breast cancer HR=1.29 (1.09–1.51); p=sig. HR=1 (referent) HR=1.22 (1.06–1.40); p=sig.		Multivariate Cox proportional hazards regression models Adjustments‡ Limitations: Health cohort effect Limited number of premenopausal breast cancer cases

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Nulliparous		HR=1.28 (1.13–1.45); p=sig.	
Ritte et al., 2013[228] Denmark, France, Italy, Germany, Greece, Norway, Spain, Sweden, Netherlands & UK	EPIC cohort Cohort dates: 1992−2000 Prospective study Age at enrolment: 25−70 y Duration of follow–up: 3,346,356 person–y	311,097 women 9,456 cases; 3,567 ER+ PR+ 998 ER–PR– cases	Ever a full term birth Overall	ER+ PR+ breast cancer	HR=0.87 (0.78−0.96); p=0.01	Cox proportional hazards models§ Publication bias: NR Limitations: Classification of ER–PR– tumours is controversial Insufficient information to complete detailed molecular sub–classifications
			Number of full term childbirths			
			1		HR=1.00 (referent)	
			2		HR=0.92 (0.84−1.01)	
			>3		HR=0.76 (0.68−0.85); p−trend<0.001	
			Ever a full term birth Overall	ER–PR– breast cancer	HR=0.98 (0.80−1.20); p=0.78	
			Number of full term childbirths			
			1		HR=1.00 (referent)	
			2		HR=1.01 (0.84−1.22)	
			>3		HR=0.89 (0.73−1.10); p–trend=0.19	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: E3N, Étude Épidémiologique des femmes de la Mutuelle Génerale de l'Édcuation Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; ER, oestrogen receptor; FFTP, first full term pregnancy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; p, p–value; HR+, hormone receptor positive; NR, not reported; OR, odds ratio; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for the measure of trend; PR, progesterone receptor; RR, relative risk or risk estimate; SD, standard deviation; TNBC, triple–negative breast cancer; UK, United Kingdom; USA, United States of America; y, year/s.

†Count taken from supplementary tables. In text 3 cohort studies and 14 case–control studies reported.

‡Adjusted for age, first–degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at first full term pregnancy, physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and ultraviolet radiation dose, oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).

§Stratified by age at recruitment and centre and further adjusted for BMI, height, menopausal status at enrolment, hormone therapy use, physical activity, smoking status, alcohol consumption and attained level of education

Table D.24 Age at first birth and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Lambertini et al., 2016[227] Studies published to 2014 China, Japan, Norway, Poland & USA	12 studies 3 prospective cohort studies 9 case–control studies (7 population–based studies)	21,941 breast cancer patients 864,177 controls Women aged 20–<84 y	Advanced age at first birth (>24 y) vs young age at first birth (≤24 y)	Luminal HER2+ TNBC	pOR=1.15 (1.00–1.32); p=0.05; I^2=86.9%, p(heter)<0.001 pOR=0.91 (0.72–1.16); p=0.41; I^2=64.3%, p(heter)=0.002 pOR=0.94 (0.80–1.11); p=0.45; I^2=64.5%, p(heter)=<0.001	Mixed effects model Adjustments: Correlation within studies heterogeneity between studies Publication bias for HER2+ (p<0.05) Limitations: All data extracted directly from publications Subtypes not based on gene expression HER2+/HR+ breast cancer could not be evaluated
Nelson et al., 2012[226] Studies published 1996–2011 New Zealand & USA	4 case–control studies 1 cohort study	32,891 women 4,179 cases Age: 40−49 y	Age first child born 25−29 y ≥30 y 20−24 y <20 y		RR=1 (referent) RR=1.20 (1.02–1.42); I^2=17.9%, p(heter)=0.30 RR=0.96 (0.82–1.11); I^2=0%, p(heter)=0.62 RR=0.96 (0.82–1.11); I^2=0%, p(heter)=0.81	Random effects model Adjustments† Publication bias: NR Limitations: Studies reported different measures Some women included outside target age group Between study variations in

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						adjustment for confounders Publication bias and selective reporting
Cohort studies						
Sisti et al., 2016[229] USA	Nurses Health Studies (NHS & NHSII) Cohort dates: 1976−2006 (NHS) 1989−2003 (NHSII) Age at enrolment: 30–55 y in 1976 (NHS) 25–42 y in 1989 (NHSII) Duration of follow–up: NR	121,700 women (NHS) 116,430 women (NHSII)	Age at first birth Dose response (per year increase)	All subtypes Luminal A Luminal B HER2+ Basal–like Unclassified breast cancer	HR=1.03 (1.02–1.03); p(heter)=0.04 HR=1.03 (1.02–1.05) HR=1.01 (0.99–1.03) HR=1.03 (0.99–1.07) HR=1.01 (0.98–1.09) HR=1.03 (0.97–1.09)	Cox proportional hazards model Adjustments‡ Limitations: Not many tissue samples obtained for cases Low proportion of non–luminal tumours
Ritte et al., 2013[228] Denmark, France, Italy, Germany, Greece, Netherlands, Norway, Spain, Sweden & UK	EPIC study Cohort dates: 1992−2000 Prospective study Median age at recruitment: 51.1 y Duration of follow–up:	311,097 women 9,456 first primary invasive breast cancer cases	Age at first full term birth ≤19 y ≥35 y ≥35 y ≥35 y ≥35 y	 ER+PR+ ER–PR– ER+ ER–	 HR=1 (referent) HR=1.47 (1.15–1.88); p–trend<0.001 HR=0.93 (0.53–1.65); p–trend=0.96 HR=1.46 (1.20–1.77); p–trend<0.001 HR=0.89 (0.56–1.43); p–trend=0.80	Cox proportional hazards model Adjustments§ Limitations: Accuracy of classifying an ER or PR–negative tumour is controversial Insufficient information on HER2 status

Authors	Study details	Study sample	Exposures		Outcomes	Risk estimates	Author comments
	3,346,356 person–y			≥35 y	PR+	HR=1.46 (1.15–1.86); p–trend<0.001	
				≥35 y	PR–	HR=1.39 (1.01–1.93); p–trend=0.002	
				≥35 y	ER+ PR–	HR=1.70 (1.13–2.55); p–trend<0.001	
				≥35 y	ER–PR+	HR=1.19 (0.40–3.59); p–trend=0.23	
				≥35 y	ER or PR missing	HR=1.13 (0.87–1.46); p–trend<0.001	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BMI, body mass index; EPIC, European Prospective Investigation into Cancer and Nutrition; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; HT, hormone therapy; NHS, Nurses' Health Study; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; pOR, pooled odds ratio; PR, progesterone receptor; RR, relative risk or risk estimate; TNBC, triple negative breast cancer; USA, United States of America; y, year/s.

†Adjusted for Age, race, family history of breast cancer, BMI and stratified by site

‡Mutual adjustment for reproductive variables, in addition to BMI at 18, weight change since 18, history of benign breast disease, family history of breast cancer, total physical activity, alcohol intake, height, and cohort.

§Stratified by age at recruitment and centre and further adjusted for BMI, height, menopausal status at enrolment, HT use, physical activity, smoking status, alcohol consumption and attained level of education.

Table D.25 Breastfeeding and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2014 East Asia , Europe & North America	13 cohort studies (including one pooled analysis) 4 cohort studies 5 cohort studies	11,610 participants 1,321 women 7,359 women	Lactation Dose response (per 5 months)	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=0.98 (0.97–0.99), p=sig.; I^2=0.0%, p(heter)=0.518 RR=0.95 (0.89–1.01); I^2=63%, p(heter)=0.04 RR=1.00 (0.99–1.02); I^2=4.6%, p(heter)=0.4	No publication biases (p>0.05)
Lambertini et al., 2016[227] Studies published to 2014 China, Japan, Norway, Poland & USA	15 cohort & case–control studies 11 studies included for breastfeeding	21,941 breast cancer cases 864,177 controls 169,870 women 14,266 women 176,340 women Age: 20–80 y	Breastfeeding ever vs never	Breast cancer subtype Luminal breast cancer HER2 TNBC	 OR=0.77 (0.66–0.88), p=0.003; I^2=79.1%, p(heter)<0.001 OR=0.78 (0.59–1.03), p=0.07; I^2=45.6%, p(heter)=0.07 OR=0.79 (0.66–0.94), p=0.01; I^2=65.1%, p(heter)=0.001	Random effects model Adjustments: Correlation within studies and heterogeneity between studies No publication biases (p≥0.05) Limitations: Not possible to investigate the impact of other important factors (race/ethnicity, number of children, different ages at first birth, & duration of breastfeeding) Molecular subtype of breast cancer was not available
Islami et al., 2015[234] Studies published to 2014 Australia, North	27 studies (including adjusted and unadjusted studies) 8 cohort studies	Cohort studies: 736,308 participants 13,223 cases Case–control studies:	Breastfeeding ever vs never	Breast cancer subtype ER–PR– TNBC	 RR=0.84 (0.72–0.97); I^2=49.8%, p=0.063 RR=0.73 (0.62–0.87) ; I^2=0%, p(heter)=0.43	Random effects model Adjustments: For at least age, body mass index, parity & family history of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
America, Europe, Asia	19 case–controls	23,658 cases 31,304 controls		ER+ and/or PR+	RR=0.97 (0.88–1.07); I^2=78%, p(heter)=<0.001	No publication biases (p>0.05) Limitations: No further confounders included as it would limit study number No dose response analyses conducted due to potential biases Small number of TNBC cohort studies
				ER+ PR+	RR=1.00 (0.90–1.10); I^2=54%, p(heter)=0.09	
Zhou et al., 2015[233] Studies published 2008–2014 Africa, Asia, Europe & Latin America	27 studies 8 studies 19 studies 23 case–controls 3 cohorts	13,907 breast cancer cases Sources of control: 2,828 population–based 11,079 hospital–based	Breastfeeding Ever vs never Longest vs shortest Case–control studies Cohort studies	Breast cancer	RR=0.613 (0.442–0.850) I^2=89.9%, p(heter)< 0.001 RR=0.471 (0.368–0.602) I^2=76.6%, p(heter)<0.001 RR=0.444 (0.362–0.546); I^2=71.4%, p(heter)<0.001 RR=0.995 (0.914–1.083); I^2=0.0%, p(heter)=0.844	Random effects model No publication bias (p=0.108) All studies adjusted for age Limitations: Prone to biases inherent in the original studies Individual studies may have failed to control for potential confounders Significant heterogeneity and a possible publication bias
Pooled analysis						
Ma et al., 2017[235] USA	3 population–based case–control studies (Women's CARE, BCIS & LIFE studies)	2,658 cases 2,448 controls 3,509 Caucasian women 1,597 African–	Duration of breastfeeding Never Ever <6 months 6–11 months ≥12 months	TNBC	OR=1 (referent) OR=0.80 (0.63–1.02) OR=0.96 (0.74–1.26) OR=0.55 (0.37–0.82) OR=0.69 (0.50–0.96); p–trend=0.006	Multivariate adjusted model Adjustments† Limitations: 36% of case participants had missing data on at least one of the receptors

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		American women	Never	Luminal A–like	OR=1 (referent)	Potential misclassification of tumour subtypes
			Ever		OR=0.78 (0.65–0.94)	
			<6 months		OR=0.83 (0.68–1.02)	
		Women aged 20–64 y	6–11 months		OR=0.76 (0.59–0.99)	
			≥12 months		OR=0.71 (0.56–0.90); p–trend=0.004	
			Never	Luminal B–like	OR=1 (referent)	
			Ever		OR=0.89 (0.65–1.23)	
			<6 months		OR=0.99 (0.70–1.41)	
			6–11 months		OR=0.70 (0.44–1.12)	
			≥12 months		OR=0.85 (0.56–1.30); p–trend=0.28	
			Never	HER2–enriched	OR=1 (referent)	
			Ever		OR=0.91 (0.63–1.32)	
			<6 months		OR=0.68 (0.43–1.07)	
			6–11 months		OR=1.28 (0.78–2.09)	
			≥12 months		OR=1.10 (0.69–1.75); p–trend=0.36	

Note: Risk estimates are presented with 95% confidence intervals. Abbreviations: BCIS, breast carcinoma in situ; CARE, Contraceptive and Reproductive Experiences; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; LIFE, Learning the Influence of Family and Environment; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; PR, progesterone receptor; RR, relative risk or risk estimate; TNBC, triple–negative breast cancer; UK, United Kingdom; USA, United States of America; WCRF, World Cancer Research Fund; y, year.

†Included sub–study (the Women's CARE Study or the Women's BCIS Study, the Women's LIFE Study), study site (Los Angeles, Detroit), ethnicity (white, African–American), reference age (in 5 year age categories), education (≤ high school, technical school or some college, college graduate), first–degree breast cancer family history (no, yes), body mass index (<25, 25–29, ≥30 kg/m^2), a variable combining menopausal status and hormone therapy use (premenopausal; postmenopausal: never used hormone therapy, ever used hormone therapy; unknown menopausal status), lifetime recreational physical activity (inactive, ≤2.2, 2.3–6.6, 6.7–15.1, ≥15.2 annual metabolic equivalents of energy expenditure, hour/week), alcohol intake (never, former, current), cigarette smoking status (never, former, current), age at menarche (≤12, 13, ≥14 years), number of completed pregnancies (never pregnant, 1, 2, ≥3, only non–completed pregnancy), oral contraceptive use (never, <1, 1–4, 5–9, ≥10 years).

Table D.26 Age at menopause and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Li et al., 2017[237] Studies published to 2015 China & Japan	6 case–control studies	8,637 cases 13,001 controls 1,229 cases 2,624 controls 629 cases 2,624 controls	Age at menopause <50 y ≥50 y <50 y ≥50 y	Luminal breast cancer ER–PR–	 OR=1.00 (referent) OR=1.15(1.00–1.32); p(heter)=0.26 OR=1.00 (referent) OR=1.19(1.00–1.43); p(heter)=0.06	Random effects model All studies adjusted for age No publication bias Limitations: Limited sample size
Collaborative Group on Hormonal Factors in Breast Cancer, 2012[220] Studies published to 2011 35 countries mostly from Europe & North America	117 studies 35 cohort studies 56 population–based case–control studies 26 hospital–based case–control studies	118,964 cases 306,091 controls Median birth y: 1939 Median age at diagnosis: 54 y Mean age at menopause: Cases 50.0 y Controls 49.5y	Age at menopause for every year older at menopause 45–49 y 50–54 y ≥55 y	Postmenopausal breast cancer	RR=1.029 (1.025–1.032); p<0.0001 RR=0.86 (0.84–0.89) RR=1.00 (0.98–1.02) RR=1.12 (1.07–1.17)	Conditional logistic regression model Adjustments† Publication bias: NR Limitations: NR
Cohort studies						
Ritte et al., 2013[228] Denmark, France, Germany, Greece,	EPIC cohort Enrolled in study: 1992–2000	311,097 women 9,456 cases At recruitment:	Age at menopause ≤48 y 49–50 y	ER+PR+	 HR=1.00 (referent) HR=1.12 (0.98–1.29)	Cox proportional hazards model Adjustments‡

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Italy, Netherlands, Norway, Spain, Sweden & UK	Median age at recruitment: 51.1 y Follow–up: 11.3 y	46.5% postmenopausal women	51–54 y		HR=1.06 (0.91–1.24)	Limitations: Accurate classification of an ER or PR–negative tumour is controversial
			≥55 y		HR=1.17 (0.95–1.44); p–trend=0.18	
				ER–PR–		
			≤48 y		HR=1.00 (referent)	
			49–50 y		HR=1.09 (0.84–1.42)	
			51–54 y		HR=0.87 (0.64–1.20)	
			≥55 y		HR=1.03 (0.69–1.54); p–trend=0.79	

Note: Risk estimates are presented with 95% confidence intervals. Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; ER, oestrogen receptor; HR, hazard ratio; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; PR, progesterone receptor; RR, relative risk or risk estimate; UK, United Kingdom; y, year/s.

†Stratified by study, year of birth, age, parity and age at first birth, height, current body mass index (BMI), smoking and alcohol consumption.

‡Stratified by age at recruitment and centre and further adjusted for BMI, height, menopausal status at enrolment, hormone therapy (HT) use, physical activity, smoking status, alcohol consumption and attained level of education.

Table D.27 PCOS and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Shobeiri & Jenabi, 2016[255] Studies published to 2015 From Denmark, Italy, Iran, Taiwan, USA & UK	8 studies 5 cohort studies 3 case–control studies	45,470 women Participant information: NR Age at enrolment: 24–69 y Follow–up: 243,064 person–y	PCOS vs no PCOS (ref)	Breast cancer	*ES=1.18 (0.93–1.43); I^2=0.0%, p=0.721 *ES=0.87 (0.44–1.31); I^2=5.2%, p=0.348	Model: NR Adjustments: NR Significant publication bias: Egger & Begg's test Limitations: Limited number of eligible Not all studies adjusted for covariates Authors could not assess the effect of confounding variables which may lead to selection bias
Chittenden, 2009[256] Studies published 1968–2008 Italy & USA	3 case–control studies	23,842 women 11,836 cases 12,006 controls US women 20–75 y identified from cancer registries Italian women 23–74 y identified through hospital admission	PCOS vs no PCOS (ref)	Breast cancer	OR=0.88 (0.44–1.77); I^2=72.8%	Model: NR Adjustment: NR Publication bias: NR Limitations: Definition of PCOS has changed over time Population sample in this analysis was heterogeneous Paucity of data available for analysis

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: HR, hazard ratio; NR, not reported; NS, not significant; OR, odds ratio; PCOS, polycystic ovarian syndrome; p, p–value; SIR, standardised incident rate; UK, United Kingdom; USA, United State of America; y, year/s.

*ES, this abbreviation has not been explicitly stated.

†Adjusted for age; common comorbidities, including hypertension, diabetes mellitus, dyslipidaemia, congestive heart failure, chronic pulmonary diseases, coronary artery diseases, and cerebrovascular diseases; urbanisation; and monthly income.

*ES, this abbreviation has not been explicitly stated.

†Adjusted for age; common comorbidities, including hypertension, diabetes mellitus, dyslipidaemia, congestive heart failure, chronic pulmonary diseases, coronary artery diseases, and cerebrovascular diseases; urbanisation; and monthly income.

Exogenous hormones

Table D.28 Hormonal contraception—combined and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Anothaisintawee et al., 2013[267] Studies published to 2011 Australia, Brazil, Canada, China, Costa Rica, Cyprus, Denmark, France, Iran, Italy, Japan, Malaysia, Netherlands, New Zealand, Norway, South Africa, Sweden, UK & USA	Ever vs never use: 66 case–control/cohort studies Duration of use: 6 case–control/ cohort studies	Ever use: 35,527 women Never use: 180,318 women	Oral contraceptive Never use Ever use <5 y 5–10 y >10 y	Breast cancer	 OR=1 (referent) OR=1.10 (1.02–1.18); I^2=85.7%, p(heter)=0.00 OR=0.95 (0.78–1.16) OR=0.98 (0.77–1.25) OR=1.17 (0.92–1.49)	Random effects model No adjustments Publication bias: NR Limitations: Use of summary data from observational studies Most data not adjusted for confounding Pooling might be prone to bias
Gierisch et al., 2013[266] Studies published from 2000 Australia, Brazil, Canada, China, France, Israel, Netherlands, Norway, Pakistan, Poland, South Africa, Sweden, UK	Ever vs never: 15 case–control studies 8 cohort studies Duration of use: 14 studies Time since last use: 11 studies	Case–control studies: 38,682 women Cohort studies: 317,341 women 3,981,072 person–y in 3 studies	Oral contraceptive Never use Ever use ≤12 months 13–60 months 61–120 months >120 months 0–5 y 5–10 y 10–20 y	Breast cancer	 OR=1.00 (referent) OR=1.08 (1.00–1.17); Q=73.35, p(heter)<0.001 OR=0.95 (0.83–1.09) OR=1.03 (0.92 –1.15) OR=1.01 (0.90 – 1.13) OR=1.04 (0.93–1.17); t=5.84, p(heter)<0.0001 OR=1.21 (1.04–1.41) OR=1.17 (0.98 –1.38) OR=1.13 (0.97–1.31)	Random effects model Adjustments: NR Publication bias: NR Limitations: Potential confounding Significant heterogeneity Outdated oral contraceptive formulas

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
& USA			>20 y		OR=1.02 (0.88–1.18); t=4.95, p(heter)=0.0004	All included studies were observational (i.e. bias) High level of heterogeneity across studies (for duration of use)
Zhu et al., 2012[257] Studies published 1989–2010 China, France, Japan, Netherlands, Norway, South Korea, Sweden, UK & USA	Ever vs never: 13 prospective cohort studies Dose–response: 5 studies	859,894 women 11,722 cases Ages: >20–70 years	Oral contraceptive use Never use Ever use overall Dose response (per 5 y increment)	Breast cancer	RR=1.00 (referent) RR=1.08 (0.99–1.17); I^2=61.4%, p(heter)=0.002 RR=1.07 (1.03–1.11); I^2=0.0%, p(heter)=0.436	Fixed effects model (no heterogeneity)/ random effects model (heterogeneity present) Adjustments: NR No publication bias (p=0.77) Limitations: No distinction in type of oral contraceptive Confounders such as personal history not included Potential misclassification in duration of use
Cohort studies						
Iversen et al., 2017[265] UK	Royal College of General Practitioners' Oral Contraception Study Cohort dates: 1968–1969	Ever users: 22,920 Never users: 23,102	Oral contraceptive Never use Ever use overall <5 y 5–15 y 15–25 y 25–35 y	Breast cancer	IRR=1.00 (referent) IRR=1.04 (99% CI: 0.91–1.17); p=NS IRR=1.48 (99% CI: 1.10–1.97); p=sig. IRR=1.12 (99% CI: 0.91–1.39) IRR=1.05 (99% CI: 0.88–1.24) IRR=1.10 (99% CI: 0.94–1.28)	Poisson regression model Adjustments: Age, parity, smoking and social class Limitations: No adjustment for HT

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Prospective study Mean age at enrolment: 28.8 y Follow–up: 44 y		≥35 y		IRR=0.75 (99% CI: 0.60–0.93); p=sig.	Findings may not be current due to older progesterone in formulas
Hunter et al., 2010[268] USA	The Nurses' Health Study II Cohort dates: 1989−2001 Prospective study Age at enrolment: 24−43 y Follow–up: 1,246,967 person–y	116,413 women 1,344 cases	Oral contraceptive use Never Past Current 0−8 y ≥8 y Triphasic preparations Levonorgestrel	Breast cancer	RR=1 (referent) RR=1.12 (0.95−1.33) RR=1.33 (1.03−1.73) RR=1.16 (0.80−1.69) RR=1.42 (1.05−1.94) RR=3.05 (2.00–4.66); p<0.0001	Cox proportional hazard model Adjustments† Publication bias: NR Limitations: Small number of cases in women currently using oral contraceptives
Dartois et al., 2016[44] France	E3N cohort Prospective study Cohort dates: 1993–2008 Age at baseline: 42–72y Follow up: 15 y	67,634 women 497 premenopausal breast cancer cases 3,138 postmenopausal breast cancer cases	Oral contraceptive or progestagen alone use Recent use Past use <10 y ago Past use ≥10 y ago	Postmenopausal breast cancer	HR=1.38 (1.18–1.61) HR=1.06 (0.97–1.15) HR=1.00 (referent)	Multivariate Cox proportional hazards regression models Adjustments¶ Limitations: The E3N population prone to a healthy cohort effect Measurement errors for some retrospectively collected data

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: E3N, Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale; HR, hazard ratio; HT, hormone therapy; IRR, incident rate ratio; NS, not significant; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; sig, significant; UK, United Kingdom; USA, United States of America; y, year/s.

¶Adjusted on age (as the time scale), first–degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at first full term pregnancy (FFTP), physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and daily ultraviolet radiation dose, oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).

Table D.29 Hormonal contraception—progestogen only and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Fabre et al., 2007[270] France	E3N cohort Cohort dates: 1990–2002 Prospective study Age at enrolment: 40–64 y Mean follow–up: 9.07 y	73,664 women Ever users: 28,370 Never users: 45,294 2,390 cases	Oral progesterone Ever vs never use	Premenopausal breast cancer	RR=1.01 (0.93–1.11)	Cox proportional hazard model Adjustments† Limitations: Intermittent versus continuous use could not be analysed Information was self–reported and exposures could be misclassified
Backman et al., 2005[273] Finland	Cohort dates: 1990–2000 Retrospective study Mean age of levonorgestrel system users: 35.4 y Follow–up: 141,892 person–y	17,360 women 165 cases	30–34 y Overall Finnish female population Levonorgestrel–releasing intrauterine system users 35–39 y Overall Finnish female population Levonorgestrel–releasing intrauterine system users 40–44 y Overall Finnish female population Levonorgestrel releasing intrauterine system users	Breast cancer	Incidence per 100,000 25.5 27.2; p=0.84 49.2 74.0; p=0.056 122.4 120.3; p>0.99	No model used Adjustments not required Limitations: Possible non–response bias No official registry of all levonorgestrel system users and total users in population can be confirmed Unable to control for confounding factors

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			45–49 y			
			Overall Finnish female population		232.5	
			Levonorgestrel–releasing intrauterine system users		203.6; p=0.41	
			50–54 y			
			Overall Finnish female population		272.6	
			Levonorgestrel–releasing intrauterine system users		258.5; p=0.85	
Kumle et al., 2002[271] Norway & Sweden	Cohort dates: 1991–1999 End of follow–up: 31 Dec 1999 or emigration, death or diagnosis Prospective study Age at enrolment: 30–49 y Follow–up: NR	103,027 women 1,008 cases Median age at diagnosis: 47 y	Progestin–only pills	Breast cancer		Proportional hazard regression model No adjustments Limitations: Possible surveillance bias No information about stage of the disease Low response rate
			Never use		RR=1 (referent)	
			Ever use		RR=1.1 (0.8–1.7)	
			Current vs never use			
			Overall		RR=1.6 (1.0–2.4)	
			30–39 y		RR=1.7 (0.8–3.7)	
			40–49 y		RR=1.6 (0.9–2.6)	
Case–control studies						
Strom et al., 2004[275] USA	Women's CARE population–based study Breast cancer diagnosis:	4,574 incident cases 4,682 controls Ethnicity:	Contraceptive implants (progestin–based)	Breast cancer		Conditional unadjusted logistic regression model Adjustments¶ Limitations:
			Never used		OR=1 (referent)	
			Ever used		OR=0.67 (0.21−2.13)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	1994–1998 Age at recruitment: 35–64 y	Caucasian & African–American	Contraceptive injection (progestin–based) Never used Ever used		 OR=1 (referent) OR=0.87 (0.66–1.15)	Recall bias Sample size Exclusion of women under the age of 35 y
Marchbanks et al., 2002[272] USA	Women's CARE population–based study Breast cancer diagnosis: 1994–1998 Age at recruitment: 35–64 y	4,575 incident cases 4,682 controls Ethnicity: Caucasian & African–American	Oral contraceptive pill (progestin–based) No use Estrane progestins Any use Current use** Gonane progestins Any use Current use	Breast cancer	 OR=1 (referent) OR=0.9 (0.8–1.0) OR=1.1 (0.8–1.5) OR=1.0 (0.8–1.2) OR=1.0 (0.7–1.5)	Conditional logistic regression model Adjustments# Limitations: Use of oral contraception was not validated Representation of only white and black women; Absence of information on diet and environmental exposures and small subgroups No information on women under the age of 35 y
Shapiro et al., 2000[274] South Africa	Hospital–based study Breast cancer treated: 1994–1997	484 incident cases 1,625 frequency matched controls	Injectable progestogen contraceptives Any use	Breast cancer	 RR=0.9 (0.7–1.2)	Unconditional multiple logistic regression model Adjustments: Age, ethnic group,

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Age at recruitment: 20−54 y	Ethnicity: African & coloured women of mixed race	Current user (exposed <1 y previously)		RR=1.6 (1.1−2.3)	socioeconomic status, and any combined oestrogen/progestogen oral contraceptive use Limitations: NR

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: CARE, Contraceptive and Reproductive Experiences; E3N, Étude épidémiologique auprés des femmes de la mutuelle générale de l'éducation nationale; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; USA, United States of America; y, year/s.

†Adjusted for body mass index before and after menopause (<22/22–25/25–30/>=30), menopausal status (premenopausal/artificial menopause/natural menopause), age at menopause (<48/48–52/>52), parity and age at first full term pregnancy (FFTP) (nulliparous/FFTP at age <30/FFTP at age ≥30, num=1/FFTP at age ≥–30, num>1), age at menarche (<13/13–15/>15), familial history of breast cancer in sisters, mother, children (no/1/more than 1), familial history of breast cancer in other relatives (yes/no), personal history of benign breast disease 1(yes/no), personal history of benign uterine or ovarian disease (yes/no), use of oral contraceptive (never/current or <5 years after stop/4–5 years after stop), use of hormone therapy (No/oestrogen alone/oestrogen+progestin/ oestrogen+progesterone/others) and previous mammography (yes/no).

‡Age (continuous variable), parity (0, 1, 2, 3), age at first birth (20/21–24/25), age at menarche (continuous variable), use of hormone therapy (ever/never), menopausal status (pre–/postmenopausal), history of breast cancer in first–degree relatives (yes/no), duration of breastfeeding (continuous variable), body mass index (continuous variable), region (Sweden and five health regions in Norway), and a term for interaction between body mass index and menopausal status.

§All analyses were stratified by study, age at diagnosis, parity, and, where appropriate, the age a woman was when her first child was born, and the age she was when her risk of conception ceased.

¶ Conditioned on 60 matched groups (2 races x 6 age categories x 5 sites).

Odds ratios were derived by conditional logistic regression with the study site, race, and age (in five–year categories) as conditioning variables and were adjusted for menopausal status, age at menarche, age at menopause, number of term pregnancies, age at first term pregnancy, body mass index, presence or absence of a family history of breast cancer, and use or non–use of hormone therapy. Unknown oral contraceptive formulations were classified as combination formulations.

** Current use was defined as use of combination oral contraceptives containing the specified progestin within six months before the reference date.

Table D.30 Menopausal hormone therapy—combined and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Munsell et al., 2014[276] Studies published 1980–2012 Europe & North America	32 studies 17 case–control studies 12 cohort studies 2 RCTs	32,043 cases from case–control studies 23,541 cases from cohort studies & RCTs	Oestrogen–progestin hormone use	Postmenopausal breast cancer		Random effects model No publication bias (p>0.05) Adjustments: Most studies adjusted for age Limitations: Combination of adjusted relative risk estimates taken directly from the published papers along with crude estimates Studies not evaluated on indicators of quality, such as participation rates or loss to follow–up
			Never used		RR=1.00 (referent)	
			Ever used		RR=1.34 (1.24–1.46); I^2=79%, p<0.001	
				ER+PR+	RR=1.40 (1.08–1.82); I^2=74%, p=0.02	
				ER–PR–	RR=1.09 (0.87–1.37); I^2=0%, p=0.40	
			Never used	Postmenopausal breast cancer	RR=1.00 (referent)	
			Current use		RR=1.72 (1.55–1.92); I^2=79%, p<0.001	
				ER+PR+	RR=1.92 (1.60–2.30); I^2=60%, p=0.11	
				ER–PR–	RR=1.11 (0.78–1.57); I^2=0%, p=0.98	
				Unknown	RR=2.55 (1.65–3.92); I^2=87%, p=0.006	
Anothaisintawee et al., 2013[267] Studies published to 2011 Asia, Canada, Europe & USA	94 studies 34% cohort studies 55% case–control studies 34 studies for combined HT	Sample: NR 69% of studies focused on postmenopausal women	Combined oestrogen–progesterone use	Breast cancer		Random effects model Publication bias: NR Adjustments: NR Limitations: Pooled ORs without adjustments for confounding effects Results might be prone to bias
			Ever vs never		OR=1.33 (1.30–1.36)	
Collins et al., 2005[284]	Collaborative	52,705 women with	Oestrogen–progestin	Postmenopausal		Mantel–Haenszel model

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
(Narrative review) Studies published to 2005 Europe & North America	re–analysis	breast cancer 108,411 women without breast cancer RCTs: 19,756 patients	Non–users User <5 y User >5 y	breast cancer	Mean RR=1.00 (referent) Mean RR=1.15 (0.78–1.52) Mean RR=1.53 (0.88–2.18)	No publication bias Adjustments: NR Limitations: NR
Shah et al., 2005[285] Studies published 1966–2003 Europe & USA	4 cohort studies 4 case–control studies	655,559 women Mostly US based population	Combined oestrogen–progestogen therapy Non–users User <5 y User >5 y	Postmenopausal breast cancer	 OR=1.00 (referent) OR=1.35 (1.16–1.57) OR=1.63 (1.22–2.18)	Random effects model No publication bias (non–parametric test) Adjustments: NR Limitations: Confounding and 'healthy user' bias
Cohort studies						
Jones et al., 2016[280] UK	Breakthrough Generations Study Cohort dates: 2003–2009 Retrospective cohort Age at enrolment: ≥16 y Follow–up: 6 y	58,148 postmenopausal women 39,183 women with known menopausal age 775 cases Mean menopausal age: 50.2 y Mean postmenopausal BMI: 25.7 kg/m^2	Oestrogen plus progestogen Current use vs no previous use No previous use Current use Past use Duration of use >0–4 y 5–9 y 10–14 y ≥15 y	Invasive and in situ breast cancer Invasive breast cancer	 HR=2.74 (2.05–3.65) HR=1.00 (referent) HR=2.96 (2.19–3.99) HR=1.01 (0.79–1.28) HR=1.62 (0.88–2.95) HR=3.86 (2.40–6.21) HR=4.28 (2.39–7.65) HR=3.69 (1.73–7.90)	Cox hazard regression model Adjustments: Attained age & age at menopause Limitations: Analyses included women with simple hysterectomy before menopause or who started MHT before cessation of menstrual bleeding

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		Median combined MHT use: 5.4 y				
Román et al., 2015[281] Norway	Norwegian Prescription Database Cancer Registry of Norway Cohort dates: 2004–2008 Prospective cohort Age at baseline: 45–75 y Mean follow–up: 4.8 y	178,383 women users of hormonal therapy 508,231 never used hormone therapy 7,910 cases 776 cases of women with continual use 96 cases of women with sequential use	Estradiol—NETA Non–users Current use Continuous use Sequential use Route of administration Oral Transdermal	Breast cancer	 RR=1.00 (referent) RR=2.74 (2.55–2.95) RR=2.80 (2.59–3.02) RR=2.31 (1.88–2.83) RR=2.76 (2.52–2.97) RR=1.62 (0.81–3.23)	Multivariate model Adjustments: Age (5–y), number of births, age at first birth & time (offset) Limitations: Time–related biases Underestimation of the effect & risk of hormone therapy use Short follow–up time
Fournier et al., 2014[283] France	E3N cohort Cohort dates: 1992–2008 Prospective cohort Women born: 1925–1950 Mean follow–up: 11.2 y	78,353 postmenopausal women 3,678 cases 21,601 MHT never users 31,223 MHT past users 17,986 MHT current users	Oestrogen–progesterone/ dydrogesterone Never use Current use Past use Short term use (≤5 y) Current use 3 m–5 y since last use 5–10 y since last use >10 y since last use Long term use (>5 y) Current use	Postmenopausal breast cancer	 HR=1.00 (referent) HR=1.22 (1.11–1.35) HR=0.96 (0.87–1.06) HR=1.13 (0.99–1.29) HR=0.96 (0.82–1.12) HR=0.85 (0.71–1.01) HR=1.14 (0.91–1.44) HR=1.31 (1.15–1.48)	Cox proportional hazards models Adjustments† Limitations: Lack of statistical power among long term MHT users who stopped treatment more than 10 years earlier Limited ability to describe with precision the risks of breast cancer within a 2–year period after stopping treatment

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		Participants are insured by a national health insurance fund that mainly covers teachers	3 m–5 y since last use 5–10 y since last use >10 y since last use Oestrogen + progestogen Never use Current use		HR=1.15 (0.93–1.42) HR=1.08 (0.80–1.46) HR=0.98 (0.46–2.06) HR=1.00 (referent) HR=1.87 (1.71–2.04)	Risk of screening bias since hormone users generally have mammograms more frequently than non–users In situ breast cancers not considered
Bakken et al., 2011[287] Denmark, France, Germany, Greece, Italy, Norway, Spain Sweden, Netherlands & UK	EPIC cohort Cohort recruitment: 1992–2000 Prospective cohort Mean age at recruitment: 58.1 y Mean follow–up: 8.6 y	133,744 women 4,312 cases Denmark: 21,794 women France: 33,125 women Germany: 11,575 women Italy:14,074 women Norway: 10,578 women Spain: 9,360 women Netherlands: 10,935 women UK: 22,303 women	Combined oestrogen–progestin Never use Current use Duration of use ≤1 y 1–3 y 3–5 y 5–10 y >10 y	Breast cancer	 RR=1.00 (referent) RR=1.77 (1.40–2.24) RR=1.44 (1.09–1.89) RR=1.73 (1.44–2.08) RR=1.81 (1.44–2.29) RR=1.93 (1.58–2.35) RR=1.98 (1.12–3.50)	Multivariable model Adjustments‡ Limitations: Lack of information of MHT use after recruitment Models not adjusted for age at menopause, personal history of benign breast disease, physical activity or history of breast cancer in first–degree relatives
Lee et al., 2006[286] USA (Hawaii & Los Angeles)	Multiethnic Cohort Study Prospective study Cohort dates: 1993–1996 Mean age at	55,371 postmenopausal women 1,615 cases of breast cancer 9,494 African–American,	Oestrogen–progestin therapy Never use Current use 0–5 y 5–10 y >10 y	Postmenopausal breast cancer	RR=1.00 (referent) RR=1.43 (1.06–1.93) RR=1.82 (1.53–2.17) RR=2.18 (1.86–2.56)	Multivariate–analysis Adjustments: Ethnicity, age at menarche, age at first birth, number of children, age and type of menopause, BMI, alcohol consumption, family history and time on study

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	enrolment: 61.1 y Mean follow–up: 7.3 y	3,637 Native Hawaiian 16,789 Japanese–American 11,792 Latina 13,659 White				Limitations: Possibility of differential follow–up Upward bias since hormone therapy users are more likely to be screened for breast cancer than never users
Porch et al., 2002[291] USA	Women's Health Study Cohort start date: 1993 Prospective study Age at enrolment: ≥45 y Mean follow–up: 5.9 y	17,835 postmenopausal women 411 cases No PMH: 6,595 women HT: 5,616 women	PMH HT Never use Current use Duration <5 y ≥5 y Continuous <2 weeks/m	Postmenopausal breast cancer	 RR=1.00 (referent) RR=1.37 (1.05–1.78) RR=1.11 (0.81–1.52) RR=1.76 (1.29–2.39); p–trend=0.0004 RR=1.82 (1.34–2.48 RR=1.04 (0.74–1.46)); p–trend=0.0003	Multivariable adjusted model Adjustments** Limitations: PMH use information not updated PMH use and breast cancer risk may differ between women who undergo surgical menopause and women with natural menopause
Randomised controlled trials						
Chlebowski et al., 2015[279] USA	Women's Health Initiative Recruitment dates: 1993–1998 Age at enrolment: 50–79 y Median follow–up: 13 y	27,347 postmenopausal women 8,506 CEE + MPA 8,102 placebo 84% white women	Oestrogen plus progestin use vs placebo Intervention Post–intervention Early post–intervention Late post–intervention	Breast cancer	 HR=1.24 (1.01–1.53) HR=1.32 (1.08–1.61) HR=1.23 (0.90–1.70) HR=1.37 (1.06–1.77)	Cox proportional hazard models Adjustments: NR Limitations: Unblinded reporting of breast cancers after intervention Need for re–consent
Manson et al., 2013[278]	Women's Health Initiative	27,347 postmenopausal	Menopausal hormone therapy use	Breast cancer		Cox proportional hazards models

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		women enrolled	vs placebo			
USA	Recruitment dates: 1993–1998	8,506 CEE + MPA	CEE + MPA			Adjustments: NR
			Intervention phase		HR=1.24 (1.01–1.53)	
	Age at enrolment: 50–79 y	8,102 placebo	Post–intervention		HR=1.32 (1.08–1.61)	Limitations:
			Cumulative follow–up		HR=1.28 (1.11–1.48)	Only 1 dose, formulation, and route of administration was assessed
	Cumulative follow–up: 13 y	206 cases for CEE+MPA				
						Unblinded reporting
		155 cases for placebo				
						Possible false–positive and false–negative results
		Ethnicity: 84% white women				

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BMI, body mass index; CEE, conjugated equine oestrogens; E3N, Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale; EPIC, The European Prospective Investigation into Cancer and Nutrition, ER, oestrogen receptor; HR, hazard ratio; HT, hormone therapy; m, month/s; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; NR, not reported; OR, odds ratio; p, p–value; PMH, postmenopausal hormone; PR, progesterone receptor; p–trend, p–value for trend; RCT, randomised controlled trial; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

*Adjusted on age (as the time scale), first–degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at first full term pregnancy (FFTP), physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and daily ultraviolet radiation dose (UVRd), oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).

†Years of schooling, parity and age at first birth, BMI, type of menopause, age at menarche, pap smear frequency, history of breast cancer in first–degree relatives, history of breast cancer in other relatives, personal history of benign breast disease, mammogram in the previous follow–up period, use of oral contraceptives before menopause, use of progestogens alone before menopause.

‡Age (continuous time scale), type of menopause (natural/artificial), BMI (<18.5/[18.5–25]/[25–30]/>30 kg/m^2), ever–use of oral contraceptives (yes/no), number of full term pregnancies (0/1/2/>3), age at first full term pregnancy (<25/[25–30]/>30 y old/unknown), age at menarche (<12/[12–16]/>16 y old/unknown), alcohol consumption (none/[0–15]/[15–30]/30> g/day/unknown). Further stratified by EPIC–participating centre.

**Adjusted for age, age at menopause, menopause type, age at menarche, nulliparity, age at first pregnancy, abortions/miscarriages, full term pregnancies, ever use of oral contraceptives, history of benign breast disease, use of breast cancer screening, family history of breast cancer, race, body mass index, cigarette use, alcohol use and exercise.

Table D.31 Menopausal hormone therapy—oestrogen only and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Anothaisintawee et al., 2013[267] Studies published to 2011 Europe & USA	94 studies 34% cohort studies 55% case–control studies 29 studies for oestrogen only MHT	Number of participants: NR 69% studies focused on postmenopausal women	Oestrogen–only HT	Breast cancer	OR=1.09 (1.06–1.12)	Random effect model (heterogeneity present)/fixed effect model (heterogeneity not present) Publication bias: NR Adjustments: NR Limitations: Increased HT effect size limited to Caucasian women due to small number of studies on Asian women
Collins et al., 2005[284] (Narrative review) Studies published to 2005 North America & Europe	20 epidemiological studies (ever & current use) Collaborative re–analysis 4 RCTs	7,055 cases 4,640 women 1,056 cases 12,643 women 103 cases	Oestrogen–only HT Current use Ever use <5 y use >5 y use Oestrogen–only HT vs placebo	Breast cancer	Mean RR=1.18 (1.01–1.38)† Mean RR=1.08 (0.97–1.20)† Mean RR=0.99 (0.83–1.15)§ Mean RR=1.34 (1.16–1.52)§ Mean RR=0.78 (0.61–1.01)¶	Inverse variance model No publication bias for collaborative re–analysis Adjustments: NR Limitations: NR
Cohort studies						
Jones et al., 2016[280] UK	Breakthrough Generations Study Recruitment dates: 2003–2009	58,148 women 23 cases currently using MHT	Oestrogen–only MHT Overall Per year of use Current use vs no previous use	Postmenopausal breast cancer	HR=1.00 (0.66–1.54) HR=4.2 (–1.8–10.5); p=0.99	Cox proportional hazards regression model Adjustments: Attained age & menopausal

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						age (continuous)
	Retrospective study	Mean menopausal age: 50.2 y	Duration			
			>0–4 y		HR=0.80 (0.38–1.69)	
			5–9 y		HR=0.96 (0.43–2.16)	Limitations:
	Age at enrolment: ≥16 y	Mean post–menopausal BMI: 25.7 kg/m^2	10–14 y		HR=1.41 (0.62–3.17)	Misclassification of MHT/HT use & underestimation of the excess HR
			15+ y		HR=1.14 (0.42–3.08)	
	Follow–up: 6 y		Time since last use			
			1 y		HR=0.40 (0.10–1.62)	
			2–4 y		HR=1.02 (0.63–1.63)	
			5–9 y		HR=0.99 (0.61–1.62)	
			10+ y		HR=1.35 (0.63–2.86)	
Román et al., 2015[281]	Norwegian Prescription Database Cancer Registry of Norway	686,614 women	Oestrogen–only HT use vs non–use			Multivariate model
			Baseline use	Breast cancer	RR=1.30 (1.12–1.50); p=NS	
Norway			New use		RR=0.94 (0.82–1.08)	Adjustments:
	Cohort dates: 2004–2008	Estradiol use: 64,023 women 377 cases	Oral use		RR=1.40 (1.16–1.68)	Age (5–year), number of births, age at 1st birth & time (offset)
			Transdermal use		RR=1.40 (1.00–1.95)	
	Prospective study		1 mg use		RR=1.52 (1.11–2.10)	Limitations:
			2 mg use		RR=1.68 (1.30–2.15)	Time–related biases
	Age at baseline: 45–79 y		Baseline use		RR=1.18 (0.93–1.50); p=NS	
		Estriol use: 14,405 women 96 cases				Underestimation of the effect & risk of hormone therapy use
	Mean follow–up: 4.8 y		New use		RR=0.89 (0.61–1.29)	
						Short follow–up time
Fournier et al., 2014[283]	E3N cohort	78,353 women	Oestrogen–only MHT			Cox proportional hazards model
			Never use	Postmenopausal breast cancer	HR=1.00 (referent)	
France	Cohort dates: 1992–2008	3,678 cases	Current use overall		HR=1.17 (0.99–1.38)	Adjustments#
			≤5 y of use, time since last use			Limitations:
	Prospective cohort	Mean age at end of follow–up (current users): 63.1 y	Current use		HR=1.11 (0.89–1.38)	Limited precision in describing risks of breast cancer within a 2–year period after stopping treatment
	Women born: 1925–1950		3 months–5 y		HR=1.10 (0.91–1.33)	
			5–10 y		HR=1.11 (0.92–1.33)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Follow up: 11.2 y	Mean age at end of follow–up (never users): 67.1 y	>10 y		HR=0.92 (0.74–1.15)	
			>5 y of use, time since last use			
			Current use		HR=1.22 (0.96–1.54)	
			3 months–5 y		HR=0.79 (0.46–1.34)	
			5–10 y		HR=1.54 (0.92–2.57)	
			>10 y		HR=1.81 (1.02–3.22)	
			Past use overall		HR=1.06 (0.95–1.19)	
Bakken et al., 2011[287] Denmark, France, Germany, Italy, Netherlands, Norway & UK	EPIC cohort Prospective study Mean age at enrolment: 58.1 y Mean follow–up: 8.6 y	133,744 women 4,312 cases	Oestrogen–only MHT	Postmenopausal breast cancer		Multivariable Cox proportional hazards model Adjustments** Limitations: Lack of information of MHT use after recruitment
			Never use		RR=1.00 (referent)	
			Current use overall		RR=1.42 (1.23–1.64)	
			Per year of use		RR=1.02 (0.99–1.06)	
			<1 y		RR=1.01 (0.70–1.46)	
			3–5 y		RR=1.40 (1.01–1.93)	
			>10 y		RR=1.72 (1.15–2.57)	
Randomised controlled trials						
Manson et al., 2013[278] USA	WHI trials: 2 RCTs Study duration: Oral CEE + MPA 1993−2002 Oral CEE 1993−2004 Age at recruitment: 50−79 y Median cumulative follow–up: 13 y	27,347 women 16,608 women with a uterus 361 cases 10,739 women with prior hysterectomy 239 cases 396 cases	CEE/MPA hormone therapy	Postmenopausal breast cancer		Cox proportional hazards model Adjustments: Stratified by age, prior disease (if appropriate), & randomisation status Limitations: Multiple testing limitations attending subgroup analyses
			Intervention phase			
			Oral CEE + MPA vs placebo		HR=1.24 (1.01−1.53); p=0.04	
			Oral CEE vs placebo		HR=0.79 (0.61−1.02); p=0.07	
			Post–intervention phase			
			Oral CEE + MPA vs placebo		HR=1.32 (1.08−1.61); p=0.007	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		145 cases	Oral CEE vs placebo		HR=0.80 (0.58−1.11); p=0.19	
			Overall combined phases			
			Oral CEE + MPA vs placebo			
		757 cases	Overall		HR=1.28 (1.11−1.48); p<0.001	
			50−59 y		HR=1.34 (1.03−1.75)	
			60−69 y		HR=1.27 (1.02−1.57)	
			70−79 y		HR=1.25 (0.94−1.67); p–trend=0.72	
			Oral CEE vs placebo			
			Overall		HR=0.79 (0.65−0.97); p=0.02	
			50−59 y		HR=0.76 (0.52−1.11)	
		384 cases	60−69 y		HR=0.78 (0.58−1.05)	
			70−79 y		HR=0.85 (0.56−1.28); p–trend=0.70	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BMI, body mass index; CEE, conjugated equine oestrogens; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; HT, hormone therapy; IARC, International Agency for Research on Cancer; MHT, menopausal hormone therapy; MPA, medroxy–progesterone acetate; NS, not significant; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; RCT, randomised controlled trial; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; WHI, Women's Health Initiative; y, year/s.

†Random–effects model. §Mantel–Haenszel model. ¶Inverse variance model.

#Age (time scale), all variables listed in Table 1 (Age at end of follow–up, age at menopause, year of birth, years of schooling, parity and age at first birth, BMI, type of menopause, age at menarche, pap smear frequency, history of breast cancer in first–degree and other relatives, personal history of benign breast cancer, mammogram in previous follow–up period, oral contraceptive use before menopause, progestagen use before menopause; and all categories of MHT exposure described in the table (current and past use, as well as duration of use and time since last use).**Age (continuous time scale), type of menopause (natural/artificial), BMI (<18.5/[18.5–25]/[25–30]/30 or more kg/m^2), ever–use of oral contraceptives (yes/no), number of full–term pregnancies (0/1/2/3 or more), age at first full–term pregnancy (<25/[25–30]/30 or more y old/unknown), age at menarche (<12/[12–16]/16 or more y old/unknown), alcohol consumption (none/[0–15]/[15–30]/30 or more g/day/unknown). Further stratified by EPIC–participating centre.

Table D.32 Hormonal infertility treatment and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Gennari et al., 2015[295] Studies published 1996–2014 Countries of origin: NR	20 cohort studies IVF: 7 studies No IVF: 3 studies <10 y: 10 studies >10 y: 10 studies	207,914 women exposed to hormonal infertility treatments 2,347 cases 16 studies used general population as control group 4 studies used internal controls	Hormonal infertility treatments vs no treatment IVF No IVF (enrolled before 1980)† Duration of follow–up‡ <10 y >10 y	Breast cancer	SRR=1.05 (0.96–1.14); I^2=58.5%, p(heter)=0.001 SRR=0.96 (0.81–1.14); I^2=50.4%, p(heter)=0.06 SRR=1.26†† (1.06–1.50); p=0.05; I^2=28.3%, p(heter)=0.248 SRR=0.95 (0.85–1.06); I^2=34.1%, p(heter)=0.135 SRR=1.13 (1.02–1.26); I^2=53.5%, p(heter)=0.02, p(subgroup)=0.2	Random effects model Adjustments: NR Publication bias: NR Limitations: Confounding effect of pregnancy Observational studies, including selection bias and ascertainment bias It is not possible to identify a control group that is closely comparable, in terms of BC risk, to a group of women receiving treatments for infertility
Cohort studies						
Lundberg et al., 2017[296] Sweden	Swedish Multi–Generation Register Retrospective study Cohort 1: Parous women who had their first live birth in 1982–2012 Mean follow–up: 9.6 y for ART birth &	Cohort 1: 38,047 women who gave birth after ART treatment 13,414 cases Cohort 2: 39,469 women had gone through COS & 26,232 had received ovulation	ART vs spontaneous conception Infertility related diagnosis but no COS vs no infertility related diagnosis or COS Other hormonal	Breast cancer	HR=0.84 (0.74–0.95) HR=0.83 (0.76–0.91) HR=0.79 (0.60–1.05)	Cox proportional hazard model Adjustments§ Limitations: Not able to identify all women with infertility–related problems Unidentified or unmeasured confounders affected the results

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	14.6 y for no ART birth Cohort 2: Women born 1960–1992 Mean follow–up: 7.4 y for COS women, 7.2 y for women with ovulation induction, & 6.3 y for women who received no ovarian stimulation Age at enrolment: NR	induction 7,229 cases	treatment vs no infertility related diagnosis or COS COS vs no infertility related diagnosis or COS		HR=0.86 (0.69–1.07)	Information on ART births 1982–2006 was collected from IVF clinics retrospectively and might have lower coverage
Reigstad et al., 2017[298] Norway	All women born in Norway in 1960–1996 & registered in the National Registry. Data was also from the Norwegian Prescription Database, medical Birth Registry of Norway & Cancer Registry of Norway Cohort dates: 2004–2014 Retrospective study	1,353,724 eligible for the study 33,431 received treatment with ART 38,927 with clomiphene citrate 6,690 cases 112 ART women cases & 6,578 unexposed cases 140 clomiphene citrate cases &	Exposure to ART Nulliparous Parous Exposure to clomiphene citrate Nulliparous Parous Dose of clomiphene citrate Nulliparous ≤3 4–6 >6 Parous ≤3 4–6	Breast cancer	HR=1.00 (0.81–1.22) HR=1.11 (0.75–1.66) HR=0.96 (0.76–1.22) HR=1.12 (0.93–1.35) HR=0.73 (0.47–1.12) HR=1.26 (1.03–1.54) HR=0.77 (0.43–1.36) HR=0.85 (0.41–1.73) HR=0.44 (0.14–1.41) HR=1.24 (0.94–1.63) HR=1.33 (0.94–1.88)	Cox regression model Adjustments: Region of residence, birth cohort, and concomitant exposure to clomiphene citrate Limitations: Misclassification of exposure Comorbidity data are unavailable Information on fertility diagnoses are unavailable Confounding factors

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Age at enrolment: women born 1960–1996 Median follow–up: 11 y	6,550 unexposed cases	>6		HR=1.21 (0.79–1.84)	associated with cancer and infertility not unavailable Information on BRCA mutations, socioeconomic factors, smoking, and BMI was unavailable Surveillance bias Correction for multiple analyses were not performed
van den Belt–Dusebout et al., 2016[294] Netherlands	OMEGA cohort study Cohort dates: 1989–2013 Retrospective study Mean age at baseline: 32.8 y Median follow–up: 21.1 y	25,108 women 19,158 women in the IVF group 5,950 women in the non–IVF group 839 cases of invasive breast cancer	Incidence of breast cancer vs general population IVF Non–IVF Breast cancer risk according to fertility treatment and reproductive characteristics IVF Non–IVF Time since first IVF cycle in the IVF group <5 5–9 10–14 15–19 ≥20 Time since first IVF cycle in the non– IVF	Invasive breast cancer	SIR=1.01 (0.93–1.09) SIR=1.00 (0.88–1.15) HR=1.01 (0.86–1.19) HR=1 (referent) SIR=0.95 (0.71–1.25) SIR=1.07 (0.88–1.29) SIR=1.06 (0.91–1.23) SIR=0.98 (0.85–1.13) SIR=0.92 (0.73–1.15); p–trend=0.47	Cox proportional hazards models Adjustments¶ Limitations: Age at menopause and menopausal status at end of follow–up were unknown Person–years were included from 1989 onward because cancer incidence before 1989 was only known for responding women and not for non–responding women Results are largely based on IVF treatment protocols used until 1995

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			group			
			<5		SIR=1.02 (0.53–1.78)	
			5–9		SIR=0.95 (0.61–1.40)	
			10–14		SIR=1.07 (0.79–1.42)	
			15–19		SIR=0.94 (0.71–1.22)	
			≥20		SIR=1.03 (0.82–1.29); p–trend=0.93	
Luke et al., 2015[297] USA	SART CORS database Cohort dates: 2004–2009 to 2010 Prospective study Follow–up: 263,457 person–y (mean 4.87 y) Mean age at cancer diagnosis: 40.8 y	113,226 women 185 cases	Comparison of incidence ratios with women treated with ART	Breast cancer	SIR=0.83 (0.75–0.91)	Cox proportional hazard model Adjustments# Limitations: Lack of information on family history of cancer, age at menarche, first birth, breastfeeding history, use of contraceptive drugs and hormone replacement therapy

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: ART, assisted reproductive technologies/techniques; COH, controlled ovarian hyperstimulation; COS, controlled ovarian stimulation; HR, hazard ratio; IVF, in vitro fertilisation; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; p(subgroup), p–value for subgroup comparison; RR, relative risk or risk ratio; SART CORS, Society for Assisted Reproductive Technology Clinic Outcomes Reporting System; SIR, standardised incidence ration; SRR, summary relative risk; USA, United States of America; y, year/s.

†Meta–regressional model comparing IVF, hormonal treatments outside of IVF protocols and mixed/unspecified treatments.

‡Meta–regressional model comparing <10 y and ≥10 y.

§Adjusted for attained age, parity, calendar time, education level, country of birth, family history of BC and age at first birth.

¶Adjusted for age at first birth and number of births because for these variables, the IVF–specific risks (yes vs no or number of cycles) were changed by more than 10% when the variables were added to the model, which was not the case for the other potential confounders (4.5% maximum change): subfertility diagnosis, type of luteal phase support, clomiphene use, family history of breast cancer, body mass index, multiple pregnancies, breast feeding, age at menarche, use of oral contraceptives, and hormonal replacement therapy.

#Age at cycle start was adjusted for State and year of ART treatment. Parity, infertility diagnosis, and number of infertility diagnoses were adjusted for age at cycle start, State, and year of ART treatment. Number of ART cycles was adjusted for infertility diagnosis and number of infertility diagnoses, parity, age at cycle start, and year of ART treatment. Cumulative FSH dosage was adjusted for infertility diagnosis, number of ART cycles and diagnoses, parity, age at cycle start, State, and year of ART treatment. ART outcome was adjusted for cumulative FSH dosage, infertility diagnosis, number of ART cycles and diagnoses, parity, age at cycle start, State, and year of ART treatment.

††The SRR reported is from the study's Forest plot. The text of the study reports the SRR as 1.23.

Table D.33 DES in utero and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Pooled analyses						
Hoover et al., 2011[309] Studies published 1977–1984 USA	3 cohort studies	4,653 DES–exposed women 1,927 unexposed women 61 cases among 3,693 exposed in women aged ≥40 y 21 cases among 1,647 unexposed in women aged ≥40 y	DES, in utero Non–exposed Exposed VEC present VEC absent	Breast cancer at ≥40 y	 HR=1 (referent) HR=1.82 (1.04–3.18) CR=3.6% (1.4%–5.8%) CR=2.3% (0.2%–4.4%)	Cox proportional hazards model Adjustments: Date of birth and cohort Publication bias: NR Limitations: NR for breast cancer
Troisi et al., 2007[307] Countries of origin: NR	4 cohorts: National Cooperative Diethylstilbestrol Adenosis project; daughters of women from the Dieckmann cohort; daughters of women from the Horne Cohort; Women's Health Study Daughters Cohort Follow–up: 1978–2001 (follow–up of Women's Health Study Daughters from 1995–2001)	4,806 exposed women 2,067 unexposed women 223 cases: 75 cases in exposed group 26 cases in unexposed group	DES, in utero Exposed vs not exposed All ages ≥40 y <40 y	Breast cancer	 RR=1.35 (0.85–2.1) RR=1.83 (1.1–3.2) RR=0.60 (0.26–1.3)	Poisson regression model Adjustments: 5–year categories Limitations: Incomplete retrieval of medical records for confirmation of the cancers Loss to follow–up

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Median follow–up: 24 y or 97,831 person–y (exposed) and 22 y or 34,810 person– y (unexposed)					
Cohort studies						
Verloop et al., 2010[300] Netherlands	Cohort dates: 1992–2008 Prospective study Median age at registration: 29 y Follow–up: 180,941 women–y exposed to DES	12,091 women 165 cases	DES, in utero Overall <40 y ≥40 y	Breast cancer	 SIR=1.05 (0.90–1.23) SIR=0.95 (0.69–1.29) SIR=1.09 (0.91–1.31)	Poisson distribution Adjustments: Stratification for age (<40 and ≥ 40 y), educational level, parity, and maternal age at birth did not alter these results Limitations: DES exposure was not documented for majority of participants Women enrolled in cohort differ from the background population of DES daughters No internal comparison group, preventing adjustment for several risk factors

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: CR, cumulative risk; DES, diethylstilbesterol; HR, hazard ratio; NR, not reported; SIR, standardised incidence ratio; RR, relative risk or risk estimate; USA, United States of America; VEC, vaginal epithelial changes; y, year/s.

Table D.34 DES maternal exposure and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Titus–Ernstoff et al., 2001[310] USA	Mothers and Dieckmann Study cohorts Review of obstetrics records: 1940–1960 Retrospective study Dieckmann study cohort: women enrolled in early 1950s Follow–up: 143,657 person–y in exposed women & 139,735 person–y in unexposed women	3,844 exposed women 3,716 unexposed women	DES exposure when pregnant vs no exposure DES exposure when pregnant vs general population	Breast cancer	RR=1.27 (1.07–1.52) SIR=1.10 (0.98–1.23)	Poisson regression model Adjustments: RR adjusted for age, calendar year and the interaction between age and calendar year Time since exposure RR values further adjusted for cohort Limitations: There was a long interim between evaluations of the Dieckmann cohort and consequent losses to follow–up Only parous women included in study

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: DES, diethylstilbesterol; RR, relative risk or risk estimate; SIR, standardised incidence ratio; USA, United States of America; y, year/s.

Lifestyle factors

Table D.35 Adiposity and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2015 Asia, Europe & North America	37 studies (including 3 pooled analyses)	16,371 cases	BMI Dose response (per 5 kg/m^2)	Premenopausal breast cancer	RR=0.93 (0.90–0.97); I^2=54.5%, p(heter)=0.001	Model: NR Adjustments: Age, alcohol intake, reproductive factors, weight change or adult BMI/waist–hip ratio Publication bias for postmenopausal breast cancer (p<0.05) Limitations: NR
	56 studies (including 4 pooled analyses)	80,404 cases		Postmenopausal breast cancer	RR=1.12 (1.09–1.15); I^2=73.6%, p(heter)=0.000	
	12 studies (including 1 pooled analysis)	4,953 cases 18–30 y	BMI in young adulthood Dose response (per 5 kg/m^2)	Premenopausal breast cancer	RR=0.82 (0.76–0.89); I^2=14.9%, p(heter)=0.310	
	17 studies (including 1 pooled analysis)	10,229 cases 18–30 y		Postmenopausal breast cancer	RR=0.82 (0.76–0.88); I^2=43.5%, p(heter)=0.042	
	6 studies	2,423 cases	Waist circumference Dose–response (per 10 cm) BMI adjusted	Premenopausal breast cancer	RR=1.14 (1.04–1.26); I^2=0%, p(heter)=0.853	
			BMI unadjusted		RR=0.99 (0.95–1.04); I^2= 0%, p(heter)=0.904	
	11 studies	14,033 cases	Waist circumference Dose–response (per 10 cm) BMI adjusted	Postmenopausal breast cancer	RR=1.06 (1.01–1.12); I^2=72.0%, p(heter)=0.006	
			BMI unadjusted		RR=1.11 (1.09–1.13); I^2=0%, p(heter)=0.590	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	11 studies (including 1 pooled analysis)	3,465 cases	Waist–to–hip ratio Dose–response (per 0.1 unit)	Premenopausal breast cancer		
			BMI adjusted		RR=1.15 (1.01–1.31); I^2=56.1%, p(heter)=0.034	
			BMI unadjusted		RR=1.06 (0.98–1.16); I^2=27.1%, p(heter)=0.203	
	18 studies (including 1 pooled analysis)	15,643 cases	Waist–to–hip ratio Dose–response (per 0.1 unit)	Postmenopausal breast cancer		
			BMI adjusted		RR=1.06 (0.99–1.15); I^2=41.4%, p(heter)=0.115	
			BMI unadjusted		RR=1.10 (1.05–1.16); I^2=0.0%, p(heter)=0.590	
Freisling et al., 2017[319] Publication search dates: NR Europe & North America	CHANCES consortium 7 prospective cohort studies Mean age: 63 y Median follow–up: 12 y	24,751 women 555 cases	BMI [Dose response per 4.6 kg/m^2]	Postmenopausal breast cancer		Random effects model Adjustments†‡ Publications bias: NR Limitations: Adiposity measures across all cancer sites not compared Differences in study design between cohorts Confounding
			Never used HT		HR=1.28 (1.11–1.47)	
			Ever used HT		HR=0.91(0.76–1.10)	
			Unknown use of HT		HR=1.02 (0.73–1.43)	
			Waist circumference [Dose response per 11.6 cm]			
			Never used HT		HR=1.21 (1.05–1.40)	
			Ever used HT		HR=0.93 (0.78–1.11)	
			Unknown use of HT		HR=1.00 (0.71–1.41)	
			Hip circumference [Dose response per 9.3 cm]			
			Never used HT		HR=1.24 (1.08–1.42)	
			Ever used HT		HR=0.96 (0.80–1.14)	

Authors	Study details	Study sample	Exposures	Outcomes		Risk estimates	Author comments
			Unknown use of HT			HR=1.13 (0.82–1.55)	
Pooled analyses							
Premenopausal Breast Cancer Collaborative Group, 2018[318] Participants recruited 1963–2013 Australia, Canada, European countries, France, Japan, Norway, Singapore, Sweden, UK & USA	19 prospective cohort studies	758,592 women 13,082 cases Median age at enrolment: 40.6 y Median follow–up: 9.3 y	BMI Age 18–24 y Trend (per 5 unit difference) BMI<18.5 BMI 18.5–22.9 BMI 25.0–29.9 BMI≥30.0	Premenopausal breast cancer		HR=0.77 (0.73–0.80) HR=1.14 (1.07–1.21) HR=1.00 (referent) HR=0.75 (0.68–0.82) HR=0.55 (0.45–0.68)	Cox proportional hazards regression model Adjustments§ Limitations: BMI does not measure overall body fat level Weight was usually self–reported Insufficient power to assess associations in Asian population
Cohort studies							
Horn–Ross et al., 2016[50] USA	California Teachers Study cohort Cohort dates: 1997–2011 Prospective study Age at enrolment: 18 y Duration of follow–up: 10 y	109,862 women 3,844 ER+ cases	BMI Current use of HT <25 kg/m^2 ≥25 kg/m^2 No current use of HT <25 kg/m^2 ≥25 kg/m^2	Postmenopausal breast cancer	ER+	HR=1 (referent) HR=1.21 (1.07–1.37) HR=1 (referent) HR=1.07 (0.95–1.21)	Multivariable Cox proportional hazards regression Adjustments¶#** Limitations: Small case numbers in some subgroups Only 16 body–size phenotypes included Data limited to specific time points

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						Potential menopausal status and HT use misclassification Self–reported anthropometric data
Neuhouser et al., 2015[321] USA	WHI clinical trials cohort Cohort dates: 1993–1998 Age at enrolment: 50–79 y Median follow–up: 13 y	67,142 women 3,388 cases	BMI With uterus Never used HT <25 kg/m² 25–<30 kg/m² 30–<35 kg/m² ≥35 kg/m² Current use of oestrogen & progestin <25 kg/m² 25–<30 kg/m² 30–<35 kg/m² ≥35 kg/m² Past use of oestrogen & progestin <25 kg/m² 25–<30 kg/m² 30–<35 kg/m² ≥35 kg/m²	Postmenopausal breast cancer	HR=1 (referent) HR=1.14 (0.95–1.37) HR=1.29 (1.05–1.59) HR=1.46 (1.17–1.83) HR=1 (referent) HR=1.21 (1.03–1.42) HR=1.36 (1.13–1.64) HR=1.53 (1.22–1.91) HR=1 (referent) HR=1.57 (0.98–2.51) HR=1.64 (0.97–2.78) HR=1.84 (0.97–3.48)	Multivariable Cox model Adjustments†† Limitations: Fewer race/ethnic minority participants Lack of data on tumour molecular characteristics, and on longer term weight and body composition changes Inability to distinguish from unintentional weight loss Insufficient power to examine distant stage

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BMI, body mass index; CHANCES, Consortium on Health and Ageing; network of Cohorts in Europe and the United States; cm, centimetres; ER, oestrogen receptor; HR, hazard ratio; HT, hormone therapy; kg/m², kilograms per square metre; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; WCRF, World Cancer Research Fund; WHI, Women's Health Initiative; y, year/s.

†Waist–to–hip ratios (WHR) HR adjusted for: age (1–y categories), and sex, and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/day), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height; in the pooled analysis, models were additionally stratified by cohort and WHR–residual.

‡HR for BMI adjusted for: age (1–y categories), and sex, and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/day), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height; in the pooled analysis, models were additionally stratified by cohort and mutually adjusted using waist circumference (WC)– and hip circumference (HC)–residuals.

§Adjusted for age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth, and family history of breast cancer.

¶Premenopausal breast cancer: adjusted for history of benign breast disease and family history of breast cancer in a first–degree relative; age was the time metric and the model was stratified by age at baseline.

#Postmenopausal breast cancer (no hormone therapy): adjusted for age at menarche, nulliparity and age at first full term pregnancy, history of benign breast disease, family history of breast cancer in a first–degree relative, and consumption of a plant–based diet; age was the time metric and the model was stratified by age at baseline.

**Postmenopausal breast cancer (hormone therapy): adjusted for nulliparity and age at first full term pregnancy, history of benign breast disease, family history of breast cancer in a first–degree relative, average alcohol consumption in the year prior to baseline, and neighbourhood socioeconomic status; age was the time metric and the model was stratified by age at baseline.

††Adjusted for age, race/ethnicity, education, parity, age at first birth, bilateral oophorectomy, family history of breast cancer, estrogen–alone use and duration, oestrogen and progesterone use and duration, smoking status, diabetes mellitus, alcohol consumption, and stratified by baseline age group, hormone therapy trial randomization group, dietary trial randomization group, hysterectomy status, Calcium/Vitamin D Randomized Trial randomization group (time–dependent) and extended follow–up (time–dependent).

Table D.36 Adiposity—weight gain and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2015 Asia, Europe & North America	5 cohort, case–control & nested case–control studies	3,512 premenopausal cases	Weight gain Dose response (per 5 kg)	Premenopausal breast cancer	RR=0.99 (0.96–1.03); I^2=13%, p(heter)=0.33	Model: NR Adjustments: NR No publication bias (p>0.05) Limitations: NR
	15 cohort, case–control & nested case–control studies	16,600 postmenopausal cases	Overall	Postmenopausal breast cancer	RR=1.06 (1.05–1.08); I^2=38%, p(heter)=0.07	
			Hormone therapy use			
			Current		RR=1.00 (0.98−1.03); I^2=19%	
			Ever		RR=1.08 (1.00−1.16); I^2=44%	
			Never		RR=1.06 (1.03−1.09); I^2=0%	
			Never/former		RR=1.09 (1.07−1.12); I^2=37%	
				ER+PR+	RR=1.13 (1.04−1.22); I^2=91%	
				ER+ PR–	RR=1.00 (0.95−1.04); I^2=0%	
				ER–PR–	RR=1.02 (0.98−1.06); I^2=4%	
Cohort studies						
Nitta et al., 2016[51] Japan	Japan Collaborative Cohort study Cohort dates: 1988−2009 Prospective study Age at enrolment: 40−79 y	38,610 women 273 cases 9,367 premenopausal women 84 premenopausal cases 29,243 postmenopausal	Weight gain since age 20	Premenopausal breast cancer		Cox proportional hazards regression model Adjustments: Age at baseline survey, age at menarche, number of live births and age at first delivery Limitations: Possible misclassification of menopausal status
			<3.3 kg		HR=1 (referent)	
			3.3–6.6 kg		HR=0.89 (0.42–1.89)	
			6.7–9.9 kg		HR=1.27 (0.59–2.70)	
			≥10.0 kg		HR=1.46 (0.78–2.73); p–trend=0.221	
			<3.3 kg	Postmenopausal breast cancer	HR=1 (referent)	
			3.3–6.6 kg		HR=1.45 (0.78–2.70)	
			6.7–9.9 kg		HR=2.48 (1.40–4.41)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		women	≥10.0 kg		HR=2.94 (1.84–4.70); p–trend<0.001	Self–reported information at baseline
	Mean follow–up: 13 y	189 postmenopausal cases				
Neuhouser et al., 2015[321]	WHICT study	67,142 postmenopausal women	Weight gain >5% (per BMI range)	Postmenopausal breast cancer		Cox proportional hazards regression model†
USA	Cohort dates: 1993–1998	3,388 cases	Overall		HR=1.12 (1.00–1.25)	Limitations:
	Prospective		<25 kg/m^2		HR=1.36 (1.11–1.65)	Fewer race/ethnic minority participants
	Age at enrolment: 50–79 y		25–<30 kg/m^2		HR=0.98 (0.81–1.18)	Lack of data on tumour molecular characteristics
	Median follow–up: 13 y		30– <35 kg/m^2		HR=1.14 (0.92–1.42)	Fewer data on longer term weight and body composition changes
			≥30 kg/m^2		HR=1.00 (0.74–1.34)	Inability to distinguish from unintentional weight loss

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; ER, oestrogen receptor; HR, hazard ratio; kg/m^2, kilograms per square metre; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; PR, progesterone receptor; RR, relative risk or risk estimate; USA, United States of America; WCRF, World Cancer Research Fund; WHICT, Women's Health Initiative Clinical Trial; y, year/s.

†Adjusted for age, race/ethnicity, education, parity, age at first birth, bilateral oophorectomy, family history of breast cancer, estrogen–alone use and duration, oestrogen and progesterone use and duration, smoking status, diabetes mellitus, alcohol consumption, baseline BMI group, and stratified by baseline age group, hormone therapy trial randomization group, dietary trial randomization group, hysterectomy status, Calcium/Vitamin D Randomized Trial randomization group (time–dependent), and extended follow–up (time dependant).

Table D.37 Adiposity—weight loss and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Winder et al., 2017[327] Studies published to 2016 Canada, Sweden & USA	4 meta–analyses, cohort studies & case series Follow–up: 11.7 y	9,235 bariatric cases (114 breast cancer cases) 16,492 controls (516 breast cancer cases) female patients ≥18 y with a BMI ≥35 kg/m^2	Bariatric surgery vs control	Breast cancer	OR=0.585 (0.247–1.386); p=0.223; I^2=90.53%, p(heter)<0.0001	Random effects model Publication bias: NR Adjustments: NR Limitations: Selection bias Difference in ages between groups may be significant Non–randomised studies in analysis Matching cases for controls to bariatric patients is difficult
Cohort studies						
Chlebowski et al., 2017[328] (Conference abstract) USA	Women's Health Initiative Cohort dates: 1993–1998 Prospective study Age at enrolment: 50–79 y Mean follow–up: 11.4 y	61,335 postmenopausal women BMI ≥18.5 3,061 cases	Weight loss ≥5% ≥15%	Breast cancer	HR=0.88 (0.78–0.98) HR=0.63 (0.45–0.90)	Multivariable Cox proportional hazards regression models Adjustments: NR Limitations: NR
Neuhouser et al., 2015[321]	Women's Health Initiative	67,142 postmenopausal women	Weight loss >5% Main effect	Breast cancer	HR=1.00 (0.89–1.12)	Cox regression model Adjustments¶

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
USA	Cohort dates: 1993–1998 Prospective cohort Age at enrolment: 50–79 y Median follow–up: 13 y	3,388 cases	BMI <25 BMI 25–<30 BMI 30–<35 BMI ≥35 Weight loss 2–5% Main effect BMI <25 BMI 25–<30 BMI 30–<35 BMI ≥35		HR=1.03 (0.81–1.32) HR=1.05 (0.87–1.27) HR=0.92 (0.74–1.14) HR=0.99 (0.77–1.27) HR=1.07 (0.95–1.21) HR=1.02 (0.80–1.31) HR= 1.17 (0.96–1.43) HR=1.01(0.79–1.29) HR=1.03 (0.76–1.40)	Limitations: Fewer race/ethnic minority participants Lack of data on tumour molecular characteristics Lack of data on longer term weight & body composition changes Inability to distinguish from unintentional weight loss

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BMI, body mass index; HR, hazard ratio; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; USA, United States of America; y, year/s.

¶Analyses were adjusted for age, race/ethnicity, education, parity, age at first birth, bilateral oophorectomy, family history of breast cancer, oestrogen alone use and duration, oestrogen and progesterone use and duration, smoking status, diabetes, alcohol consumption, baseline BMI group, and stratified by baseline age group, hormone therapy trial randomisation group, dietary trial randomisation group, hysterectomy status, calcium plus vitamin D trial randomisation group (time–dependent) and extended follow–up (time–dependent).

Table D.38 Alcohol consumption and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2015 Asia, Europe & North America	23 cohort studies	98,046 cases	Consumption of alcoholic drinks ***(total)*** (per 10 g ethanol/day)	Breast cancer	RR=1.07 (1.05–1.09); I^2=74%, p<0.001	Most studies adjusted at least for age No publication bias
	10 cohort studies	4,277 cases		Premenopausal breast cancer	RR=1.05 (1.02–1.08); I^2=0%, p(heter)=0.79	
	22 cohort studies	35,221 cases		Postmenopausal breast cancer	RR=1.09 (1.07–1.12); I^2=70.9%, p(heter)<0.001	
	23 cohort studies	44,780 cases	Alcohol from beer (per 10 g ethanol/day)	Breast cancer	RR=1.05 (1.03–1.08); I^2=0%, p=0.75	
	3 cohort studies	818 cases		Premenopausal breast cancer	RR=1.32 (1.06–1.64); I^2=0%, p=0.71	
	7 cohort studies	7,798 cases		Postmenopausal breast cancer	RR=1.06 (0.94–1.21); I^2=66%, p=0.007	
	24 cohort studies	66,318 cases	Alcohol from wine (per 10 g ethanol/day)	Breast cancer	RR=1.06 (1.02–1.10); I^2=60%, p=0.04	
	3 cohort studies	818 cases		Premenopausal breast cancer	RR=1.17 (0.79–1.73); I^2=74%, p=0.02	
	6 cohort studies	3,913 cases		Postmenopausal breast cancer	RR=1.12 (1.08–1.17); I^2=0%, p=0.96	
	23 cohort studies	43,574 cases	Alcohol from liquor (per 10 g ethanol/day)	Breast cancer	RR=1.04 (0.99–1.09); I^2=80%, p=0.002	
	3 cohort studies	818 cases		Premenopausal breast cancer	RR=1.10 (0.92–1.30) ;I^2=0%, p=0.92	
	7 cohort studies	7,798 cases		Postmenopausal breast cancer	RR= 1.05 (0.93–1.17); I^2=73%, p=0.001	
Chen et al., 2016[336] Studies published to 2015 Europe & North America	26 studies	21,149 breast cancer cases	Wine drinking Highest vs lowest	Breast cancer	RR=1.36 (1.20–1.54); p<0.001; I^2=67.0%, p(heter)<0.001	Random effects model No publication bias (p=0.151) Adjustments: Family history, body mass
	8 cohort studies 18 case–control studies	2,062 premenopausal cases		Premenopausal breast cancer	RR=1.79 (1.34–2.40); p=0.344	
				Postmenopausal breast cancer	RR=1.20 (0.94–1.53); p=0.027	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		7,396 postmenopausal cases	Per 1 g ethanol from wine/day	Breast cancer	RR=1.0059 (0.9670–1.0464); p=0.6156	index, total energy, other alcohol beverage, smoking, menopause, hormone therapy, pregnancy, education, physical activity Limitations: Majority of the cases were extracted from case–control studies All the studies included only covered the Whites, lacking the diversity of races Potential misclassification of wine ingestion dose
Jayasekara et al., 2016[337] Studies published to 2015 Europe & North America	16 studies 3 cohort studies 13 case–control studies	Age at baseline: >20 y Population characteristics: NR	Alcohol consumption Highest vs lowest	Breast cancer	RR=1.28 (1.07–1.52); I^2=73.5%, p(heter)= 0.000 RR=1.48 1.33–1.64; I^2=0%, p(heter)=0.434 RR=1.25 (0.99–1.57); I^2=73.9%, p(heter)<0.001	Random effects model No publication bias: p=0.62 for cohorts & p=0.98 for case–controls Limitations: Incompleteness of the literature search Heterogeneity between studies Confounding Misclassification of alcohol intake
Jung et al., 2016[339] Dates of	Pooling Project of Prospective Studies of Diet & Cancer	1,089,273 women 37,191 cases	Total alcohol consumption Non–drinker	Breast cancer ER+	RR=1 (referent)	Random–effects model Adjustments†

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
publication: NR Australia, Canada, Italy, Netherlands, Sweden & USA	20 prospective cohort studies Baseline age: 18–104 y Maximum follow–up: 6–18 y	21,624 ER+ cases 5,113 ER– cases 11–86% of women were drinkers	≥30 g/day		RR=1.35 (1.23–1.48); p–trend<0.001, p(heter)=0.13	Limitations: Baseline alcohol intake data may not incorporate possible diet changes during follow–up Hormone receptor status information was missing for 3–56% of cases across studies Could not distinguish breast cancers detected by symptoms from those diagnosed by mammography
			Non–drinker ≥30 g/day	ER–	RR=1 (referent) RR 1.28 (1.10–1.49); p–trend<0.001, p(heter)=0.55	
			Non–drinker ≥30 g/day	PR+	RR=1 (referent) RR=1.36 (1.21–1.54); p–trend<0.001, p(heter)=0.01	
			Non–drinker ≥30 g/day	PR–	RR=1 (referent) RR=1.30 (1.16–1.46); p–trend<0.001, p(heter)=0.86	
			Past use postmenopausal hormone therapy	Breast cancer	RR=1.10 (1.04–1.15)	
			Current use postmenopausal hormone therapy		RR=1.07 (1.02–1.13)	
Seitz et al., 2012[332] Studies published to 2011 Asia, Europe, North America, other	113 studies 39 cohort studies 74 case–control studies	44,552 cases (non–drinkers) 77,539 cases (light drinkers) 51% of studies from North America, 38% from Europe, 6% from Asia 10% from other regions or from more than one region	Light drinking ≤12.5g ethanol/day or ≤1 drink/day vs non–drinking	Breast cancer	RR=1.05 (1.02–1.08); I^2=59%, p(heter)=0.0002 RR=1.05 (1.02–1.09); I^2=46%, p(heter)=0.0013 RR=1.05 (1.00–1.10); I^2=64%, p(heter)=0.030	Random effects model Publication bias: NR Adjustments: 36% of estimates were adjusted for age, family history, parity, menopausal status, oral contraceptive/hormonal replacement therapy use) Limitations: NR
Bagnardi et al., 2012[338]	110 studies	41,995 cases in reference group	Light drinking ≤12.5 g ethanol/day	Breast cancer	RR=1.05 (1.02–1.08); p=0.0002	Random effects model

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Studies published to 2010 Asia, Europe, North America & other	39 cohort studies 71 case–control studies	72,902 cases in light drinking category	or ≤1drink per day vs no drinking			No publication bias Adjustments: NR Limitations: Heterogeneity across studies Could not investigate the role of different drinking patterns in modifying the effect of the total amount of alcohol consumed Possible interaction effect between alcohol consumption &tobacco smoking Possible existence of publication bias Under–reporting of alcohol consumption & misclassification

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; ER–, oestrogen receptor negative; ER+, oestrogen receptor positive; HR, hazard ratio; PR–, progesterone receptor negative; PR+, progesterone receptor positive; RR, relative risk or risk estimate; NR, not reported; p(heter), p–value for the measure of heterogeneity; p–trend; p–value for trend across tertiles; USA, United States of America; WCRF, World Cancer Research Fund; y, year/s.

†Adjusted for ethnicity (Caucasian, African American, Hispanic, Asian, others), education (< high school, high school,>high school), body mass index (<23, 23–<25, 25–<30, ≥30 kg/m^2), height (<1.60, 1.60–<1.65, 1.65–<1.70, 1.70–<1.75, ≥1.75 m), physical activity (low, medium, high), smoking status (never, past, current), age at menarche (<11, 11–12, 13–14, ≥15 years), joint effects of menopausal status and hormone therapy (premenopausal; perimenopausal; or uncertain; postmenopausal, never user of hormone therapy; postmenopausal, past user of hormone therapy; and postmenopausal, current user of hormone therapy), oral contraceptive use (never, ever), joint effects of parity and age at first birth (nulliparous, parity 1–2 and age at first birth <30 years, parity 1–2 and age at first birth >30 years, parity<3 and age at first birth <30 years and parity >3 and age at first birth <30 years), family history of breast cancer (yes, no), personal history of benign breast disease (yes, no) and total energy intake (continuous, kcal/day); age in years and year of questionnaire return were included as stratification variables.

Table D.39 Bras and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
So et al., 2015[345] Studies published to 2014 China, Europe & USA	6 case–control studies 5 case–control studies that adjusted for confounders 1 case–control study that did not adjust for confounders	1,484 cases 1,874 controls Hospital–based case–controls	Wearing a bra during sleep time vs not wearing	Breast cancer	OR=2.04 (1.65–2.52); I^2=none detected, p(heter)=0.44 OR=2.30 (1.79–2.96); I^2=none detected, p(heter)=0.81 OR=1.50 (1.01–2.22)	Fixed effect model Publication bias: NR Adjustments: varies across studies Limitations: Only 6 studies (out of 12 identified) reported data on wearing a bra while sleeping Inconsistent results among studies that did report numerical data Case–control studies prone to recall bias Poor adjustment for confounders across most studies
Case–control studies						
Chen et al., 2014[75] USA	Population–based case–control Study duration: 2000–2004 Age at enrolment: 55–74 y	Postmenopausal women 454 IDC cases 590 ILC cases 469 controls (general	Lifetime average hours/day wearing a bra ≤10 hours 10.1–11.5 hours 11.6–13.9 hours ≥14 hours ≤10 hours 10.1–11.5 hours	Postmenopausal IDC Postmenopausal ILC	 OR=1.00 (referent) OR=0.9 (0.6–1.3) OR=1.1(0.7–1.6) OR=0.9 (0.6–1.3); p=0.801 OR=1 (referent) OR=0.7 (0.5–1.0)	Polytomous logistic regression Adjustments: Age at the reference date (5–year categories) Reference year (continuous) & county Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Use of the Cancer Surveillance System & the region's population–based cancer registry participating in the Surveillance, Epidemiology and End Results program of the National Cancer Institute	population) Mostly non–Hispanic Caucasian	11.6–13.9 hours		OR=0.9 (0.7–1.4)	Recall bias and/or non–differential misclassification
			≥14 hours		OR=0.8 (0.6–1.2); p=0.609	
			Currently wearing a bra vs not wearing a bra	IDC	OR=1.0 (0.8–1.4)	
				ILC	OR=0.9 (0.7–1.1)	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; NR, not reported; United States of America, USA: y, years.

Table D.40 Coffee, tea, caffeine and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Lafranconi et al., 2018[347] Studies published to 2017 Denmark, France, Germany, Greece, Italy, Japan, Netherlands, Norway, Spain, Sweden, UK & USA	21 cohort studies	1,068,098 participants 36,597 cases Follow–up: 5–26 y	Coffee consumption Highest vs lowest intake	Breast cancer	RR=0.96 (0.93−1.00); I^2=7%, p(heter)=0.37	Random effects model† No publication bias (p>0.05) Limitations: No data on methods of preparation have been provided in the studies Possibility of recall bias & reverse causation
				Premenopausal breast cancer	RR=0.98 (0.89−1.07); I^2=0.0%, p(heter)=0.46	
				Postmenopausal breast cancer	RR=0.92 (0.88−0.98); I^2=0.0%, p(heter)=0.57	
			0 cup/d	Breast cancer	RR=1 (referent)	
			1 cup/d		RR=0.99 (0.98−1.00)	
			2 cups/d		RR=0.98 (0.96−0.99)	
			3 cups/d		RR=0.97 (0.94−0.99)	
			4 cups/d		RR=0.96 (0.93−0.99)	
			5 cups/d		RR=0.95 (0.91−0.98)	
			6 cups/d		RR=0.93 (0.89−0.98)	
			7 cups/d		RR=0.92 (0.88−0.98); p(heter)=0.58	
			0 cup/d	Postmenopausal breast cancer	RR=1 (referent)	
			1 cup/d		RR=0.97 (0.95–1.00)	
			2 cups/d		RR=0.95 (0.90−1.00)	
			3 cups/d		RR=0.92 (0.86−1.00)	
			4 cups/d		RR=0.90 (0.82−0.99)	
			5 cups/d		RR=0.88 (0.78−0.99)	
			6 cups/d		RR=0.85 (0.74−0.99)	
			7 cups/d		RR=0.83 (0.70−0.99); I^2=39.6%, p(heter)=0.14	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Grosso et al., 2017[349] Studies published to 2016 Countries: NR	9 prospective case–control studies Follow–up: NR	15,775 cases	Caffeine Highest vs lowest intake	Breast cancer	RR=0.99 (0.94–1.04); I^2=0%	Model: NR Adjustments: NR Publication bias: NR Limitations: Lack of consistency among studies in exposure dose Most of the evidence referred to 'the highest compared with the lowest' category of exposure Lack of information on concerns relative to genetic polymorphisms. Lack of consistent information on how the coffee was processed, prepared or consumed
WCRF, 2017[10] Studies published to 2015 Asia, Europe & North America	14 cohort studies	25,335 cases	Coffee per 1 cup/d	Breast cancer	RR=0.99 (0.98–1.00); p=borderline sig; I^2=3.1%, p(heter)=0.41	Model: NR Adjustments: NR No publication bias: Egger tests p=NS Limitations: NR
	7 studies			Premenopausal breast cancer	RR=1.00 (0.97–1.03); p=NS; I^2=44.4%, p(heter)=0.095	
	7 studies			Postmenopausal breast cancer	RR=0.98 (0.95–1.00); p=borderline sig; I^2=45.6%, p(heter)=0.09	
	14 cohort studies	16,808 cases	Tea per 1 cup/d	Breast cancer	RR=1.03 (0.98–1.09); p=NS; I^2=71.6%, p(heter)=0.003	
	6 studies					
	4 studies			Premenopausal breast cancer	RR=1.00 (0.96–1.05); I^2=0%, p(heter)=0.46	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	5 studies			Postmenopausal breast cancer	RR=1.05 (0.99–1.11); p=NS; I^2=68.2%, p(heter)=0.01	
	6 studies		Green tea per 1 cup/d	Breast cancer	RR=0.99 (0.97–1.02); p=NS; I^2=0%, p(heter)=0.56	
Jiang et al., 2013[354] Studies published to 2012 Australia, Canada, Denmark, Finland, France, Greece, Israel, Italy, Japan, Netherlands, Norway, Poland, Sweden, Switzerland, UK & USA	37 case–control & cohort studies 20 studies on coffee	41,805 cases Age: all ages	Coffee intake Highest vs lowest intake per 2 cups/d	Breast cancer	RR=0.97 (0.92–1.01); I^2=14.2%, p(heter)=0.09 RR=0.98 (0.96–1.00); p=0.053	Fixed effects model (I^2<50.0%)‡ No publication bias: Egger test p=NS Limitations: Only 3 studies included for *BRCA1* mutation carriers Misclassification of coffee consumption in original studies Confounder adjustment varied between studies included Potential publication bias
Li et al., 2013[355] Studies published to 2012 Denmark, Finland, France, Germany, Japan, Israel, Italy, Netherlands, Norway, Sweden & USA	26 studies 10 case–control studies 16 cohort studies	863,067 participants 49,497 incident cases	Coffee intake Highest vs lowest intake	Breast cancer	Pooled RR=0.96 (0.93–1.00); I^2=0%, p(heter)=0.769	Random effects model Adjustments: NR No publication bias (p>0.05) Limitations: Misclassification of intake due to self–reported data Residual inherent confounding Most studies conducted in Europe, USA & Asia
				ER–	Pooled RR=0.81 (0.67–0.97); I^2=26.1%, p(heter)=0.211	
				ER+	Pooled RR=1.01 (95% CI 0.93–1.09); I^2=0%, p(heter)=0.909	
			per 2 cups/d	Breast cancer	Pooled RR=0.98 (0.97–1.00); I^2=0%, p(heter)=0.795	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						Potential publication bias

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; *BRCA1*, *BRCA1* gene mutation; d, day; ER, oestrogen receptor; NR, not reported; NS, not significant; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; sig., significant; WCRF, World Cancer Research Fund; UK, United Kingdom; USA, United States of America; y, year/s.

†Adjustments to individual risk estimates; smoking, alcohol intake, physical activity and education.

‡Adjustments to individual risk estimates; smoking and/or alcohol, body mass index, energy intake, physical activity, oral contraceptive use, postmenopausal hormone therapy, family history of breast cancer and history of benign breast disease.

§Adjusted for menopausal status at baseline, smoking status, duration of education, body mass index, physical activity level, alcohol consumption (g/day), number of children, age at first birth, use of hormone therapy, and maternal history of breast cancer.

Table D.41 Diet—calcium and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2013 Asia, Europe &North America	5 cohort studies	17,483 cases	Dietary calcium intake per 300 mg/day	Breast cancer	RR=0.97 (0.94–1.00); p=NS; I^2=22.0%, p(heter)=0.275	Adjustments: Age, alcohol intake (except for Singaporean study), BMI & reproductive factors No publication bias (p=0.061)
	5 cohort studies	2,980 cases		Premenopausal breast cancer	RR=0.87 (0.76–0.95); I^2=66.9%, p(heter)=0.017	Publication bias (p=0.013)
	6 cohort studies	10,137 cases		Postmenopausal breast cancer	RR=0.96 (0.94–0.99); I^2=0.0%, p(heter)=0.675	No publication bias (p=0.790)
Hidayat et al., 2016[356] Studies published to 2016 Europe, Singapore & USA	11 prospective cohort studies	872,895 women 26,606 cases Follow–up: 7–25 y Ethnicity: European North American & Singaporean Chinese	Calcium intake Highest vs lowest intake	Breast cancer		Random effects model Adjustments†
			Total calcium		RR=0.92(0.85–0.99); I^2=44.2%, p(heter)=0.026	Publication bias (p<0.05)
			Dietary calcium		RR=0.93 (0.84–1.03); I^2=46.1%, p(heter)=0.063	Limitations: Publication bias
			Supplemental calcium		RR=0.90 (0.84–0.97); I^2=43.9%, p(heter)=0.051	Difficult to assess effects of calcium intake due to its relationship with vitamin D
			per 300 mg/d		RR=0.98 (0.92–1.03); I^2=0, p(heter)=0.426	Moderate heterogeneity
			Dietary calcium		RR=0.98 (0.96–0.99); I^2=30.8%, p(heter)=0.123	Residual confounding factors
			Supplemental calcium		RR=0.97 (0.95–0.98); I^2=18.7%, p(heter)=0.277	
			Highest vs lowest	Premenopausal breast cancer	RR=0.99 (0.97–1.01); I^2=12.9%, p(heter)=0.328	
					RR=0.75 (0.59–0.96); I^2=55.2%, p(heter)=0.048	
				Postmenopausal breast cancer	RR=0.94 (0.87–1.01); I^2=7.3%, p(heter)=0.373	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; NS, not significant; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; WCRF, World Cancer Research Fund; USA, United States of America; y, year/s.

†Studies individually adjusted for a wide range of potential confounding factors, such as age, BMI, family history of breast cancer, hormone therapy use and total energy intake.

Table D.42 Diet–dairy and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2015 Asia, Europe & North America	6 studies	7,766 women	Dairy intake (per 200 g)	Breast cancer	RR=0.96 (0.94–0.99); I^2=0%, p=0.75	Publication bias (Egger's test=0.51)
	7 cohort studies	2,862 cases		Premenopausal breast cancer	RR=0.95 (0.92–0.99), I^2=59%, p(heter)=0.59	Publication bias (Egger's test=0.66)
	8 cohort studies	8,145 women		Postmenopausal breast cancer	RR=0.97 (0.93–1.01); I^2=39%, p=0.12	Publication bias (Egger's test=0.74) All studies adjusted for multiple confounders, including age, reproductive factors, BMI, & alcohol consumption
Wu et al., 2016[360] Studies published to 2015 Asia, Europe & North America	46 studies	Follow–up: 3.9–65 y				Random effects model All studies adjusted at least for age
	5 cohort studies 8 cohort studies	586,726 women 16,664 cases	Skim milk per 200 g High vs low intake	Breast cancer	RR=0.96 (0.92–1.00); I^2=11.9% RR=0.93 (0.85–1.00); I^2=40.1%	Publication bias (Begg's test (p=0.266–1.000), Egger's test (p=0.292–0.77)) Limitations: Confounders Most studies used a single FFQ & assumed diet did not change over years of follow–up
	11 cohort studies 18 cohort studies	775,778 women 19,747 cases	Total milk per 200 g High vs low intake		RR=0.97 (0.93–1.01) I^2=36.4% RR=0.92 (0.84–1.02); I^2=53.5%	
	5 cohort studies 9 cohort studies	554,775 women 13,781 cases	Whole milk per 200 g High vs low intake		RR=1.02 (0.92–1.13); I^2=32.8% RR=0.99 (0.87–1.12); I^2=37.4%	
	3 cohort studies	225,057 women 6,793 cases	Yogurt per 200 g		RR=0.87 (0.72–1.06); I^2=0.0%	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	7 cohort studies		High vs low intake		RR=0.90 (0.82–1.00); I^2=0.0%	Different studies used different units to measure food
Zang et al., 2015[358] Studies published to 2014 Japan, Europe & USA	22 prospective cohort studies Most cohorts are population–based (3 studies conducted in nurses)	1,566,940 women 37,925 breast cancer cases Median follow–up: 10 y	Dairy intake High (>600 g/d) vs low intake (<400 g/d) Modest intake (400–600 g/d) vs low intake (<400 g/d) No dairy 250 g/d 500 g/d 750 g/d 1,000 g/d	Breast cancer	RR=0.90 (0.83–0.98); I^2=32.2%, p(heter)=0.111 RR=0.94 (0.91–0.98); p=NS; I^2=0%, p=0.975 RR=1 (referent) RR=0.97 (0.95–0.99) RR=0.94 (0.89–0.99) RR=0.91 (0.85–0.98) RR=0.88 (0.80–0.98); p–trend=0.016	Random effects model No significant publication bias (Egger's test) Most studies adjusted for age, BMI, family history of breast cancer, reproductive factors, hormone therapy & total energy intake Limitations: Residual or unknown confounders Possible misclassification of dairy consumption due to self–report methods Possible misreporting of consumption or changes in consumption during follow–up Heterogeneity due to methodological differences between studies Case–control studies may provide a lower level of evidence
	5 case–control studies (from Asia only)	33,372 women 7,418 cases	High (>600 g/d) vs low intake (<400g/d) No dairy 250 g/d 500 g/d 750 g/d 1,000 g/d		OR=0.74(0.62–0.88); I^2=62.5%, p(heter)=0.014 OR=1 (referent) OR=0.85 (0.76–0.94) OR=0.71 (0.58–0.88) OR=0.60 (0.44–0.83) OR=0.51 (0.33–0.78); p–trend=0.002	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; FFQ, food frequency questionnaire; g, grams; g/d, grams per day; NR, not reported; NS=not significant; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; RR, relative risk or risk estimate; y, year/s.

†HR values adjusted for age, area, tobacco smoking status, drinking status, family history of breast cancer, age at menarche, age at first birth, parity, energy intake, hormone therapy, daily walking, education and BMI.

Table D.43 Diet—dietary fibre and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Chen et al., 2016[363] Studies published to March 2016 Canada, China, Europe, Italy, France, Germany, Malaysia, Netherlands, Sweden, Switzerland, UK, USA	24 studies 20 cohort studies 4 case–control studies	3,662,421 participants 51,939 cases	Dietary fibre per 10 g/d	Breast cancer	RR=0.88 (0.83–0.93); I^2=59.1%, p(heter)=0 RR=0.96 (0.92–0.98); p=0.002; p(heter)=0.43	Random effects model Adjustments: Smoking, age, BMI, total energy intake, family history of cancer.
	3 studies 10 studies		Overall intake	Premenopausal breast cancer Postmenopausal breast cancer	RR=0.78 (0.62–0.94); I^2=43.2%, p(heter)=0.172 RR=0.88 (0.79–0.97); I^2=52.1%, p(heter)=0.027	No publication bias (p>0.05)
WCRF, 2017[10] Studies published to 2015 Asia, Europe & North America	16 cohort studies	35,910 cases	Dietary fibre intake per 10 g/d	Breast cancer	RR=0.95 (0.93–0.98); I^2=0.0, p(heter)=0.81	Adjustments: All studies adjusted for at least age & most studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI & alcohol consumption. No publication bias (p=0.74)
	4 studies	2,013 cases		Premenopausal breast cancer	RR=0.91 (0.75–1.10); I^2=43.0%, p(heter)=0.15	
	11 studies	18,591 cases		Postmenopausal breast cancer	RR=0.95 (0.92–0.99); I^2=0.0, p(heter)=0.73	
	5 studies	14,976 cases	Soluble fibre intake per 10 g/d	Breast cancer	RR=0.74 (0.63–0.88); I^2=0%, p(heter)=0.76	No publication bias (p=0.29)
	6 studies	14,976 cases	Insoluble fibre intake Per 10 g/d		RR=0.97 (0.87–1.07); I^2=30.0%, p(heter)=0.21	No publication bias (p=0.97)
Cohort studies						
Narita et al., 2017[364] Japan	JPHC study cohort Data collected:	44,444 women 180 cases 164 cases	Total fibre Q1 (7.9 g/d) Q2 (11.3 g/d)	Breast cancer	 HR=1 (referent) HR=0.89 (0.70–1.13)	Multivariable Cox proportional hazards model†

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	1995 & 1998 Prospective Age at enrolment: 45–74 y Mean follow–up: 14 y	170 cases	Q3 (14.1 g/d)		HR=0.83 (0.63–1.10)	Limitations: Bias from self–reported questionnaire FFQ method may attenuate HRs compared to a 24–hour recall method health–conscious behaviours due to breast screening
		167 cases	Q4 (18.1 g/d)		HR=0.78 (0.55–1.09); p–trend=0.15	
		52 cases	Subtertile 3 (highest)		HR=0.63 (0.40–0.98)	
		52 cases	Subtertile 2 (middle)		HR=0.68 (0.45–1.04)	
		63 cases	Subtertile 1 (lowest)		HR=0.93 (0.64–1.34); p–trend=0.04	
		52 cases	Q1 (8.3 g/d)	Premenopausal breast cancer	HR=1 (referent)	
		54 cases	Q2 (11.6 g/d)		HR=1.09 (0.71–1.67)	
		48 cases	Q3 (14.3 g/)		HR=0.91 (0.54–1.53)	
		28 cases	Q4 (18.3 g/d)		HR=0.62 (0.32–1.20); p–trend=0.11	
		116 cases	Q1 (8.0 g/d)	Postmenopausal breast cancer	HR=1 (referent)	
		104 cases	Q2 (11.4 g/d)		HR=0.80 (0.59–1.07)	
		114 cases	Q3 (14.2 g/d)		HR=0.78 (0.56–1.08)	
		131 cases	Q4 (18.1 g/d)		HR=0.82 (0.56–1.22); p–trend=0.48	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; FFQ, food frequency questionnaire; g/d, grams per day; HR, hazard ratio; JPHC, Japan Public Health Centre; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; Q[1–4/5], quartile[1–4]/quintile[1–5]; RR, relative risk or risk estimate; WCRF, World Cancer Research Fund; y, year/s.

†Age, areas of public health centres, BMI at 5–year follow–up (<18.5, 18.5–23.9, >23.9), age at menarche (≤13, 14, 15, ≥16 years), age at first birth (<26, ≥26 years), parity (nulliparous, 1–2, 3, ≥4), age at menopause (pre–menopause, ≤44, 45–54, ≥55 years), use of exogenous female hormones (never, ever), smoking status (never: non–smokers, ever: past or current smokers), leisure–time physical activity (≤3 days/month, 1–2 days/week, ≥3 days/week), alcohol intake (regular drinker: >150 g of ethanol/week, non–regular drinker: ≤150 g of ethanol/week), total energy intake, and total energy adjusted intakes of fat, isoflavones, carbohydrates, and vitamin D.

Table D.44 Diet—fruit and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2015 Asia, Europe, North America	11 cohort studies 3 studies 8 studies	25,059 cases 1,635 cases 10,891 cases	Fruit intake per 200 g/day	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=0.94 (0.90–0.98); I^2=31.4%, p(heter)=0.14 RR=1.00 (0.81–1.23); I^2=64.1%, p(heter)=0.06 RR=0.92 (0.87–0.98); I^2=11.3%, p(heter)=0.34	Publication bias (Egger's test p=0.07) Adjustments¶
Fabiani et al., 2016[370] Studies published to 2015 Brazil, China, Italy, Mexico, multinational & USA	8 studies 3 cohort studies 5 case–control studies	Study sample: NR	Apple intake Highest vs lowest	Breast cancer	RR=0.89 (0.79–1.00); p=0.047; I^2=68.7%, p(heter)=0.002, RR=0.97 (0.94–1.01); p=0.192; I^2=0%, p(heter)=0.631 OR=0.79 (0.73–0.87); p<0.001; I^2=0.88%, p(heter)=0.401	Random effects model Adjustments: NR No publication bias (Egger's & Begg) Limitations: Heterogeneity Confounding effect Wide variations in dietary assessments of apple intake. Low number of data available
Cohort studies						
Emaus et al., 2016[365] Europe	EPIC cohort Recruitment: 1992–2000 Enrolment age:	335,054 women without a prevalent cancer diagnosis (excluding non–melanoma skin cancer)	Fruit intake (citrus, apples, pears, grapes, stone fruit, berries, bananas, kiwi fruit). Juice was excluded Q1, 36–86 g/day	Breast cancer	HR=1.00 (referent)	Cox proportional hazard models Adjustments† Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	25–70 y Median follow–up: 11.5 y	10,197 cases Mean age: 50.8 y	Q2, 20–153 g/day Q3, 189–230 g/day Q4, 269–323 g/day Q5, 399–565 g/day		HR=1.01 (0.95–1.08) HR=0.96 (0.90–1.02) HR=1.00 (0.94–1.07) HR=1.01 (0.94–1.09); p–trend=0.70	Fruit intake was assessed only once & could have changed during follow–up
Farvid et al., 2016[366] USA	Nurses' Health Study II cohort Prospective 1991–2013 Age at baseline: 27–44 y Follow–up: 22 y	90,476 premenopausal women 3,235 cases Study sample: Nurses & predominantly white women	Fruit intake Highest vs lowest intake during adolescence	Invasive breast cancer Premenopausal breast cancer Postmenopausal breast cancer	HR=0.75 (0.62–0.90); p–trend=0.01 HR=0.69 (0.52–0.90); p–trend=0.02 HR=0.80 (0.60–1.05); p–trend=0.17	Multivariable adjusted models Adjustments‡ Limitations: Sample were nurses, who were also predominantly white women Adolescent diet might be misclassified due to recall bias Residual confounding, where women who eat a lot of fruit & vegetables have healthier lifestyles Possibility of type I errors due to multiple comparisons
			Highest vs lowest intake during early adulthood	Invasive breast cancer Premenopausal breast cancer Postmenopausal breast cancer	HR=0.96 (0.85–1.09); p–trend=0.46 HR=0.99 (0.84–1.17); p–trend=0.94 HR=0.91 (0.74–1.11); p–trend=0.46	
Pooled analysis						
Farvid et al., 2018[371] USA	Nurses' Health Study dates: 1980−2012 Dietary questionnaire completed in	182,145 women 10,911 cases	Total fruit consumption excluding juices§ Dose response (per 2 servings/day)	Invasive breast cancer All subtypes ER+ –ER–	 HR=0.94 (0.88−1.00) HR=0.94 (0.88−1.01) HR=0.90 (0.79−1.03)	Cox proportional hazards regression model Adjustments† Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	1980, 1984, 1986 & every 4 years thereafter Nurses' Health Study II dates: 1991–2013 Dietary questionnaire completed every 4 years from 1991 onwards Prospective study Age at baseline: 27–59 y Mean follow–up: 23.7 y			ER+PR+	HR=0.96 (0.89–1.04)	Possibility of type I error due to multiple comparisons Note that there was a significantly lower risk of breast cancer associated with 8–12 years of fruit and vegetable intake combined There was a more strongly associated decreased breast cancer risk with 12–16 years of total fruit intake alone prior to breast cancer diagnosis
				ER+ PR–	HR=0.89 (0.75–1.04)	
				ER–PR–	HR=0.87 (0.75–1.01)	
				HER2+	HR=0.58 (0.40–0.82)	
				Luminal A	HR=0.90 (0.80–1.02)	
				Luminal B	HR=1.02 (0.86–1.22)	
				Basal–like	HR=0.88 (0.64–1.20)	
			≤4 servings/week	Invasive breast cancer	HR=1 (referent)	
			>4 to 6 servings/week		HR=1.01 (0.94–1.08)	
			>6 servings/week to 1.5 servings/day		HR=0.95 (0.90–1.01)	
			>1.5 to 2.5 servings/day		HR=0.99 (0.93–1.05)	
			>2.5 servings/day		HR=0.91 (0.84–0.99); p–trend=0.07	
			Lagged analyses			
			0–4 y lag			
			≤4 servings/week		HR=1 (referent)	
			>4 to 6 servings/week		HR=0.99 (0.92–1.06)	
			>6 servings/week to 1.5 servings/day		HR=0.98 (0.92–1.04)	
			>1.5 to 2.5 servings/day		HR=0.97 (0.91–1.03)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			>2.5 servings/day		HR=0.93 (0.86−1.01); p–trend=0.08	
			4−8 y lag			
			≤4 servings/week		HR=1 (referent)	
			>4 to 6 servings/week		HR=0.99 (0.92−1.07)	
			>6 servings/week to 1.5 servings/day		0.99 (0.93−1.05)	
			>1.5 to 2.5 servings/day		1.00 (0.94−1.07)	
			>2.5 servings/day		HR=0.97 (0.90−1.06); p–trend=0.66	
			8−12 y lag			
			≤4 servings/week		HR=1 (referent)	
			>4 to 6 servings/week		HR=0.95 (0.88−1.03)	
			>6 servings/week to 1.5 servings/day		HR=0.92 (0.86−0.99)	
			>1.5 to 2.5 servings/day		HR=0.97 (0.90−1.04)	
			>2.5 servings/day		HR=0.96 (0.88−1.04); p–trend=0.67	
			12−16 y lag			
			≤4 servings/week		HR=1 (referent)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			>4 to 6 servings/week		HR=0.99 (0.90−1.08)	
			>6 servings/week to 1.5 servings/day		HR=0.92 (0.85−0.99)	
			>1.5 to 2.5 servings/day		HR=0.93 (0.86−1.01)	
			>2.5 servings/day		HR=0.91 (0.83−1.00); p–trend=0.05	
			16−20 y lag			
			≤4 servings/week		HR=1 (referent)	
			>4 to 6 servings/week		HR=1.03 (0.93−1.13)	
			>6 servings/week to 1.5 servings/day		HR=0.92 (0.84−1.00)	
			>1.5 to 2.5 servings/day		HR=0.93 (0.85−1.02)	
			>2.5 servings/day		HR=0.91 (0.82−1.02); p–trend=0.05	
			Total fruit & vegetable intake (lagged analyses)			
			0−4 y lag			
			≤2.5 servings/day		HR=1 (referent)	
			>2.5 to 3.5 servings/day		HR=0.95 (0.89−1.02)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			>3.5 to 4.5 servings/day		HR=0.98 (0.91–1.05)	
			>4.5 to 5.5 servings/day		HR=0.95 (0.88–1.02)	
			>5.5 servings/day		HR=0.94 (0.87–1.00); p–trend=0.10	
			4–8 y lag			
			≤2.5 servings/day		HR=1 (referent)	
			>2.5 to 3.5 servings/day		HR=0.98 (0.92–1.05)	
			>3.5 to 4.5 servings/day		HR=0.91 (0.85–0.98)	
			>4.5 to 5.5 servings/day		HR=0.97 (0.89–1.04)	
			>5.5 servings/day		HR=0.99 (0.92–1.06); p–trend=0.94	
			8–12 y lag			
			≤2.5 servings/day		HR=1 (referent)	
			>2.5 to 3.5 servings/day		HR=0.90 (0.84–0.97)	
			>3.5 to 4.5 servings/day		HR=0.89 (0.83–0.96)	
			>4.5 to 5.5 servings/day		HR=0.92 (0.85–1.00)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			>5.5 servings/day		HR=0.90 (0.83–0.97); p–trend=0.05	
			12–16 y lag			
			≤2.5 servings/day		HR=1 (referent)	
			>2.5 to 3.5 servings/day		HR=0.95 (0.88–1.03)	
			>3.5 to 4.5 servings/day		HR=0.94 (0.86–1.02)	
			>4.5 to 5.5 servings/day		HR=0.93 (0.85–1.02)	
			>5.5 servings/day		HR=0.89 (0.82–0.97); p–trend=0.01	
			16–20 y lag			
			≤2.5 servings/day		HR=1 (referent)	
			>2.5 to 3.5 servings/day		HR= 0.97 (0.89–1.06)	
			>3.5 to 4.5 servings/day		HR=0.94 (0.86–1.03)	
			>4.5 to 5.5 servings/day		HR=0.94 (0.85–1.04)	
			>5.5 servings/day		HR=0.89 (0.80–0.98); p–trend=0.02	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NR, not reported; OR, odds ratio; PR, progesterone receptor; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend across quintiles; RR, risk estimate or relative risk; Q[1–5], quintiles [1–5] RR, relative risk or risk estimate; USA, United States of America y, year/s.

¶All studies adjusted for age and most studies also adjusted for parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

‡Stratified by age in months at state of follow–up and calendar year of current questionnaire cycle, smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day), race (white/non–white), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25, parity ≤2 and age at first birth 25–<30, parity ≤2 and age at first birth ≥30, parity 3–4 and age at first birth <25, parity 3–4 and age at first birth 25–<30, parity 3–4 and age at first birth ≥30, parity ≥5 and age at first birth <25, parity ≥5 and age at first birth ≥25), height (<157, 157–<165, 165–<173, ≥173 cm), BMI at age 18 (<18.5, 18.5–<22.5, 22.5–<25, 25.0–<30, ≥30.0), weight change since age 18 (continuous, missing indicator), age at menarche (<12, 12, 13, ≥14), family history of breast cancer (yes, no), history of benign breast disease (yes, no), oral contraceptive use (never, past, current), adolescent alcohol intake (non–drinker, <5, ≥5 g/day), adult alcohol intake (nonS–drinker, <5, 5–<15, ≥15 g/day), adolescent energy intake (fifth). In postmenopausal women, additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users), age at menopause (<45, 45–46, 47–48, 49–50, 51–52, ≥53). Among all women, additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status) and age at menopause (premenopausal, unknown menopause, <45, 45–46 years, 47–48, 49–50, 51–52, ≥53).

†Stratified on cohort, calendar year, and age in months and adjusted for family history of breast cancer (yes, no), history of benign breast disease (yes, no), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, and ≥1.75 meters), BMI at age 18 years (<18.5, 18.5 to <20, 20 to <22.5, 22.5 to <25, 25.0 to <30, ≥30.0 kg/m2), weight change since age 18 (continuous), smoking (never, past, current 1 to 14/day, current 15 to 24/day, current ≥25/day), physical activity (quintiles of MET–h per week, missing), oral contraceptive use (never, < 2 years, 2 to <5 years, 5 to <10 years, ≥10 years), alcohol intake (g/day, quintiles), total energy intake (kcal/day, quintiles), age at menarche (<12, 12, 13, 14, >14 years), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity≤2 and age at first birth 25 to <30 years, parity ≤2 and age at first birth ≥30 years, parity 3 to 4 and age at first birth <25 years, parity 3 to 4 and age at first birth 25 to <30 years, parity 3 to 4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), and menopausal status, age at menopause, and postmenopausal hormone use (premenopausal, postmenopausal and age at menopause<50 years and never postmenopausal hormone use, postmenopausal and age at menopause<50 years and past postmenopausal hormone use, postmenopausal and age at menopause<50 years and current postmenopausal hormone use, postmenopausal and age at menopause≥50 years and never postmenopausal hormone use, postmenopausal and age at menopause≥50 years and past postmenopausal hormone use, postmenopausal and age at menopause≥50 years and current postmenopausal hormone use, missing).

§Cumulative average

Table D.45 Diet—vegetables and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2015 Asia, Europe & North America	12 studies	24,756 cases	Non–starchy vegetables consumption per 200 g/d	Breast cancer	RR=0.98 (0.93–1.02); I^2=27%, p(heter)=0.18	No publication bias (p=0.75) Publication bias (p=0.004) Adjustments: All studies adjusted for at least age Most studies also adjusted for parity, age at menarche, age at menopause, physical activity, BMI & alcohol consumption
	3 studies	1,635 cases		Premenopausal breast cancer	RR=0.96 (0.83–1.11); I^2=0%, p(heter)=0.43	
	8 studies	10,891 cases		Postmenopausal breast cancer	RR=1.03 (0.97–1.09); I^2=0%, p(heter)=0.45	
Pooled analysis						
Jung et al., 2013[369] Europe, Japan, North America Studies commenced 1980–1995 and ended 1986–2008	Pooling Project of Prospective Studies of Diet & Cancer 20 cohort studies	993,466 women 19,869 ER+ 4,821 ER– Follow–up: 11–20 y	Vegetable intake Highest vs lowest intake	Breast cancer	RR=0.99 (0.95–1.04)	Random–effects model Adjustments§ Limitations: Between–studies variation in the dietary assessment methods & confounding Single measurement of fruit & vegetable consumption at baseline Misclassification in estimated fruit and vegetable intake
				ER+	RR=1.04 (0.97–1.11)	
				ER–	RR=0.82 (0.74–0.90)	
				PR+	RR=1.02 (0.96–1.10)	
				PR–	RR=0.94 (0.84–1.03)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Emaus et al., 2016[365] Denmark, France, Germany, Greece Italy, Norway, Spain, Sweden, Netherland, UK	EPIC Prospective Cohort dates: 1992–2000 Follow–up: median 11.5 y Age at baseline: 25–70 y	335,054 female participants 10,197 incident cases Cohort: without a prevalent cancer diagnosis from 10 European countries	Total vegetables Intake Q1(57–92 g/d) Q5 (352–489 g/d)	Breast cancer	HR=1.00 (referent) HR=0.87 (0.80–0.94)	Cox proportional hazards models Adjustments¶ Limitations: Misclassification due to single exposure measurement Risk factor information was only available at recruitment Lack of data on breast cancer subtypes
Farvid et al., 2016[366] USA	Nurses' Health Study II Prospective study Cohort dates: 1991 Age at baseline: 27–44 y Follow–up: 22 y	90,476 premenopausal women 3,235 cases Women with implausible total energy intake were excluded (<600 or >3500 kcal/d) Adolescent dietary information for 1,347 cases	Fruit & vegetable intake Highest vs lowest intake during adolescence Highest vs lowest intake during early adulthood	Breast cancer	HR=0.86 (0.73–1.01) HR=0.96 (0.86–1.07)	Cox proportional hazards regression model Adjustments: Adjusted for age in months at state of follow–up & calendar year of current questionnaire cycle Limitations: Participants were restricted to nurses & predominantly white women Adolescent diet might be misclassified Residual confounding is possible
Pooled analysis						
Farvid et al., 2018[371]	Nurses' Health	182,145 women	Total vegetable	Invasive breast		Cox proportional hazards

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			consumption excluding potatoes§	cancer		regression model
USA	Study dates: 1980–2012	10,911 cases		All subtypes	HR=0.95 (0.91–0.99)	Adjustments†
	Dietary questionnaire completed in 1980, 1984, 1986 & every 4 years thereafter			ER+	HR=0.96 (0.91–1.00)	Limitations:
				ER–	HR=0.85 (0.77–0.93)	Possibility of type I error due to multiple comparisons
				ER+PR+	HR=0.95 (0.90–1.00)	
			Dose response (per 2 servings/day)	ER+ PR–	HR=0.99 (0.89–1.11)	
				ER–PR–	HR=0.85 (0.77–0.94)	Note that there was a lower risk of breast cancer associated with 8–12 years of fruit and vegetable intake combined
	Nurses' Health Study II dates: 1991–2013			HER2+	HR=0.77 (0.61–0.99)	
				Luminal A	HR=0.93 (0.85–1.01)	
	Dietary questionnaire completed every 4 years from 1991 onwards			Luminal B	HR=0.95 (0.85–1.07)	There was an association for breast cancer risk with 12–16 years of total vegetable intake alone prior to breast cancer diagnosis
				Basal–like	HR=0.85 (0.68–1.06)	
			≤1.5 servings/day	Invasive breast cancer	HR=1 (referent)	
			>1.5 to 2.5 servings/day		HR=0.93 (0.88–0.99)	
	Prospective study		>2.5 to 3.5 servings/ day		HR=0.94 (0.88–1.00)	
	Age at baseline: 27–59 y		>3.5 to 4.5 servings/day		HR=0.89 (0.82–0.96)	
	Mean follow–up: 23.7 y		>4.5 servings/day		HR=0.91 (0.84–1.00); p–trend=0.03	
			(lagged analyses)			
			0–4 y lag			
			≤1.5 servings/day		HR=1 (referent)	
			>1.5 to 2.5 servings/day		HR=0.97 (0.91–1.03)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			>2.5 to 3.5 servings/ day		0.95 (0.89–1.01)	
			>3.5 to 4.5 servings/day		0.95 (0.87–1.02)	
			>4.5 servings/day		HR=0.94 (0.86–1.02); p–trend=0.11	
			4–8 y lag			
			≤1.5 servings/day		HR=1 (referent)	
			>1.5 to 2.5 servings/day		0.95 (0.89–1.02)	
			>2.5 to 3.5 servings/ day		0.89 (0.83–0.96)	
			>3.5 to 4.5 servings/day		0.95 (0.88–1.03)	
			>4.5 servings/day		HR=0.95 (0.87–1.03); p–trend=0.36	
			8–12 y lag			
			≤1.5 servings/day		HR=1 (referent)	
			>1.5 to 2.5 servings/day		HR=0.90 (0.84–0.96)	
			>2.5 to 3.5 servings/ day		HR=0.87 (0.81–0.94)	
			>3.5 to 4.5 servings/day		HR=0.91 (0.83–0.99)	
			>4.5 servings/day		HR=0.90 (0.82–0.98); p–trend=0.09	
			12–16 y lag			

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			≤1.5 servings/day		HR=1 (referent)	
			>1.5 to 2.5 servings/day		HR=0.93 (0.86–1.00)	
			>2.5 to 3.5 servings/ day		HR=0.92 (0.84–0.99)	
			>3.5 to 4.5 servings/day		HR=0.91 (0.83–1.00)	
			>4.5 servings/day		HR=0.88 (0.80–0.97); p–trend=0.03	
			16–20 y lag			
			≤1.5 servings/day		HR=1 (referent)	
			>1.5 to 2.5 servings/day		HR=0.97 (0.89–1.06)	
			>2.5 to 3.5 servings/ day		HR=0.98 (0.89–1.07)	
			>3.5 to 4.5 servings/day		HR=0.93 (0.84–1.04)	
			>4.5 servings/day		HR=0.90 (0.80–1.02); p–trend=0.08	
			Total fruit & vegetable intake (lagged analyses)			
			0–4 y lag			
			≤2.5 servings/day		HR=1 (referent)	
			>2.5 to 3.5 servings/ day		HR=0.95 (0.89–1.02)	
			>3.5 to		HR=0.98 (0.91–1.05)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			4.5 servings/day			
			>4.5 to 5.5 servings/day		HR=0.95 (0.88–1.02)	
			>5.5 servings/day		HR=0.94 (0.87–1.00); p–trend=0.10	
			4–8 y lag			
			≤2.5 servings/day		HR=1 (referent)	
			>2.5 to 3.5 servings/ day		HR=0.98 (0.92–1.05)	
			>3.5 to 4.5 servings/day		HR=0.91 (0.85–0.98)	
			>4.5 to 5.5 servings/day		HR=0.97 (0.89–1.04)	
			>5.5 servings/day		HR=0.99 (0.92–1.06); p–trend=0.94	
			8–12 y lag		HR=0.90 (0.83–0.97); p–trend=0.05	
			≤2.5 servings/day		HR=1 (referent)	
			>2.5 to 3.5 servings/ day		HR=0.90 (0.84–0.97)	
			>3.5 to 4.5 servings/day		HR=0.89 (0.83–0.96)	
			>4.5 to 5.5 servings/day		HR=0.92 (0.85–1.00)	
			>5.5 servings/day		HR=0.90 (0.83–0.97)	
			12–16 y lag			
			≤2.5 servings/day		HR=1 (referent)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			>2.5 to 3.5 servings/ day		HR=0.95 (0.88–1.03)	
			>3.5 to 4.5 servings/day		HR=0.94 (0.86–1.02)	
			>4.5 to 5.5 servings/day		HR=0.93 (0.85–1.02)	
			>5.5 servings/day		HR=0.89 (0.82–0.97); p–trend=0.01	
			16–20 y lag			
			≤2.5 servings/day		HR=1 (referent)	
			>2.5 to 3.5 servings/ day		HR= 0.97 (0.89–1.06)	
			>3.5 to 4.5 servings/day		HR=0.94 (0.86–1.03)	
			>4.5 to 5.5 servings/day		HR=0.94 (0.85–1.04)	
			>5.5 servings/day		HR=0.89 (0.80–0.98); p–trend=0.02	
			Cruciferous vegetable intake§			
			≤2 servings/week		HR=1 (referent)	
			>2 to 3 servings/week		HR=0.97 (0.92–1.02)	
			>3 to 4 servings/week		HR=0.92 (0.87–0.98)	
			>4 to 5 servings/week		HR=0.94 (0.87–1.01)	
			>5 servings/week		HR=0.90 (0.84–0.96); p–trend=0.0002	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Yellow/orange vegetable intake§			
			≤2 servings/week		HR=1 (referent)	
			>2 to 3 servings/week		HR=0.98 (0.93−1.03)	
			>3 to 4 servings/week		HR=0.95 (0.89−1.01)	
			>4 to 5 servings/week		HR=0.93 (0.85−1.01)	
			>5 servings/week		HR= 0.91 (0.84–0.99); p–trend=0.004	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; d, day; EPIC; European Prospective Investigation into Cancer and Nutrition; ER, oestrogen receptor; g/d, grams per day; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; kcal/d, kilocalories per day; kg/m2, kilograms per square metre; m, metre; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; PR, progesterone receptor; Q[1–5], quintile [1–5]; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; WCRF, World Cancer Research Fund; y, year/s.

†Adjusted for age, area, tobacco smoking status, drinking status, family history of breast cancer, age at menarche, age at first birth, parity, energy intake, hormone therapy, daily walking, education, and BMI.

¶Stratified by age and centre and adjusted for energy intake (kcal/d, continuous) divided into energy from fat and energy from non–fat sources, saturated fat intake (g/d, continuous), age at menarche (never,12, 12–14, or >14 y), oral contraceptive use (never, past, or current), age at first full term pregnancy (nulliparous; ≤20, >20 and ≤25, >25 and ≤30, or >30 y), menopausal status (premenopausal, perimenopausal/unknown, or postmenopausal), hormone therapy use (never, past, or current), BMI (kg/m2, continuous), BMI 3 menopausal status, physical activity (inactive, moderately inactive, moderately active, or active), smoking status and intensity (never; former: quit >20 y ago, quit 11–20 y ago, or quit ≤10 y ago; current: pipe/cigar smoking, 1–15 cigarettes/d, 16–25 cigarettes/d, or ≥26 cigarettes/d), alcohol user (yes or no), alcohol consumption (g/d, continuous), educational level (none, primary school, technical/professional school, secondary school, or university degree).

§The relative risks were adjusted for ethnicity (White, African–American, Hispanic, Asian, others), family history of breast cancer (yes, no), personal history of benign breast disease (yes, no), alcohol consumption(non–drinkers, >0 to <5, 5–<15, 15–<30, ≥30 g/d), smoking status (never, past, current), education (<high school, high school, >high school), physical activity (low, medium, high), age at menarche (<11, 11–12, 13–14, ≥15 y), body mass index (<23, 23–<25, 25–<30, ≥30 kg/m^2), height (<1.60, 1.60–<1.65, 1.65–<1.70, 1.70–<1.75, ≥1.75 m), oral contraceptive use (never, ever), menopausal status(premenopausal women, never user of hormone therapy among postmenopausal women, past user of hormone therapy among postmenopausal women, and current user of hormone therapy among postmenopausal women), energy intake (kcal/d, continuous), combination between parity (0, 1–2, ≥3) and age of first birth (≤25, >25 y). Age in years and year of questionnaire return were included as stratification variables.

†Stratified on cohort, calendar year, and age in months. Adjusted for family history of breast cancer (yes, no), history of benign breast disease (yes, no), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, and ≥1.75 meters), BMI at age 18 years (<18.5, 18.5 to <20, 20 to <22.5, 22.5 to <25, 25.0 to <30, ≥30.0 kg/m2), weight change since age 18 (continuous), smoking (never, past, current 1 to 14/day, current 15 to 24/day, current ≥25/day), physical activity (quintiles of MET–h per week, missing), oral contraceptive use (never, < 2 years, 2 to <5 years, 5 to <10 years, ≥10 years), alcohol intake (g/day, quintiles), total energy intake (kcal/day, quintiles), age at menarche (<12, 12, 13, 14, >14 years), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity≤2 and age at first birth 25 to <30 years, parity ≤2 and age at first birth ≥30 years, parity 3 to 4 and age at first birth <25 years, parity 3 to 4 and age at first birth 25 to <30 years, parity 3 to 4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), and menopausal status, age at menopause, and postmenopausal hormone use (premenopausal, postmenopausal and age at menopause<50 years and never postmenopausal hormone use, postmenopausal and age at menopause<50 years and past postmenopausal hormone use, postmenopausal and age at menopause<50 years and current postmenopausal hormone use, postmenopausal and age at menopause≥50 years and never postmenopausal hormone use, postmenopausal and age at menopause≥50 years and past postmenopausal hormone use, postmenopausal and age at menopause≥50 years and current postmenopausal hormone use, missing).

§Cumulative average

Table D.46 Diet—foods high in carotenoids and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2015 Asia, Australia, Europe & North America	18 cohort studies	3,055 participants	Dietary β–carotene per 5000 µg/day	Breast cancer	RR=1.00 (0.98–1.02); I^2=0%, p(heter)=0.98	
	11 cohort studies	3,558 participants	Circulating β–carotene per 50 µg/dL		RR=0.78 (0.66–0.92); I^2=0%, p(heter)=0.77	
	10 cohort studies	3,506 participants	Circulating α–carotene per 10 µg/dL		RR=0.90 (0.77–1.05); I^2=0%, p(heter)=NR	
	9 cohort studies	3,407 participants	Circulating total carotenoids per 100 µg/dL		RR=0.82 (0.71–0.96); I^2=0%, p(heter)=NR	
	7 cohort studies	1,296 participants	Circulating lutein per 25 µg/dL		RR=0.72 (0.55–0.93); I^2=0%, p(heter)=0.82	
	10 cohort studies	3,517 participants	Circulating β–cryptoxanthin per 15 µg/dL		RR=0.87 (0.68–1.11); I^2=59%, p(heter)=0.09	
	10 cohort studies	3,506 participants	Circulating lycopene per 25 µg/d		RR=0.90 (0.70–1.16); I^2=39%), p(heter)=0.19	
Cohort studies						
Bakker et al., 2016[375] Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden & UK	EPIC cohort study Enrolment: 1992–1998 Prospective study Mean age at enrolment: 49.98 y in cases	3,004 participants 1,502 cases 1,502 controls	Plasma β–carotene levels (nmol/L) Q1 (24.87–348.94) Q2 (348.94–497.32) Q3 (497.32–718.63) Q4 (718.63–1066.96) Q5 (1066.96–7698.56)	ER–	OR=1 (referent) OR=0.42 (0.28–0.64) OR=0.66 (0.44–1.00) OR=0.51 (0.33–0.79) OR=0.41 (0.26–0.65); p–trend=0.002	Conditional logistic regression model† Limitations: Long term exposure and also day–to–day variations in biomarker levels Carotenoids are fat soluble and plasma lipid levels were not adjusted for
			Plasma alpha–carotene (nmol/L)			

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	50.00 y in controls Median follow–up: 11.5 y		Q1 (14.00–56.95)		OR=1 (referent)	Residual confounding
			Q2 (56.95–88.31)		OR=1.08 (0.74–1.57)	
			Q3 (88.31–124.03)		OR=0.73 (0.49–1.09)	
			Q4 (124.03–198.07)		OR=0.81 (0.53–1.24)	
			Q5 (198.07–1520.25)		OR=0.61 (0.39–0.98); p–trend=0.02	
			Plasma beta–carotene levels (nmol/L)	ER+		
			Q1 (24.87–348.94)		OR=1 (referent)	
			Q2 (348.94–497.32)		OR=0.95 (0.63–1.42)	
			Q3 (497.32–718.63)		OR=1.06 (0.71–1.57)	
			Q4 (718.63–1066.96)		OR=1.00 (0.66–1.51)	
			Q5 (1066.96–7698.56)		OR=1.02(0.66–1.57); p–trend=0.91	
			Plasma a–carotene (nmol/L)			
			Q1 (14.00–56.95)		OR=1 (referent)	
			Q2 (56.95–88.31)		OR=1.00 (0.67–1.50)	
			Q3 (88.31–124.03)		OR=0.79 (0.52–1.19)	
			Q4 (124.03–198.07)		OR=1.22 (0.81–1.83)	
			Q5 (198.07–1520.25)		OR=0.77(0.49–1.19); p–trend=0.28	
			Plasma vitamin C levels (µmol/L)			
			Q1(2.50–28.5)		OR=1 (referent)	
			Q2 (28.5–39.4)	ER+PR+	OR=0.99 (0.61–1.60)	
			Q3 (39.4–46.4)		OR=0.81 (0.49–1.36)	
			Q4 (46.4–56.1)		OR=0.61 (0.37–1.02)	
			Q5 (56.1–145.30)		OR=0.64 (0.35–1.17); p–trend=0.04	
			Plasma vitamin C	ER–PR–		

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			levels (µmol/L)			
			Q1(2.50–28.5)		OR=1 (referent)	
			Q2 (28.5–39.4)		OR=0.74 (0.44–1.26)	
			Q3 (39.4–46.4)		OR=0.63 (0.35–1.13)	
			Q4 (46.4–56.1)		OR=0.86 (0.50–1.48)	
			Q5 (56.1–145.30)		OR=0.59 (0.33–1.05); p–trend=0.16	
			Retinol (µmol/L)	ER–		
			Q1(0.32–1.37)		OR=1 (referent)	
			Q2 (1.37–1.63)		OR=1.05 (0.64–1.73)	
			Q3 (1.63–1.90)		OR=1.67 (1.01–2.77)	
			Q4 (1.90–2.25)		OR=1.35 (0.81–2.25)	
			Q5 (2.25–6.70)		OR=1.65 (0.97–2.81); p–trend=0.08	
			Retinol (µmol/L)	ER+		
			Q1(0.32–1.37)		OR=1 (referent)	
			Q2 (1.37–1.63)		OR=1.10 (0.74–1.63)	
			Q3 (1.63–1.90)		OR=0.92 (0.62–1.37)	
			Q4 (1.90–2.25)		OR=1.15 (0.76–1.75)	
			Q5 (2.25–6.70)		OR=1.02 (0.64–1.63); p–trend=0.92	
			α–Tocopherol (µmol/L)	ER–		
			Q1(8.93–18.29)		OR=1 (referent)	
			Q2 (18.29–21.54)		OR=1.26 (0.64–2.50)	
			Q3 (21.54–24.84)		OR=0.78(0.40–1.54)	
			Q4 (24.84–29.34)		OR=0.85 (0.44–1.63)	
			Q5 (29.34–84.65)		OR=0.88 (0.46–1.68); p–trend=0.51	
			α–Tocopherol (µmol/L)	ER+		
			Q1(8.93–18.29)		OR=1 (referent)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Q2 (18.29–21.54)		OR=1.04 (0.73–1.49)	
			Q3 (21.54–24.84)		OR=1.04 (0.70–1.56)	
			Q4 (24.84–29.34)		OR=0.77 (0.50–1.18)	
			Q5 (29.34–84.65)		OR=0.88 (0.56–1.40); p–trend=0.40	
			γ–Tocopherol (μmol/L)	ER–		
			Q1(0.07–2.33)		OR=1 (referent)	
			Q2 (2.33–3.59)		OR=1.00 (0.69–1.45)	
			Q3 (3.59–5.15)		OR=1.14 (0.75–1.74)	
			Q4 (5.15–7.87)		OR=1.16 (0.74–1.82)	
			Q5 (7.87–28.95)		OR=1.54 (0.87–2.71); p–trend=0.13	
			γ–Tocopherol (μmol/L)	ER+		
			Q1(0.07–2.33)		OR=1 (referent)	
			Q2 (2.33–3.59)		OR=1.18 (0.70–1.97)	
			Q3 (3.59–5.15)		OR=1.01 (0.61–1.68)	
			Q4 (5.15–7.87)		OR=1.08 (0.64–1.82)	
			Q5 (7.87–28.95)		OR=0.91 (0.53–1.58); p–trend=0.38	
Case–control studies						
Wang et al., 2015[376] USA	Nested case–control from CPSII Nutrition cohort study 1999–2007 Prospective study Mean age at	496 matched cases & controls	Plasma alpha–carotene (μg/L)			Multivariable–adjusted conditional and unconditional logistic regression model‡ Limitations: A single measurement of blood carotenoids may result in misclassification of exposures during long term follow–up
			Q1 (<47)	Postmenopausal breast cancer	OR=1 (referent)	
			Q2 (47.0–<69.8)		OR=0.56 (0.36–0.89)	
			Q3 (69.8–<111.0)		OR=0.55 (0.35–0.88)	
			Q4 (≥111.0)		OR=0.50 (0.29–0.85); p–trend=0.041	
			Plasma beta–carotene (μg/L)			
			Q1 (<150.3)		OR=1 (referent)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	enrolment: 69.4 y Follow–up: NR		Q2 (150.3–<246.9) Q3 (246.9–<400.3) Q4 (≥400.3)		OR=0.98 (0.62–1.54) OR=1.06 (0.64–1.75) OR=1.56 (0.90–2.72); p–trend=0.051	Residual confounding
			Plasma beta–cryptoxanthin (µg/L) Q1 (<79.3) Q2 (79.3–<113.6) Q3 (113.6–<174.9) Q4 (≥174.9)		 OR=1 (referent) OR=0.75 (0.47–1.18) OR=1.23 (0.77–1.97) OR=1.01 (0.60–1.70); p–trend=0.65	
			Lycophene Q1 (<273.6) Q2 (273.6–<366.2) Q3 (366.2–<484.8) Q4 (≥484.8)		 OR=1 (referent) OR=0.77 (0.50–1.16) OR=0.70 (0.45–1.09) OR=0.95 (0.60–1.50); p–trend=0.84	
			Lutein+zeaxanthin Q1 (<153.0) Q2 (153.0–<206.0) Q3 (206.0–<281.6) Q4 (≥281.6)		 OR=1 (referent) OR=1.15 (0.74–1.79) OR=1.01 (0.62–1.64) OR=1.08 (0.65–1.80); p–trend=0.90	
			Total cartenoids Q1 (<822.4) Q2 (822.4–<1,061.6) Q3 (1,061.6–<1,412.0) Q4 (≥1,412.0)		 OR=1 (referent) OR=0.61 (0.41–0.93) OR=0.76 (0.50–1.16) OR=0.86 (0.56–1.33); p–trend=0.74	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Pooled analysis						
Farvid et al., 2018[371] USA	Nurses' Health Study dates: 1980–2012 Dietary questionnaire completed in 1980, 1984, 1986 & every 4 years thereafter Nurses' Health Study II dates: 1991–2013 Dietary questionnaire completed every 4 years from 1991 onwards Prospective study Age at baseline: 27–59 y Mean follow–up: 23.7 y	182,145 women 10,911 cases	Fruit and vegetables high in a–carotene (≥3000 mcg/100 g)§ <2 servings/month 2 to <4 servings/month 1 to <2 servings/week 2 to <3 servings/week ≥3 servings/week Fruits and vegetables high in β–carotene (≥3000 mcg/100 g)§ ≤2 servings/week >2 to 4 servings/week >4 to 6 servings/week >6 servings/ week to 1 serving/day >1 serving/day Fruits and vegetables high in lutein (≥10 mg/100 g)§ ≤1 serving/month >1 to 3 servings/month	Invasive breast cancer	 HR=1 (referent) HR=0.95 (0.88–1.01) HR=0.92 (0.86–0.99) HR=0.89 (0.82–0.96) HR=0.91 (0.84–0.98); p–trend=0.02 HR=1 (referent) HR=0.94 (0.86–1.01) HR=0.90 (0.83–0.98) HR=0.92 (0.84–1.01) HR=0.87 (0.80–0.94); p–trend=0.0004 HR=1 (referent) HR=1.01 (0.95–1.07)	Cox proportional hazards regression model Adjustments†† Limitations: Possibility of type I error due to multiple comparisons

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			>3 to 4 servings/month		HR=1.00 (0.93–1.07)	
			>1 to 3 servings/ week		HR=0.97 (0.92–1.04)	
			>3 servings/week		HR=0.94 (0.86–1.03); p–trend=0.07	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; CPSII, Cancer Prevention Study II; EPIC, European Prospective Investigation into Cancer and Nutrition; ER, oestrogen receptor; HR, hazard ratio; MET, metabolic equivalent; MHT, menopausal hormone therapy; nmol/L, nanomoles per litre; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; PR, progesterone receptor; p–trend, p–value for trend; Q[1–5], quintile[1–5]; Q[1–4], quartile[1–4]; RR, relative risk or risk estimate; µg/d, micrograms per day; µg/L, micrograms per litre; µmol/L, micromoles per litre; UK, United Kingdom; USA, United States of America; WCRF, World Cancer Research Fund; y, year/s.

†Adjusted for matching factors [study centre, age (within 1 y), menopausal status at recruitment, use of exogenous hormones, and phase of menstrual cycle, fasting status at blood collection, and time of blood collection (61 h). Also adjusting for BMI (continuous), height (continuous), age at menarche(<12,12–14,14 y, missing), age at first full–term pregnancy (nulliparous, ≤20, >20–≤25, >25–≤30, >30 y, missing), oral contraceptive use (ever/never/missing, for premenopausal women),hormone therapy use (ever/never/missing, for postmenopausal women), smoking status (never, past, current, missing), alcohol consumption (g/d), educational level (none, primary school, technical/professional school, secondary school, university degree, missing), intake of saturated fatty acids (g/d), energy intake(kcal/d), and season of blood collection (winter, spring, summer, fall).

‡Adjusted for matching factors, further adjusted for history of benign breast disease, combination of age of mother at first birth and number of live births, BMI, alcohol consumption, smoking status, MHT use, other plasma carotenoids (except for total carotenoids) and total fruit and vegetable intake (as a continuous variable).

††Stratified on cohort, calendar year, and age in months and adjusted for family history of breast cancer (yes, no), history of benign breast disease (yes, no), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, and ≥1.75 meters), BMI at age 18 years (<18.5, 18.5 to <20, 20 to <22.5, 22.5 to <25, 25.0 to <30, ≥30.0 kg/m2), weight change since age 18 (continuous), smoking (never, past, current 1 to 14/day, current 15 to 24/day, current ≥25/day), physical activity (quintiles of MET–h per week, missing), oral contraceptive use (never, < 2 years, 2 to <5 years, 5 to <10 years, ≥10 years), alcohol intake (g/day, quintiles), total energy intake (kcal/day, quintiles), age at menarche (<12, 12, 13, 14, >14 years), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity≤2 and age at first birth 25 to <30 years, parity ≤2 and age at first birth ≥30 years, parity 3 to 4 and age at first birth <25 years, parity 3 to 4 and age at first birth 25 to <30 years, parity 3 to 4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), and menopausal status, age at menopause, and postmenopausal hormone use (premenopausal, postmenopausal and age at menopause<50 years and never postmenopausal hormone use, postmenopausal and age at menopause<50 years and past postmenopausal hormone use, postmenopausal and age at menopause<50 years and current postmenopausal hormone use, postmenopausal and age at menopause≥50 years and never postmenopausal hormone use, postmenopausal and age at menopause≥50 years and past postmenopausal hormone use, postmenopausal and age at menopause≥50 years and current postmenopausal hormone use, missing).

§Cumulative average

Table D.47 Diet—Mediterranean diet and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Schwingshackl et al., 2017[377] Studies published to 2017 Australia, China, Europe, France, Iran, Italy, Netherlands, Singapore, Spain, Sweden, UK & USA	7 cohort studies 9 case–control studies	1,804 participants	Adherence to MedD Highest vs lowest	Breast cancer	RR=0.94 (0.90–0.99); p=0.03; I^2=11%, p(heter)=0.34 OR=0.89 (0.85–0.94); p<0.0001; I^2=0%, p(heter)=0.51	Random effects model Adjustments: NR No publication bias (p>0.05) Limitations: MedD diet not defined well MedD diet has changed since the 1960s Food frequency questionnaires may not reflect impact on chronic disease
van den Brandt & Schulpen, 2017[378] Studies published to 2016 Europe, Netherlands, UK & USA	5 cohort studies 2 studies 2 studies 2 studies	Number of participants: NR	Adherence to MedD Highest vs lowest	Postmenopausal breast cancer ER+ ER– ER–PR–	HR=0.98 (0.82–1.17); p=NS; I^2=47.6%, p(heter)=0.167 HR=0.73 (0.57–0.93); I^2=6.0%, p(heter)=0.302 HR=0.77 (0.63–0.94); I^2=0.0%, p(heter)=0.340	Random effects model Adjustments: NR Publication bias: NR Limitations: NR

Bloomfield et al., 2016[379] Studies published 1990–2016 Canada, Europe, Italy, Spain, Sweden, UK & USA	13 cohort studies	Number of participants: NR	Adherence to MedD Highest vs lowest	Breast cancer	RR=0.96 (0.90–1.03); I^2=53%	Random effects model Adjustments: NR Publication bias: NR Limitations: English–language publications included only Exaggerated estimates due to random effects model Possible selective reporting and publication bias
WCRF, 2017[10]† Studies published to 2015 Europe, North America, Southeast Asia & UK	8 cohort studies 4 cohort studies 8 cohort studies	Number of participants: NR	MedD score Highest vs lowest	Breast cancer Premenopausal breast cancer ER+PR+ ER–PR– Postmenopausal breast cancer ER+PR+ ER–PR–	RR=0.84 (0.59–1.20) to 1.42 (0.99–2.05) RR=0.65 (0.42–1.02) to 2.17 (1.42–3.30) RR=0.86 (0.66–1.13) RR=1.09 (0.65–1.82) RR=0.59 (0.34–1.03) to 1.10 (0.80–1.51) RR=0.92 (0.85–1.01) RR=0.80 (0.65–0.99)	Model: NR Adjustments: NR Publication bias: NR Limitations: NR
Cohort studies						
van den Brandt & Schulpen, 2017[378] Netherlands	NLCS sub–cohort Cohort dates: 1986−2007	1,665 subcohort women & 2,321 cases included in analysis	MedD by aMED & mMED scores	Breast cancer		Multivariate case–cohort analyses Adjustments‡
		100 cases	0–3 points	ER–	HR=1(referent)	

	Prospective study Age at enrolment: 55–69 y Duration of follow–up: 20.3 y	116 cases 32 cases	4–5 point 6–8 points		HR=0.92 (0.67–1.25) HR=0.60 (0.39–0.93); p–trend=0.032	Limitations: The proportion of breast cancer cases where ER/PR status was known was moderate
Randomised controlled trials						
Toledo et al., 2015[380] Spain	PREDIMED study Participant enrolment: 2003−2009 Trial end: Dec 2010 Median follow–up: 4.8 y Age at enrolment: 60−80 y	4,282 women 1,391 control diet 1,476 Mediterranean diet with EVOO 1,285 Mediterranean diet with nuts 35 incident cases of malignant breast cancer Participants were free of CVD at enrolment, & had either type 2 diabetes mellitus or at least 3 major cardiovascular risk factors	Control diet Mediterranean diet with EVOO Mediterranean diet with nuts Both Mediterranean diets	Invasive breast cancer	HR=1 (referent) HR=0.32 (0.13–0.79) HR=0.59 (0.26–1.35) HR=0.43 (0.21–0.88)	Cox regression model Adjustments§ Limitations: Breast cancer was not the primary end point Mammograms may have had suggestive findings at baseline Breast cancer case number was small Cancers could potentially be missed without mammograms Only white postmenopausal women at high cardiovascular risk included Reproductive factors not adjusted for Non–invasive cases not included in analyses Study protocol was amended in

	October 2006, affecting the intervention

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; aMED, alternate Mediterranean Diet score; ER, oestrogen receptor; EVOO, extra virgin olive oil; HR, hazard ratio; MedD, Mediterranean Diet; mMED, modified Mediterranean Diet score; NLCS, Netherlands Cohort Study; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; PREDIMED, Prevención con Dieta Mediterránea (Prevention with Mediterranean Diet); PR, progesterone receptor; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; WCRF, World Cancer Research Fund; y, year/s.

†WCRF reported the risk estimates of primary studies. WCRF did not conduct their own meta–analysis of the data obtained in their systematic review due to the low number of studies.

‡Adjusted for age at baseline (55–59, 60–64, 65–69 years), cigarette smoking (status (never, former, current), frequency (number of cigarettes per day; continuous, centred), duration (number of years; continuous, centred), body height (continuous, cm), body mass index (<18.5, 18.5–<25, 25–<30, >30 kg/m2), non–occupational physical activity (<30, >30–60, >60–90, >90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), family history of breast cancer in mother or sisters (no, yes), history of benign breast disease (no, yes), age at menarche (<12, 13–14, 15–16, >17 years), parity (nulliparous, 1–2, >3 children), age at first birth (<25, >25 years), age at menopause (<45, 4,549, 50–54, >55 years), oral contraceptive use (never, ever), postmenopausal HT (never, ever), energy intake (continuous, kcal/day) and alcohol intake (0, 0.1–<5, 5–<15, 15–30, >30 g/day). Models that 'included alcohol' did not have additional adjustments for alcohol.

§Adjusted for age, study site, body mass index, waist to height ratio, use of hormone therapy, leisure–time physical activity, total energy intake, alcohol consumption, age at menopause, and baseline adherence to the Mediterranean diet. Four cases were excluded: 1 in the Mediterranean diet with EVOO group, 1 in the Mediterranean diet with nuts group, and 2 in the control group.

Table D.48 Diet—phytoestrogens and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Grosso et al., 2017[383] Studies published to June 2016 Brazil, Canada, China, Europe, France, Germany, Italy, Japan, Mexico, Singapore, Sweden, UK & USA	39 studies 16 prospective studies 23 case–control studies	Individuals of 40–70 y age range Population description: NR	Total flavonoids Highest vs lowest	Breast cancer	RR:=0.96 (0.89–1.0); I^2=0.0%, p(heter)=0.99	Random effects model Adjustments: Most studies adjusted for age No evidence of publication bias Limitations: Recall bias Potential co–linearity between polyphenols with foods that are sources of other compounds that may be responsible for the observed associations Assessment of dietary intake in prospective studies does not take into account changes in dietary intake over time Limited number of cases in some studies Lack of data on individual polyphenols
			Flavonol Highest vs lowest		RR=0.96 (0.90–1.03); I^2=0.0%, p(heter)=0.64	
			Proanthocyanidins Highest vs lowest		RR=0.94 (0.87–1.0); I^2=0.0%, p(heter)=0.69	
			Flavanones Highest vs lowest		RR=1.04 (0.97–1.11); I^2=0%, p(heter)=0.99	
			Isoflavones Highest vs lowest		RR=0.90 (0.81–1.01); I^2=60%, p(heter)=0.002	
			Lignans Highest vs lowest		RR=0.98 (0.89–1.08); I^2=28%, p(heter)=0.23	
Wu et al., 2016[360] Studies published to 2015 China, France	10 cohort studies 7 cohort studies	452,916 participants 12,888 cases Follow up: 3.9–65 y	Soy food Highest vs lowest		RR=0.92 (0.84–1.00); I^2=0.0%, p(heter)=NR	Greenland and Longnecker method Adjustments: NR No publication bias (p=0.764)
			Dose response (per ‘serving’)		RR=0.91(0.84–1.00); I^2=0.0%, p(heter)=NR	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Japan & USA						Limitations: Unmeasured or residual confounders Few studies assessed the influence of hormone receptor status Single FFQ assessment assumes no change in diet over follow–up Different studies used different units for food intake
WCRF, 2017[10] Asia, Europe & Western countries	6 cohort studies	12,962 cases	Dietary isoflavones Dose response (per 3 mg/day)	Postmenopausal breast cancer	RR=0.99 (0.98–1.00); I^2=85.4%, p(heter)=0.243	No publication bias (p=0.498) Limitations: Insufficient data to conduct a meta–analysis for risk of breast cancer overall
Cohort studies						
Baglia et al., 2016[385] China	Shanghai Women's Health Study Enrolment: 1996–2000 Prospective study Age at enrolment 40–70 y Duration of follow–up: median 13.2 y	70,578 women 1,034 cases	Adult soy protein intake (median) Q1(3.5 g/day) Q2 (6.0 g/day) Q3 (8.2 g/day) Q4 (10.9 g/day) Q5 (16.0 g/day)	Breast cancer	RR=1.00 (referent) RR=1.01 (0.83–1.22) RR=1.00 (0.82–1.21) RR=0.87 (0.71–1.06) RR=0.78 (0.63–0.97); p–trend=0.007	Cox proportion hazard regression model Adjustments* Limitations: For some subgroup analyses, the statistical power of these study was low Possible measurement errors
			Q1(3.5 g/day) Q2 (6.0 g/day) Q3 (8.2 g/day) Q4 (10.9 g/day)	Premenopausal breast cancer	RR=1.00 (referent) RR=0.97 (0.69–1.36) RR=0.86 (0.60–1.24) RR=0.98 (0.68–1.42)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Q5 (16.0 g/day)		RR=0.46 (0.29–0.74); p–trend=0.004	
			Q1(3.5 g/day)	Postmenopausal breast cancer	RR=1.00 (referent)	
			Q2 (6.0 g/day)		RR=1.03 (0.82–1.30)	
			Q3 (8.2 g/day)		RR=1.06 (0.84–1.33)	
			Q4 (10.9 g/day)		RR=0.83 (0.65–1.06)	
			Q5 (16.0g/day)		RR=0.90 (0.71–1.16); p–trend=0.15	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: ER, oestrogen receptor; FFQ, food frequency questionnaire; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; PR, progesterone receptor; Q[1–5], quintiles 1–5RR, relative risk or risk estimate; T[1–3], tertiles 1–3; UK, United Kingdom; USA, United States of America; WCRF, World Cancer Research Fund; y, year/s.

*Adjusted for age, body mass index, age at first live birth, physical activity, education, family history of breast cancer, season of recruitment and menopause (time–varying) were used for analyses. Adult intakes additionally adjusted for total energy intake and juvenile intakes adjusted for total juvenile rice intake.

Table D.49 Diet—glycaemic index and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2015 Canada, China, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK & USA	5 cohort studies	17,767 cases	Glycaemic index dose–response (per 10 units/day)	Breast cancer	RR=1.02 (0.96–1.10); p=NS; I^2=51.9%, p(heter)=0.08	Model: NR Adjustments: main confounders Publication bias for GI and GL in premenopausal breast cancer (p<0.05) Limitations: NR
	6 studies	21,859 cases		Premenopausal breast cancer	RR=1.01 (0.93–1.10); p=NS; I^2=34%, p(heter)=0.18	
	10 studies	37,846 cases		Postmenopausal breast cancer	RR=1.06 (1.02–1.10); p=sig.; I^2=18.9%, p(heter)=0.27	
	6 studies	17,767 cases	Glycaemic load dose–response (per 50 units/day)	Breast cancer	RR=1.02 (0.93–1.11); p=NS; I^2=58.7%, p(heter)=0.03	
	7 studies	22,573 cases		Premenopausal breast cancer	RR=1.07 (0.92–1.24); p=NS; I^2=71.8%, p(heter)=0.0002	
	10 studies	37,846 cases		Postmenopausal breast cancer	RR=1.02 (0.99–1.06); p=NS; I^2=3.2%, p(heter)=0.41	
Schlesinger et al., 2017[387] Studies published to 2015 Canada, China, Denmark, European countries, Finland, France, Italy, Sweden & USA	14 prospective studies	1,102,422 women 36,900 cases	Glycaemic index dose response (per 10 units/day)	Breast cancer		Random effects model Adjustments: NR No publication bias (p>0.05) Limitations: Potential errors in measurement diet Confounding factors such as low physical activity, smoking, overweight and obesity, excess total energy and alcohol intake FFQs not specific to GI and GL Dietary information assessed at
	10 studies		Overall		RR=1.04 (1.00–1.07); p=NS; I^2=27%, p(heter)=0.194	
	5 studies		BMI<25		RR=1.08 (0.99–1.17); I^2=52.5%, p(heter)=0.077	
	5 studies		BMI>25		RR=1.03 (0.97–1.11); I^2=0%, p(heter)=0.442	
	4 studies			ER+	RR=1.04 (0.97–1.12); I^2=0%, p(heter)=0.911	
	4 studies			ER–	RR=1.03 (0.90–1.18); I^2=0%, p(heter)=0.870	
	3 studies			PR+	RR=1.02 (0.91–1.14); I^2=31.1%, p(heter)=0.234	
	4 studies			PR–	RR=1.03 (0.89–1.20); I^2=0%, p(heter)=0.577	
	3 studies			ER+PR+	RR=1.02 (0.91–1.14); I^2=31.1%, p(heter)=0.234	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	2 studies			ER+ PR–	RR=1.29 (0.96–1.73); I^2=42.2%, p(heter)=0.188	baseline only
	4 studies			ER–PR–	RR=1.01 (0.88–1.17); I^2=0%, p(heter)=0.822	Limited studies by hormone receptor status
	6 studies		Overall	Premenopausal breast cancer	RR=1.01 (0.93–1.10); p=NS; I^2=34.0%, p(heter)=0.181	
	2 studies		BMI<25		RR=0.98 (0.89–1.08); I^2=0%, p(heter)=0.472	
	2 studies		BMI>25		RR=0.88 (0.97–1.20); I^2=0%, p(heter)=0.849	
	10 studies		Overall	Postmenopausal breast cancer	RR=1.06 (1.02–1.10); p=sig.; I^2=19.2%, p(heter)=0.266	
	3 studies		BMI<25		RR=1.15 (1.01–1.32); I^2=71.9%, p(heter)=0.029	
	3 studies		BMI>25		RR=1.11 (1.02–1.20); I^2=0%, p(heter)=0.683	
	3 studies			ER+	RR=1.02 (0.93–1.13); I^2=0%, p(heter)=0.938	
	3 studies			ER–	RR=1.16 (0.96–1.40); I^2=0%, p(heter)=0.864	
	2 studies			PR+	RR=0.99 (0.85–1.15); I^2=48.5%, p(heter)=0.164	
	2 studies			PR–	RR=1.19 (0.92–1.54); I^2=0%, p(heter)=0.579	
	2 studies			ER+PR+	RR=0.99 (0.85–1.15); I^2=48.5%, p(heter)=0.164	
	2 studies			ER+ PR–	RR=1.29 (0.96–1.73; I^2=42.2%, p(heter)=0.188	
	3 studies			ER–PR–	RR=1.15 (0.94–1.39); I^2=0%, p(heter)=0.950	
	11 studies		Glycaemic load dose response (per 50 units/day)	Breast cancer	RR=1.01 (0.98–1.04); p=NS; I^2=42.7%, p(heter)=0.065	
	6 studies		BMI<25		RR=1.02 (0.99–1.04); I^2=80.7%,	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
					p(heter)<0.001	
	6 studies		BMI>25		RR=1.01 (0.99–1.02); I^2=0%, p(heter)=0.515	
	3 studies			ER+	RR=0.99 (0.95–1.02); I^2=53.8%, p(heter)=0.116	
	3 studies			ER–	RR=1.20 (1.05–1.38); I^2=0%, p(heter)=0.976	
	2 studies			PR+	RR=0.91 (0.83–1.00); I^2=0%, p(heter)=0.487	
	3 studies			PR–	RR=1.05 (0.96–1.14); I^2=72.9%, p(heter)=0.025	
	2 studies			ER+PR+	RR=0.91 (0.83–1.00); I^2=0%, p(heter)=0.487	
	2 studies			ER+ PR–	RR=1.16 (0.54–2.51); I^2=92.8%, p(heter)<0.001	
	3 studies			ER–PR–	RR=1.19 (1.02–1.38), I^2=0, p(heter)=0.987	
	7 studies		Overall	Premenopausal breast cancer	RR=1.07 (0.92–1.24); I^2=72.0%, p(heter)=0.002	
	2 studies		BMI<25		RR=0.99 (0.86–1.15); I^2=0%, p(heter)=0.579	
	2 studies		BMI>25		RR=0.79 (0.65–0.97); I^2=0%, p(heter)=0.325	
	11 studies		Overall	Postmenopausal breast cancer	RR=1.02 (0.99–1.06); I^2=3.5%, p(heter)=0.409	
	4 studies		BMI<25		RR=1.01 (0.99–1.03); I^2=39.9%, p(heter)=0.172	
	4 studies		BMI>25		RR=1.01 (1.00–1.03); I^2=0%, p(heter)=0.394	
	3 studies			ER+	RR=0.99 (0.95–1.03); I^2=53.8%, p(heter)=0.115	
	3 studies			ER–	RR=1.28 (1.08–1.52); I^2=0%, p(heter)=0.589	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	2 studies			PR+	RR=0.91 (0.83–1.00); I^2=0%, p(heter)=0.487	
	3 studies			PR–	RR=1.08 (0.96–1.21); I^2=82.6%, p(heter)=0.003	
	2 studies			ER+PR+	RR=0.91 (0.95–1.03); I^2=0%, p(heter)=0.487	
	2 studies			ER+PR–	RR=1.16 (0.54–2.51); I^2=92.8%, p(heter)<0.001	
	2 studies			ER–PR–	RR=1.29 (1.08–1.54); I^2=0%, p(heter)=0.494	
Cohort studies						
Makarem et al., 2017[388] USA	Framingham Offspring cohort Cohort dates: 1991–2013 Prospective study Mean age at enrolment: 54.4 y Median follow–up: 13.1 y	1,689 women 551 participants 48 cases 572 participants 31 cases 566 participants 45 cases 557 participants 46 cases 575 participants 44 cases 557 participants 34 cases	Glycaemic index T1<53.3 T2 53.3–56.2 T3 >56.2 Glycaemic load (g/day) <96.7 96.7–136.0 >136.0	Breast cancer	HR=1.00 (referent) HR=0.67 (0.42–1.06) HR=0.90 (0.59–1.37) HR=1.00 (referent) HR=0.75 (0.47–1.22) HR=0.54 (0.26–1.09)	Cox proportion hazard models Adjustments† Limitations: FFQ not specific to GI and GL Self–reported intakes measured by FFQ Measure of dietary GI and GL for individual foods Reference GI values limited to Australian and American foods GI and GL may not reflect glycaemic response Limited power for hormone receptor subtype analysis

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						Diet and lifestyle variables may not capture changes over time Possible residual confounding
Sieri et al., 2017[386] Italy	EPIC–Italy study Cohort dates: Follow up concluded in 2010 Prospective study Age at enrolment: NR Median follow–up: 14.9 y	47,749 participants 1,362 cases	Glycaemic index Q1 Q2 Q3 Q4 Q5 Glycaemic load Highest vs lowest§ Q1 Q2 Q3 Q4 Q5	Breast cancer	 HR=1 (referent) HR=0.91 (0.77–1.07) HR=1.00 (0.85–1.18) HR=0.98 (0.82–1.16) HR=1.00 (0.84–1.19); p–trend=0.744 HR=1.34 (1.02–1.76); p–trend=0.049 HR=1 (referent) HR=1.16 (0.97–1.38) HR=1.07 (0.87–1.28) HR=1.19 (0.97–1.46) HR=1.14 (0.89–1.46); p–trend=0.303	Cox multivariate model Adjustments‡ Limitations: FFQs not specific to GI and GL Only one dietary measurement and long term dietary intake not estimated Estimates derived from FFQs may not account for meal frequency, cooking methods, or chewing habits Residual confounding

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; EPIC–Italy, European Prospective Investigation of Cancer cohort in Italy (Florence, Milan, Ragusa province, Turin and Naples); ER, oestrogen receptor; FFQ, food frequency questionnaire; g/day, grams per day; GI, glycaemic index; GL, glycaemic load; HR, hazard ratio; NR, not reported; NS, not significant; p, p–value; p(heter), p–value for the measure of heterogeneity; Q[1–5], quintiles 1 to 5; PR, progesterone receptor; RR, relative risk or risk estimate; sig., significant; UK, United Kingdom; USA, United States of America; y, year/s.

†Adjusted for age, smoking, alcohol, energy (multivariable method for GI and GL), menopausal status, hormone therapy use, age at menopause and number of live births.

‡Stratified by food frequency questionnaire and adjusted for sex, education, smoking status, BMI, alcohol intake, fibre intake, saturated fat intake, non–alcohol energy intake and physical activity.

§Excludes participants who reported at recruitment that they were dieting.

Table D.50 Diet—total energy and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
WCRF, 2017[10] Studies published to 2015 Greece, Netherlands, Sweden & USA	9 cohort studies	7,803 cases	Total energy intake Linear dose response (per 500 kcal/d)	Postmenopausal breast cancer	RR=1.02 (0.97–1.06); p=NS; I^2=45%, p(heter)=0.07	Model: NR Adjustments: Age, alcohol intake, reproductive factors (n=6) and BMI (n=5) No publication bias (p=0.36) Limitations: Insufficient data for analysis of premenopausal breast cancer
Cohort studies						
Thomson et al., 2018[391] USA	Women's Health Initiative cohort Cohort dates: 1993−1998 Prospective study Age at enrolment: 50−79 y Duration of follow–up: 14.6 y	92,295 women 5,565 cases Mean time to diagnosis: 8.2 y	Dietary energy density† Q1 (lowest) Q2 Q3 Q4 Q5 (highest)	Postmenopausal breast cancer	HR=1.00 (referent) HR=1.0 (0.9–1.1) HR=1.0 (0.9–1.1) HR=1.0 (0.9–1.1) HR=1.06 (0.97–1.1)	Cox proportion hazards regression model No adjustments Limitations: Calculation for dietary energy density excludes beverages Database may not have fully accounted for water loss during cooking or for cup weights Errors in dietary energy reporting Residual confounding
Hartman et al.,	Cancer Prevention	56,795 women		Postmenopausal		Cox proportional hazards

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
2016[390] USA	Study II Nutrition Cohort Cohort dates: 1999–2011 Prospective study Age at enrolment: 50–74 y Median follow–up: 11.7 y	2,509 cases		breast cancer		regression model Adjustments‡ Limitations: Measurement errors associated with dietary assessment methods Use of single questionnaire Residual confounding Cohort consisted mostly of older, white middle–class women
			Dietary energy density			
		438 cases	Q1 (<1.23 kcal/d)		RR=1.00 (referent)	
		539 cases	Q2 (1.23–<1.38 kcal/d)		RR=1.16 (1.02–1.32)	
		489 cases	Q3 (1.38–<1.52 kcal/d)		RR=1.09 (0.96–1.24)	
		517 cases	Q4 (1.52–<1.71 kcal/d)		RR=1.09 (0.96–1.24)	
		526 cases	Q5 (≥1.71 kcal/d)		RR=1.17 (1.03–1.33); p–trend=0.09	
			Energy–dense food (g/d)			
		457 cases	<114		RR=1.00 (referent)	
		507 cases	114–<149		RR=1.10 (0.97–1.25)	
		515 cases	149–<186		RR=1.12 (0.98–1.27)	
		543 cases	186–<237		RR=1.16 (1.03–1.32)	
		487 cases	≥237		RR=1.06 (0.93–1.21); p–trend=0.40	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; g/d, grams per day; HR, hazard ratio; kcal/d, kilocalories per day; n, number of studies; NR, not reported; NS, not significant; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; Q[1–5], quintiles [1–5]; RR, relative risk or risk estimate; WCRF, World Cancer Research Fund; USA, United States of America; y, year/s.

† Defined as the ratio of a diet's energy content to its weight.

‡Adjusted for age, education, race/ethnicity, age at menarche, age at first birth/parity, age at menopause, family history of breast cancer, and hormone therapy use, and BMI.

Table D.51 Diet—sugar and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Schlesinger et al., 2017[387] Studies published to 2015 Europe & North America	4 prospective studies	384,651 women 12,414 cases	Total sugar intake Dose response (per 10 g/day)†	Breast cancer	RR=0.99 (0.98–1.01); I^2=53%, p(heter)=0.10	Random effects models Adjustments: NR No publication bias (p=0.21 for total sugar and p=0.73 for fructose) Limitations: Confounding factors such as low physical activity, smoking, overweight and obesity, excess intake of total energy, & alcohol intake Measurement error of diet Dietary information assessed at baseline; no information on change in dietary behaviour over time was available
	3 prospective studies	352,627 women 11,542 cases Women aged 40–79 y	Fructose intake Dose–response (per 10 g/day)†		RR=0.99 (0.96–1.01); I^2=14%, p(heter)=0.31	
Boyle et al., 2014[393] Studies published to 2012 Countries: NR	2 retrospective studies	NR	Sugar–sweetened beverages; consumption of colas	Breast cancer	No association (no risk estimates reported)	Random effects model No publication bias Limitations: Poor methodology and small numbers of studies
Cohort studies						
Hodge et al., 2018[392]	The MCC study	Wave 1: 35,593 participants	Sugar–sweetened soft drinks	Postmenopausal breast cancer		Cox proportional hazards regression model

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Australia	Firstwave of recruitment: 1990–1994 End of follow–up: Jun 2013 121–item FFQ completed at both waves for consumption in the last 12 months Prospective study Age at recruitment: 40–69 y Follow–up duration: NR	21,492 women 946 postmenopausal breast cancer cases	<1/month 1–3/month 1–6/week ≥1/day Linear model Artificially sweetened soft drinks <1/month 1–3/month 1–6/week ≥1/day Linear model		HR=1 (referent) HR=0.90 (0.75–1.08) HR=1.21 (1.03–1.43) HR=1.11 (0.85–1.45) HR=1.26 (1.00–1.58); p–trend=0.05 HR=1 (referent) HR=0.94 (0.73–1.22) HR=0.90 (0.72–1.12) HR=0.95 (0.73–1.25) HR=0.92 (0.71–1.18); p–trend=0.51	Adjustments†‡ Limitations: Intake of beverages was self–reported by FFQ Data on energy intake not included Unable to assess the amount of added sugars intake

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: g/day, grams per day; NR, not reported; FFQ, food frequency questionnaire; HR, hazard ratio; MCC, Melbourne Collaborative Cohort; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; y, year/s.

†Linear dose–response meta–analysis.

†Sugar–sweetened soft drinks adjusted for Socio–Economic Index for Areas, country of birth, alcohol intake, smoking status, physical activity, Mediterranean diet score.

‡Artificially sweetened soft drinks adjusted for all variables mentioned above plus sugar–sweetened soft drink consumption and waist circumference.

Table D.52 Diet—fat and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes		Risk estimates	Author comments
Meta–analyses							
Cao et al., 2016[395] Studies published to 2015 Canada, China, Netherlands, Norway, Finland, France, Italy, Japan, Sweden & USA	24 cohort studies	1,387,366 participants 38,262 cases	Total fat intake Highest vs lowest	Breast cancer		RR=1.10 (1.02–1.19); I^2=48.05%, p(heter)=0.009	Random effects model† Publication bias: p=0.03 Limitations: Small sample sizes in several subgroup analyses Other fatty acids (such as long–chain n–3 fatty acids and linolenic acid) were not included Adjustment for confounders varied between studies
			Adjusted for family history of breast cancer			RR=1.02 (0.93–1.11); p=0.02; I^2=38.18%, p(heter)=NR	
			Adjusted for BMI			RR=1.06 (0.98–1.13); I^2=36.49%, p(heter)=NR	
			Adjusted for reproductive variables			RR=1.05 (0.98–1.12); I^2=30.56%, p(heter)=NR	
			Highest vs lowest		ER+	RR range=1.05–1.27	
					ER–	RR range=0.47–0.84	
WCRF, 2017[10] Studies published to 2015	12 cohort studies	16,404 cases	Total fat intake Linear dose response (per 20 g/d)	Breast cancer		RR=1.02 (0.97–1.07); p=NS; I^2=27%, p(heter)=0.23	Model: NR Adjustments: Age and BMI
Europe, Japan, Singapore & North America	13 cohort studies	17,807 cases	Percentage of energy from fat Linear dose response (per 5% of energy)			RR=1.01 (0.99–1.02); I^2=0%, p(heter)=0.63	No publication bias (p>0.05) Limitations: NR
Randomised controlled trials							
Chlebowski et al., 2017[396] USA	WHI Dietary Modification Trial Study intervention: 20% fat–reduced diet with an increased intake in	Intervention group: 19,541 participants Control group: 29,294 participants 1,764 cases during	Reduced fat intake vs normal fat intake 16.1 y cumulative follow–up period	Breast cancer		HR=0.97 (0.90–1.04); p=0.34	Cox proportional hazard regression model Adjustments: Stratified by age at random assignment, random assignment status in the WHI hormone trials

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	fruits, vegetables & grains Study dates: 1993–1998 Median follow–up: 16.1 y Mean intervention time: 8.5 y	intervention time 3,030 cases during follow–up				and study period Limitations: Dietary intake measurement error Limited variation in dietary intake Common reliance on single dietary intake made before diagnosis

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; g/d, grams per day; HR, hazard ratio; NR, not reported; NS, not significant; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; WCRF, World Cancer Research Fund; USA, United States of America; WHI, Women's Health Initiative; y, year/s.

†Most studies adjusted for energy intake, BMI and reproductive factors. Around 50% of the included studies adjusted for family history of breast cancer, exogenous female hormones use, alcohol intake and education, while part of studies adjusted for smoking.

Table D.53 Diet—processed meat and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Farvid et al., 2018[401] Studies published to January 2018 Canada, Europe, France, Japan, Netherlands, Sweden, UK, USA	18 studies overall 15 studies investigated breast cancer and processed meat 7 studies pooled for risk of premenopausal breast cancer 10 studies pooled for risk of postmenopausal breast cancer	1,254,452 women 37,070 cases	Processed meat consumption (highest vs lowest category)	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=1.09 (1.03–1.16); I^2=44.4%, p(heter)=0.033 RR=1.09 (0.95–1.25); I^2=50.0%, p(heter)=0.062 RR=1.10 (1.03–1.17); I^2=30.8%, p(heter)=0.137	Random effects model Adjustments made in individual studies No publication bias (p=0.67) Limitations: Low statistical power among premenopausal women Possibility of residual confounding Highest vs lowest categorisation did not always match across studies Not direct generalisable to racial and ethnic groups
Anderson et al., 2018[402] Studies published January 2017 Europe, France, Sweden, UK, USA	10 cohort studies combined with UK Biobank 8 studies pooled for overall risk of breast cancer 5 studies pooled for risk of	1,648,994 women 40,257 cases	Processed meat consumption	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=1.06 (1.01–1.11); I^2=61.5%, p(heter)=0.011 RR=0.99 (0.88–1.10); I^2=39.5%, p(heter)=0.158 RR=1.09 (1.03–1.15); I^2=40.2%, p(heter)=0.137	Random effects model No publication bias (p>0.05) Adjustments: NR Limitations: No data on hormone receptor status

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	premenopausal breast cancer 6 studies pooled for risk of postmenopausal breast cancer					Confounders included were inconsistent between studies
Wu et al., 2016[360] Studies published to 2015 Asia, Europe & USA	12 cohort studies 4 studies 7 studies 14 cohort studies	Number of participants: NR 1,235,085 participants 26,952 cases	Processed meat Dose response (per 50 g/d) Highest vs lowest	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=1.09 (1.02–1.17); I^2=11.8%, p(heter)=0.329 RR=1.09 (0.94–1.26); I^2=21.5%, p(heter)=NR RR=1.10 (0.97 –1.26); I^2=34.7%, p(heter)=NR RR=1.07 (1.01–1.14); I^2=34.6%, p(heter)=0.098	Random effects model (highest vs lowest) Adjustments† No publication bias (p>0.05) Limitations: Unmeasured or residual confounders Different units used between studies
WCRF, 2017[10] Studies published to 2015 Europe & North America	13 cohort studies 4 cohort studies 8 cohort studies	22,735 cases 3,409 cases 13,708 cases	Processed meat Dose response (per 50 g/d)	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=1.08 (0.96–1.22); p=NS; I^2=72%, p(heter)=0.002 RR=1.02 (0.84–1.24); p=NS; I^2=31%, p(heter)=0.23 RR=1.13 (0.99–1.29); p=NS; I^2=47%, p(heter)=0.07	Model: NR Adjustments: NR No publication bias (p>0.05) Limitations: NR
Cohort studies						
Diallo et al., 2017[403] France	The French NutriNet–Santé cohort	61,476 participants 544 cases	Processed meat (pork and beef preserved by methods other than freezing)	Breast cancer		Cox proportional hazard model Adjustments§

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Cohort dates: 2009–2015‡ Prospective study Age at enrolment: ≥35 y Median follow–up: 4.1 y		Q1 (0–0.06 g/d) Q2 (0.06–5.36 g/d) Q3 (5.36–14.64 g/d) Q4 (14.64–29 g/d) Q5 (>29 g/d)		HR=1 (referent) HR=1.19 (0.88–1.62) HR=1.08 (0.83–1.39) HR=1.28 (1.00–1.64) HR=1.05 (0.80–1.38), p–trend=0.4	Limitations: Sample may be biased towards health–conscious participants and not representative of the French population
		169 cases	Q1 (0–11 g/d) Q2 (11–6.79 g/d) Q3 (6.79–16.43 g/d) Q4 (16.43–31.89 g/d) Q5 (>31.89 g/d)	Premenopausal breast cancer	HR=1 (referent) HR=1.62 (0.96–2.73) HR=1.09 (0.66–1.80) HR=1.34 (0.83–2.17) HR=1.30 (0.79–2.15); p–trend=0.5	
		375 cases	Q1 (0–0.06 g/d) Q2 (0.06–5.14 g/d) Q3 (5.14–14.29 g/d) Q4 (14.29–27.26 g/d) Q5 (>27.26 g/d)	Postmenopausal breast cancer	HR=1 (referent) HR=1.08 (0.73–1.60) HR=1.07 (0.79–1.44) HR=1.28 (0.95–1.72) HR=0.95 (0.69–1.32); p–trend=0.7	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; g/d, grams per day; HR, hazard ratio; n, number of studies; NR, not reported; NS, not significant; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; Q[1–5], quintile [1–5]; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

†Studies (n) adjusted for the following: age at menarche (n=6), age at first birth (n=7), fat (n=1), smoking (n=7), alcohol (n=7), body mass index (BMI) (n=5), BMI + alcohol (n=7), energy (n=7), OC use (n=4), hormone therapy (n=9).

‡2015 end date is reported in the Study's method section. Data tables reported Study's end date as 2016.

§Adjusted for age (timescale), sex, energy intake without alcohol, number of 24 hour dietary records, smoking status, educational level, physical activity, height, BMI, alcohol intake, family history of cancers, lipids intake, fruits, vegetables, hormone replacement therapy (for postmenopausal group), contraception (for premenopausal group), menopausal status, number of children and red meat intake.

Table D.54 Diet—red meat and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Anderson et al., 2018[402] Studies published to 2017 Europe, France, Sweden, UK, USA	UK Biobank cohort combined with 10 other cohort studies Median follow–up: 7 y 6 cohort studies 6 cohort studies	1.65 million women 40,257 cases	Red meat consumption	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=1.03 (0.99–1.08); I^2=44.0%, p(heter)=0.065 RR=1.02 (0.92–1.11); I^2=0.0%, p(heter)=0.530 RR=1.03 (0.97–1.08); I^2=34.6%, p(heter)=0.177	Random effects model Adjustments: NR No publication bias (Begg's test, Egger's test >0.05) Limitations: Inconsistent approaches in the number and range of confounders individual studies included
Farvid et al., 2018[401] Studies published to 2018 Europe, Japan and North America	13 studies 6 cohort studies 9 studies 2 studies	1,133,110 women 33,493 cases	Unprocessed red meat consumption Highest vs lowest NAT2 acetylator genotype: fast Per 25 g/d red meat NAT2 acetylator genotype: slow Per 25 g/d red meat	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer Breast cancer	Pooled RR=1.06 (0.99–1.14); I^2=56.3% RR=1.07 (0.97–1.18); I^2=30.9% RR=1.08 (0.99–1.17); I^2=53.2% OR=1.18 (0.93–1.50); I^2=67.8% OR=0.99 (0.91–1.08); I^2=0%	Model: NR Adjustments: NR Publication bias: NS Limitations Residual confounding cannot be excluded Most studies assessed diet by food frequency questionnaire, potentially leading to under or over reporting Majority of studies conducted in North America and Europe, and results may not be generalisable to other ethnic groups

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Wu et al., 2016[360] Studies published to 2015 Asia, Europe & USA	12 cohort studies 8 cohort studies	1,154,364 participants 23,667 cases	Fresh red meat Highest vs lowest Dose response (per 120 g/d)	Breast cancer	RR=1.07 (0.98–1.17); I^2=53.3%, p(heter)=NR RR=1.13 (1.01–1.26); I^2=56.4%, p(heter)=NR	Random effects model (highest vs lowest) Adjustments† No publication bias (p>0.05) Limitations: Unmeasured or residual confounders Different units used between studies
WCRF, 2017[10] Studies published to 2015 Asia, Europe & North America	6 cohort studies 3 cohort studies 5 cohort studies	9,614 cases 2,555 cases 8,784 cases	Unprocessed red meat Linear dose response (per 100 g/d) Linear dose response (per 100 g/d) Linear dose response (per 100 g/d)	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=1.12 (1.01–1.24); I^2=13.7%, p(heter)=0.33 RR=1.04 (0.84–1.29); p=NS; I^2=47%, p(heter)=0.15 RR=1.11 (0.97–1.27); p=NS; I^2=45%, p(heter)=0.12	Model: NR Adjustments: NR No publication bias (p>0.05) for breast cancer overall and postmenopausal breast cancer Limitations: NR
Cohort studies						
Diallo et al., 2017[403] France	The French NutriNet–Sante cohort Cohort dates: 2009−2015‡	61,476 participants 45,930 women 544 cases	Red meat (fresh, minced and frozen beef, veal, pork & lamb) Q1 (0–0.14 g/d) Q2 (0.14–24.67 g/d) Q3 (24.67–42.15 g/d) Q4 (42.15–65.71	Breast cancer	HR=1 (referent) HR=1.68 (1.23–2.31) HR=1.58 (1.14–2.17) HR=1.70 (1.24–2.34)	Multivariable Cox proportional hazard model Adjustments§ Limitations: Study participants were more health conscious and had higher professional and/or

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Prospective study Age at enrolment: ≥35 y Median follow–up: 4.1 y		g/d) Q5 (>65.71 g/d)		 HR=1.83 (1.33–2.51); p–trend=0.002	educational level than general population Limited cases per receptor subtype Unmeasured or residual confounders
			Q1 (0–0.29 g/d) Q2 (0.29–24 g/d) Q3 (24–42.14 g/d) Q4 (42.14–67.7 g/d) Q5 (>67.7 g/d)	Premenopausal breast cancer	HR=1 (referent) HR=3.36 (1.77–6.38) HR=2.37 (1.22–4.60) HR= 2.91 (1.52–5.57) HR= 2.04 (1.03–4.06); p–trend=0.4	
			Q1 (0–2.68 g/d) Q2 (2.68–25.37 g/d) Q3 (25.37–42.68 g/d) Q4 (42.68–65 g/d) Q5 (>65 g/d)	Postmenopausal breast cancer	HR=1 (referent) HR=1.28 (0.88–1.86) HR=1.46 (1.02–2.09) HR=1.40 (0.97–2.01) HR=1.79 (1.26–2.55); p–trend=0.002	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; g/d, grams per day; HR, hazard ratio; NAT2, N–acetyltransferase 2; NR, not reported; NS, not significant; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; Q[1–5], Quintile[1–5]; RR, relative risk or risk estimate; WCRF, World Cancer Research Fund; UK, United Kingdom; USA, United States of America; y, year/s.

†Studies (n) adjusted for the following: age at menarche (n=3), age at first birth (n=3), smoking (n=3), alcohol (n=1), BMI (n=3), BMI + alcohol (n=1), energy (n=2), OC use (n=2), hormone therapy (n=2).

‡2015 end date is reported in the Study's method section. Data tables reported Study's end date as 2016.

§Adjusted for age (timescale), sex, energy intake without alcohol, number of 24 hrs–dietary records, smoking status, educational level, physical activity, height, BMI, alcohol intake, family history of cancers, lipids intake, fruits, vegetables, menopausal status and number of children (breast cancer models), red meat intake (where processed meat was analysed) and processed meat intake (where red meat was analysed).

Table D.55 Environmental tobacco smoke and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Lee & Hamling, 2016[405] Studies published to 2015 Asia, Europe, Mexico & North America	47 studies 15 prospective cohort studies 30 case–control studies 2 case–control studies nested in prospective studies	Number of cases and controls: NR	Environmental tobacco smoke All studies Spouse Home Workplace Adulthood Childhood Prospective studies Spouse Home Workplace Adulthood Childhood Case–control studies Spouse	Breast cancer	RR=1.15 (1.07–1.23); I^2=139.64%, p(heter)<0.001 RR=1.14 (1.00–1.28); I^2=25.69%, p(heter)<0.05 RR=1.09 (1.03–1.16); I^2=70.05%, p(heter)<0.001 RR=1.03 (0.97–1.10); I^2=25.87%, p(heter)<0.05 RR=1.13 (1.04–1.22); I^2=28.96%, p(heter)<0.01 RR=1.00 (0.95–1.06); I^2=21.27%, p(heter)<NS RR=1.02 (0.97–1.08); I^2=19.69%, p(heter)=NS RR=1.07 (0.93–1.22); I^2=8.28%, p(heter)=NS RR=1.02 (0.97–1.07); I^2=17.86%, p(heter)=NS RR=1.01 (0.95–1.09); I^2=9.77%, p(heter)<0.1 RR=1.04 (0.99–1.80); I^2=0.57%, p(heter)=NS RR=0.98 (0.92–1.04); I^2=9.48%, p(heter)<0.1 RR=1.26 (1.13–1.41); I^2=100.78%, p(heter)<0.001 RR=1.24 (1.00–1.55); I^2=16.39%, p(heter)<0.05	Random effects multivariable adjusted model Individual studies adjusted for various factors. Majority of studies adjusted for at least age. Some publication bias, all studies p<.05 Limitations: Study weaknesses and publication bias

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Home		RR=1.18 (1.06–1.31); I^2=42.04%, p(heter)<0.01	
			Workplace		RR=1.08 (0.95–1.23); I^2=15.55%, p(heter)<0.05	
			Adulthood		RR=1.28 (1.11–1.49); I^2=15.10%, p(heter)<0.1	
			Childhood		RR=1.05 (0.97–1.15); I^2=8.60%, p(heter)=NS	
			All studies	Premenopausal breast cancer	RR=1.36 (1.15–1.60); I^2=68.33%, p(heter)<0.001	
				Postmenopausal breast cancer	RR=1.12 (1.00–1.25); I^2=58.28%, p(heter)<0.001	
			Prospective studies	Premenopausal breast cancer	RR=1.28 (0.92–1.77); I^2=15.48%, p(heter)<0.05	
				Postmenopausal breast cancer	RR=0.95 (0.90–1.00); I^2=4.95%, p(heter)=NS	
			Case–control studies	Premenopausal breast cancer	RR=1.40 (1.14–1.71); I^2=52.77%, p(heter)<0.001	
				Postmenopausal breast cancer	RR=1.23 (1.06–1.44); I^2=37.64%, p(heter)<0.001	
Macacu et al., 2015[406] Studies published to 2015 Asia, Europe & North America	31 Studies	34,715 cases	Ever passive smoking	Breast cancer	RR=1.20 (1.07–1.33); I^2=67%	Random effects meta–analysis models Adjustments: NR Publication bias was unlikely Limitations: Difficulty to assess exposure
	11 prospective cohort studies	18,022 cases			RR=1.07 (1.02–1.13); I^2=1%	
	20 retrospective studies	16,693 cases			RR=1.30 (1.10–1.54); I^2=74%	
Chen et al., 2014[407] Studies published to 2013	27 studies 2 cohort studies	9,591 cases 11,652 controls	Passive smoking	Breast cancer	OR=1.60 (1.39–1.82); I^2=75.1%, p<0.001	Random effects model Adjustments: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
China	25 case–control studies*		Cohort studies		OR=1.29 (0.25–2.33); I^2=74.2%, p=0.049	No evidence of publication bias Limitations: Moderate heterogeneity was observed in the primary analysis for passive smoking Cannot overcome the limitations of the original studies Potential confounding bias caused by other genetic and environmental factors
			Case–control studies		OR=1.64 (1.42–1.86); I^2=72.0%, p<0.001†	
			Heavy passive smoking from husband		OR=1.41 (0.95–2.09); I^2=81.6%, p<0.001	
			Light passive smoking from husband		OR=1.11 (0.98–1.26); I^2=0.7%,p=0.412	
			Heavy passive smoking from workplaces		OR=1.87 (0.94–3.72); I^2=62.7%, p=0.101	
			Light passive smoking from workplaces		OR=1.07(078–1.48); I^2=44.3%, p=0.180	
Yang et al., 2013[408] Studies published to 2011 Asia, Europe & USA	10 prospective cohort studies	782,534 non–smokers 14,831 cases Follow–up: mean 10.2 y	Passive smoking	Breast cancer		Random effects model and fixed effects model Adjustments‡ No evidence of publication bias Limitations: Variation in exposure measurement Heterogeneity between studies Dose response could not be conducted Language bias
			Overall		RR=1.01(0.96–1.06); I^2=41.3%, p=0.73	
			Childhood		RR=1.09 (0.99–1.20); I^2=0.0%, p=0.10	
			Adulthood		RR=1.03 (0.91–1.17); I^2=0.0%, p=0.63	
			Home		RR=0.96 (0.81–1.14); I^2=55.5%, p=0.67	
			Workplace		RR=1.01 (0.93–1.10); I^2=0.0%, p=0.76	
Chen et al., 2015[705]	8 case–control studies	4,542 cases 5,114 controls	Tobacco smoke pollution	Breast cancer	OR=1.67 (1.27–2.21)§	Random effects model and fixed effects model

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Studies published 2001–2011 China						Adjustments: NR Publication bias identified Limitations: Possibility of selection bias and information bias

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; USA, United States of America; y, year/s.

*This value is from Figure 3 in the study. In Table 1, 27 case–control studies are reported.

†This value is from Figure 3 in the study. In the results section of the study this value is represented as OR=1.66 (1.42–1.90).

‡All studies included adjustment for more than three variables, such as age, ethnicity, body mass index, menstrual status, family history of breast cancer, hormone use, socioeconomic status, alcohol, etc.

§This value is presented in the abstract. In the results section this is presented as OR=1.73 (1.29–2.33); χ^2=64.71, p(heter)=<0.00001.

Table D.56 Tobacco smoking and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Gaudet et al., 2017[414] Member cohort studies commenced 1980–2004 Australia, Norway, Singapore, Sweden & USA	14 member cohort studies from the National Cancer Institute Cohort Consortium	934,681 women 36,060 cases Mean follow–up period: 12.2–14.7 y Mean age at baseline: 53.9 y	Smoking status vs never smoked Current Former Smoking prior to first birth Never After first birth ≤5 years before birth 6–10 years before birth >10 years before birth	Breast cancer	 HR=1.07 (1.04–1.10); I^2=39% HR=1.06 (1.04–1.09); I^2<1% HR=1.00 (referent) HR=1.05 (1.00–1.11); I^2<1% HR=1.06 (1.02–1.09); I^2=34% HR=1.10 (1.06–1.14); I^2=55% HR=1.18 (1.12–1.24); I^2=36%, p–trend=2x10^{-7}	Multivariable adjusted Cox proportion hazard models Results adjusted* Limitations: Unable to define a reference group that excluded passive smokers or lifelong never drinkers Unable to harmonise variables
Macacu et al., 2015[406] Studies published to 2015 Asia, Europe & North America	7 studies 27 cohort studies 44 case–control studies 49 studies 27 cohort studies 22 case–control studies	125,251 cases 68,440 cases 56,811 cases 103,893 cases 63,087 cases 40,806 cases	Active smoking Ever Current	Breast cancer	 SRR=1.09 (1.06–1.12); I^2=46% SRR=1.10 (1.09–1.12); I^2=0% SRR=1.08 (1.02–1.14); I^2=59% SRR=1.11 (1.06–1.16); I^2=56% SRR=1.13 (1.09–1.17); I^2=35% SRR=1.08 (0.97–1.20); I^2=69%	Random effects model Adjustment; NR No evidence of publication bias Limitations: Observational epidemiologic studies limitations (selection bias) Residual confounding Limited number of available data Difficulty to assess exposure

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Gaudet et al., 2013[706] Studies published to 2012 Canada, Japan, Norway, Sweden & USA	15 cohort studies	991,100 women 31,198 cases	Active smoking vs never Current Former Smoking initiation before first birth	Breast cancer	 HR=1.12(1.08–1.16); I^2=6.9%, p=0.38 HR=1.09 (1.04–1.15); I^2=56.3%, p=0.004 HR=1.21(1.14–1.28); I^2=0.0%, p=0.62	Fixed effects model Adjustments: none No publication bias: Begg test Limitations: Unable to define a reference group that excluded passive smokers or lifelong never drinkers
Cohort studies						
Jones et al., 2017[415] UK	Generations Study cohort June 2003–December 2013 Mean follow–up: 7.7 y, or 788,361 person–y Age at recruitment: 16–102 y	102,927 women 1,815 cases Participants did not have a history of invasive or in situ breast cancer or other malignant cancer or prior mastectomy 1,073 cases 742 cases	Smoking vs never smoked Never smoked Ever smoked vs never smoked	Breast cancer	 HR=1.00 (referent) HR=1.14 (1.03–1.25); p=0.010	Cox proportional hazards regression model Adjustments† Limitations: No direct information on passive smoking, so risk estimates may be underestimated if never–smokers were exposed to passive smoking and if passive smoking is a risk factor for breast cancer
			Age started smoking vs never smoked			
		261 cases 304 cases 151 cases	<17 y 17–19 y 20+ y		HR=1.24 (1.08–1.43); p=0.0023 HR=1.15 (1.01–1.031); p=0.030 HR=1.00 (0.84–1.18); p=0.96	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		26 cases	Age unknown		HR=0.94 (0.64–1.39); p=0.76, p–trend=0.18	
			Years started after menarche			
		266 cases	1–4 y		HR=1.23 (1.07–1.41); p=0.0040	
		295 cases	5–9 y		HR=1.13 (0.99–1.29); p=0.071	
		43 cases	10–14 y		HR=1.04 (0.76–1.41); p=0.82	
		18 cases	15+ y		HR=0.81 (0.51–1.30); p=0.39	
		86 cases	Interval unknown		HR=0.99 (0.77–1.27); p=0.92, p–trend=0.031	
			Duration of smoking:			
		1,073 cases	Never smoked		HR=1.00 (referent)	
		177 cases	1–9 y		HR=1.00 (0.85–1.18); p=0.97	
		225 cases	10–19 y		HR=1.21 (1.05–1.41); p=0.009	
		141 cases	20–29 y		HR=1.21 (1.02–1.45); p=0.033	
		159 cases	30+ y		HR=1.22 (1.02–1.44); p=0.026	
		40 cases	Duration unknown		HR=0.93 (0.68–1.28); p=0.66, p–trend=0.24	
			Pack–years smoked			
		1,073 cases	Never smoked		HR=1.00 (referent)	
		182 cases	1 to <5 y		HR=1.10 (0.94–1.29); p=0.25	
		103 cases	5 to <10 y		HR=1.05 (0.85–1.28); p=0.66	
		138 cases	10 to <20 y		HR=1.27 (1.06–1.52); p=0.010	
		114 cases	20+ y		HR=1.45 (1.19–1.77); p=0.0002	
		205 cases	Amount unknown		HR=1.03 (0.88–1.20); p=0.70, p–trend=0.0069	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Dartois et al., 2016[44] France	E3N–EPIC cohort 1993–2008 Prospective cohort study Women aged 47–72 y at baseline Follow–up: 15 y or 876,468 person–y; median follow–up of 7 y for cases and 13 y for non–cases	67,634 participants 497 premenopausal cases 3,138 postmenopausal cases 63,999 non–cases	Tobacco smoking Current smoker	Premenopausal breast cancer Postmenopausal breast cancer	HR=0.96 (0.71–1.28) HR=0.99 (0.88–1.13)	Multivariable adjusted Cox proportional hazard regression model Adjustments‡ Limitations: E3N population not representative of the general population and is prone to a healthy cohort effect Limited number of premenopausal breast cancer cases observed
			Past smoker	Premenopausal breast cancer Postmenopausal breast cancer	HR=1.15 (0.95–1.40) HR=1.01 (0.94–1.09)	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BMI, body mass index; E3N, Étude épidémiologique auprés des femmes de la mutuelle générale de l'éducation nationale; ER, oestrogen receptor; HR, hazard ratio; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; SSR, summary relative risk; UK, United Kingdom; USA, United States of America; y, year/s.

*Multivariable–adjusted models included age, cohort, race/ethnicity, education, birth year, family history of breast cancer, history of benign breast disease, ever use of oral contraceptives, menopausal status and age at menopause, age at menarche, ever use of menopausal hormone therapy, age at first birth and number of live births, BMI, and amount and frequency of alcohol use.

†Adjusted for time since recruitment to cohort; birth cohort; benign breast disease; family history of breast cancer in first–degree relatives; socio–economic score; age at menarche; age at first pregnancy; parity; duration of breastfeeding; current oral contraceptive use during follow–up, before menopause; alcohol consumption; physical activity; premenopausal BMI at age 20 years; post–menopausal BMI; menopausal hormone therapy use; menopausal status (premenopausal or postmenopausal); and age at menopause.

‡HRs were adjusted for age (as the time scale), first–degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at first full term pregnancy, physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and ultraviolet (UV) radiation, oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).

Table D.57 Physical activity and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Kyu et al., 2016[423] Canada, China, Finland, Japan, Norway, Sweden & USA Studies published 1980–2016	35 prospective cohort studies	Women's age 15–102 y, with one study reporting 45+ y Follow up: median 48 months–16.4 y; 50,949,108 person–y	MET minutes/week <600 600–3,999 4,000–7,999 ≥8,000	Breast cancer	RR=1.00 (referent) RR=0.967 (0.937–0.998) RR=0.941 (0.904–0.981) RR=0.863 (0.829–0.900)	Bayesian meta–regression tool Adjustments: NR No significant evidence of publication bias for breast cancer Limitations: Missed articles as a result of restricting our search to two databases & studies published in English Could not account for the potential for residual confounding or effect modification Dose–response meta–analysis included studies that measured physical activity qualitatively could lead to regression dilution bias
WCRF, 2017[10] Studies published to 2015 Asia, Europe & North America	7 cohort studies 4 cohort studies 8 cohort studies 7 cohort studies	10,633 cases 1,834 cases 11,798 cases 17,688 cases	Total physical activity Highest vs lowest Occupational	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	RR=0.91 (0.82–1.02); I^2=38%, p(heter)=0.14 RR=0.93 (0.79–1.08); I^2=0%, p(heter)=0.95 RR=0.87 (0.79–0.96); I^2=16%, p(heter)=0.30	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			physical therapy Highest vs lowest	Breast cancer	RR=0.93 (0.87–0.99); I^2=0%, p(heter)=0.55	
	6 cohort studies	4,494 cases		Premenopausal breast cancer	RR=0.82 (0.59–1.15); I^2=76%, p(heter)=0.001	
	8 cohort studies	22,352 cases		Postmenopausal breast cancer	RR=0.89 (0.83–0.96); I^2=0%, p(heter)=0.57	
	19 cohort studies	28,659 cases	Recreational physical activity Highest vs lowest	Breast cancer	RR=0.92 (0.89–0.96); I^2=10%, p(heter)=0.33	
	10 cohort studies	>3,901* cases		Premenopausal cancer	RR=0.93 (0.74–1.16); I^2=59%, p(heter)=0.01	
	17 cohort studies	>24,253* cases		Postmenopausal cancer	RR=0.87 (0.81–0.94); I^2=37%, p(heter)=0.06	
	5 cohort studies	15,453 cases	Per 10 MET–hour/week	Breast cancer	RR=0.95 (0.92–0.99); I^2=60%, p(heter)=0.04	
	3 cohort studies	2,331 cases		Premenopausal breast cancer	RR=0.96 (0.90–1.03); I^2=69%, p(heter)=0.04	
	5 cohort studies	18,486 cases		Postmenopausal breast cancer	RR=0.98 (0.97–0.99); I^2=0%, p(heter)=0.68	
	7 cohort studies	7,694 cases	Vigorous physical activity Highest vs lowest	Breast cancer	RR=0.86 (0.79–0.93); I^2=0%, p(heter)=0.72	
	6 cohort studies	4,452 cases		Premenopausal breast cancer	RR=0.83 (0.73–0.95); I^2=17%, p(heter)=0.31	
	11 cohort studies	20,171 cases		Postmenopausal breast cancer	RR=0.90 (0.85–0.95); I^2=0%, p(heter)=0.96	
	6 cohort studies	6,944 cases	Per 30 minutes/day	Breast cancer	RR=0.95 (0.91–1.00); I^2=37%, p(heter)=0.16	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	3 cohort studies	1,473 cases		Premenopausal breast cancer	RR=0.91 (0.83–1.01); I^2=0%, p(heter)=0.63	
	3 cohort studies	3,293 cases		Postmenopausal breast cancer	RR=0.94 (0.86–1.02); I^2=0%, p(heter)=0.95	
	5 cohort studies	6,472 cases	Walking Highest vs lowest	Breast cancer	RR=0.88 (0.81–0.96); I^2=0%, p(heter)=0.47	
	4 cohort studies	7,300 cases		Postmenopausal breast cancer	RR=0.94 (0.86–1.04); I^2=0%, p(heter)=0.99	
Neilson et al., 2017[422] Studies published to 2015 Australia, Canada, China, Denmark, France, Germany, Greece, Italy, Japan, Mexico Norway, Poland, Spain, Switzerland, Netherlands, UK & USA	36 case–control studies 13 cohort studies	Baseline age: all ages Total number of participants & cases: NR	Moderate–vigorous recreational physical activity	Premenopausal breast cancer	RR=0.80 (0.74–0.87); I^2=71.1%, p(heter)<0.001	Random effects model Adjustments: NR Possible publication bias Limitations: Substantial heterogeneity observed: measurement error, covariate adjustment, & clinical heterogeneity probably all contributed Subgroup analyses were limited by the low number of premenopausal studies
	38 case–control studies 26 cohort studies			Postmenopausal breast cancer	RR=0.79 (0.74–0.84); I^2=76.1%, p(heter)<0.001	
Moore et al., 2016[425] Studies commenced 1987–2004 Europe & USA	10 prospective cohort studies from the Physical Activity Collaboration of the National Cancer Institute's Cohort Consortium Median follow–up: 7–21 y	35,178 cases Median age: 45–63 y (including male participants)	Leisure–time physical activity Higher vs lower	Breast cancer BMI adjusted	HR=0.90 (0.87–0.93); p(heter)=0.30 HR=0.93 (0.90–0.96)	Cox proportional hazards models Adjustments† Limitations: Residual confounding by diet, smoking or other factors may affect results Self–reported physical activity

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						entails some error in recall Not all cohorts assessed moderate & vigorous intensity activities separately Several cohorts lacked key details needed to calculate MET–hours per week of physical activity
Pizot et al., 2016[424] Studies published 1987–2014 Canada, Europe, Japan & USA	38 prospective cohort studies	4,124,275 women 116,304 cases Age: all ages Follow–up: 4–32 y	Physical activity Highest vs lowest	Breast cancer	RR=0.88 (0.85–0.90); I^2=29%, Q=52.19	Dose–response meta–analysis using all studies was not performed because quantification & reporting of physical activity was too heterogeneous across studies Limitations: Inclusion of in situ breast cancer could have weakened the preventive effect of physical activity Stratified results on menopausal status could be biased as menopausal status of women was unknown in 43% of women & many studies did not report results according to menopausal status
	18 prospective cohort studies			Premenopausal breast cancer	RR=0.87(0.78–0.96); I^2=51%	
	32 prospective cohort studies			Postmenopausal breast cancer	RR=0.88 (0.85–0.91); I^2=19%	
	12 prospective cohort studies			ER+PR+ Breast cancer	RR=0.89 (0.83–0.95); I^2=0%	
	11 prospective cohort studies			ER–PR– Breast cancer	RR=0.80 (0.69–0.92); I^2=7%	
	11 prospective cohort studies		≥5 hours/week vs no/limited vigorous physical activity	Breast cancer	RR=0.82 (0.77–0.87)	
Cohort studies						
Johnsson et al., 2017[426]	Population–based cohort study	29,524 women 1,506 cases	Sedentary occupation <55 y	Breast cancer	HR=1.20 (1.05–1.37); p<0.05 HR=1.54 (1.20–1.96); p<0.05	Cox regression Adjustments‡

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Sweden	Cohort dates: 1990–2013 Aged 25–64 y at enrolment Duration of follow–up: 583,293 person–y, average 19.8 y		>55 y		HR=1.03 (0.88–1.22); p>0.05	Limitations: Misclassification, in physical activity exposure (sedentariness vs light physical activity) No inclusion of leisure time physical activity in the analyses Missing data on BMI included later in follow up
Harris et al., 2016[427] Sweden	Swedish Mammography Cohort Follow–up: 15 y Women recruited 1987–1990	31,514 women 1,388 cases Women born 1914–1948	Physical activity ≥30 minutes/day combined walking/ cycling & leisure time activity	Breast cancer	HR=0.84 (0.72–0.99)§ HR=0.86 (0.73–1.01)¶	Cox proportional hazard model Adjustments§ Limitations: Measurement errors due to questionnaires being self–administered Possible misclassification in level of exposure of physical activity

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AICR, American Association for Cancer Research; BMI, body mass index; ER, oestrogen receptor; g/d, grams per day; HR, hazard ratio; NR, not reported; MET, metabolic equivalent; p, p–value; p(heter), p–value for the measure of heterogeneity; PR, progesterone receptor; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; WCRF, World Cancer Research Fund.

*Number of pre– and postmenopausal cancer cases unclear in some publications.

†Adjusted for age, sex, smoking status (never, former, current), alcohol consumption (0, 0.1–14.9, 15.0–29.9, and 30.0 g/d), education (did not complete high school, completed high school, post–high–school training, some college, completed college), and race/ethnicity (white, black, other), postmenopausal hormone therapy use (ever, never), oral

contraceptive use (ever, never), age at menarche (<10, 10–11, 12–13, ≥14 years), age at menopause (premenopausal, 40–44, 45–49, 50–54, ≥55 years), and parity (0, 1, 2, >=3 children).

‡Adjusted for: age at inclusion, competitive sports, family history of breast cancer (first degree relatives), age at birth of first child, age at menarche, use of oral contraceptive, education in years and BMI.

§HR was adjusted for age (continuous), height (continuous), education (primary school, high school, university), oral contraceptive use (ever, never), hormone therapy use (ever, never), age at menarche (≤12, 13, ≥14 years), age at menopause (premenopausal, <51, ≥51 years), family history of breast cancer (yes, no), history of benign breast disease (yes, no) and smoking status (never, former <20 pack–years, former ≥20 pack–years, current <20 pack–years, current ≥20 pack–years).

¶Adjusted as for § and with all WCRF/AICR recommendations included.

Table D.58 Shift work disrupting circadian rhythm and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Travis et al., 2016[434]	10 cohort studies	1.4 million women	Shift work	Breast cancer		Cox regression model
Studies published to 2015		4,660 cases	Ever		RR=0.99 (0.95–1.03); p(heter)=0.052	Adjustments*
	8 studies		≥20 y		RR=1.01 (0.93–1.10); p(heter)=0.011	Publication bias: NR
China, Europe & USA	4 studies		≥30 y		RR=1.00 (0.87–1.14); p(heter)=0.067	Limitations: Small number of women reporting shift work
Lin et al., 2015[435]	16 cohort studies	2,020,641 participants	Rotating shift work vs day shift	Breast cancer	ES=1.09 (1.02–1.17); I^2=0.0%, p(heter)=0.838	Random effects and fixed effects model
Studies published to 2014		10,004 cases	Fixed night shift work		ES=0.87 (0.72–1.05)	Adjustment: NR
China, Japan, Scandinavia, Netherlands & USA			Night shift work Total		ES=1.06 (1.01–1.10); I^2=9.2%, p(heter)=0.358	Publication bias: Begg's &Egger's test
			<5 y		ES=1.03 (0.97–1.09); I^2=31.6%, p(heter)=0.223	Limitations: Heterogeneity
			5 y		ES=1.02 (1.00–1.04); I^2=17.7%, p(heter)=0.302	
			5–10 y		ES=1.03 (1.01–1.04); I^2=43.7%, p(heter)=0.149	Some unmeasured or inadequately measured factors might affect the true association
			10–20 y		ES=1.07 (1.01–1.14); I^2=0.0%, p(heter)=0.531	
			>20 y		ES=1.09 (1.01–1.17); I^2=37.8%, p(heter)=0.185	Insufficient investigation on the mortality of each tumour in relation to night shift work
			Night shift work 5–year incremental		ES=1.03 (1.01–1.04; I^2=43.7%,	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			risk		p(heter)=0.149	
He et al., 2015[436] Studies published to 2014 Australia, China, Europe, Canada & USA	15 studies 4 cohort 3 nested case–control 7 case–control 12 studies 9 case–control studies 3 cohort studies	1,728,237 participants included in meta–analysis of 28 studies	Night shift work Per 10 y increment of shift work	Breast cancer	RR=1.19 (1.08–1.32); I^2=76.1%, p(heter)<0.001 RR=1.06 (0.98–1.15); p=NS RR=1.16 (1.06–1.27); p=sig. RR=1.03 (0.95–1.11); p=NS	Random effects model Adjustments: NR No publication bias: Egger's test p=0.548. Limitations: Large variation in the definition of sleep disruption The dose–response meta–analysis only includes 3 cohort studies Some of the primary studies in the meta–analyses did not appropriately adjust for confounders
Wang et al., 2013[438] Studies published to 2013 China, Scandinavia, Germany & USA	10 studies 3 cohort studies 3 nested case–control studies 4 case–control studies (3 population–based) Cohort studies only	8116 participants 4,510 cohort study participants 1,340 nest case–control participants 2,266 case–control participants	Shift work Ever Duration of night shift work (5 y incremental)	Breast cancer	RR=1.19=(1.05–1.35); I^2=NR RR=1.03 (1.01–1.05); I^2=70.0%, p(heter)<0.001 RR=1.02 (1.00–1.04); I^2=34.3%, p(heter)=0.22	Generalised least–squared trend model, random effects model and fixed effects model Adjustments: NR Publication bias: NS, p=0.365 Limitations: All cohort studies had low quality scores

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Nested case–control and case–control studies only				RR=1.06 (1.02–1.09); I^2=74.6%, p(heter)=0.001	Variations in the definition of night shift work across studies—misclassification of studies Residual confounding effect in some studies with less adjustment cannot be ruled out
Jia et al., 2013[437] Studies published to 2012 China, Scandinavia, France, Germany & USA	13 studies 5 cohort studies 8 case–control studies	Number of participants: NR	Night work	Breast cancer	RR=1.20 (1.08–1.33); p(heter)<0.001 RR=1.08 (0.97–1.21); p=0.146; p(heter)=0.019 RR=1.36 (1.24–1.48); p<0.001; p(heter)=0.137	Random effects model Most studies adjusted for age or parity No publication bias: Egger's test p=0.086 Limitations: Only 4 studies reported data on women who had worked for 15 years or longer exposure to shift work Most of the estimates of risk are 'crude' based on variable definitions of night–work, different study designs with high–risk of bias, and lack of controlling for confounders
Kamdar et al., 2013[439] Studies published to 2012 China, Europe &	15 studies 5 cohort studies	1,422,189 women 4,569 cases	Ever worked night shift work vs never worked night shift	Breast cancer	RR=1.21(1.00–1.47); p=0.056; I^2=75.8%, p(heter)<0.001 RR=1.14 (0.85–1.53); I^2=76%, p(heter)=NR	Random effects model Adjustments: NR No evidence of publication bias: Egger's test

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
USA	10 case–control studies	10,635 cases 15,716 controls			RR=1.28 (1.03–1.60); I^2=52%, p(heter)<0.01	Limitations: Some studies did not adjust for any confounders No quality appraisals of any of the included studies
Cohort studies						
James et al., 2017[441] USA	NHS II cohort 1989–2013 Prospective study Age at enrolment: 25–42 y Follow–up: over 2,187,425 person–y	109,672 women 3,549 incidence cases Registered nurses 95% Caucasian ethnicity	Cumulative outdoor light at night exposure (per IQR increase)	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	HR=1.05 (1.00–1.11) HR=1.07 (1.01–1.14) HR=1.00 (0.91–1.09)	Cox proportion hazard model Adjustments† Limitations: Exposure misclassification Participant self–selection Insufficient power to detect associations with ethnicity Correlation between outdoor light at night activity and other risk factors for breast cancer may explain the association observed
			No night shift work since 1989 Any night shift work since 1989	Breast cancer	HR=1.03 (0.97–1.09) HR=1.09 (1.01–1.18)	
Wegrzyn et al., 2017[440] USA	NHS I & NHS II cohorts Cohort enrolment dates: 1988 (NHS I); 1989 (NHS II) Age at baseline: 25–67 y	193,075 women 9,541 cases	Rotating night shift work history (1988–2012) None 1–14 y 15–29 y ≥30 y	Breast cancer	HR=1.00 (referent) HR=1.01 (0.96–1.07) HR=1.06 (0.94, 1.19) HR=0.95 (0.77–1.17); p–trend=0.63	Multivariable Cox proportion hazard adjusted model Adjustments‡§ Limitations: Exposure definition may not have captured the intensity or pattern of night shift work that is most disruptive and limited
			NHS II rotating night–			

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Prospective study Follow–up: 24 y		shift work history (1989–2013) None 1–9 y 10–19 y ≥20 y		 HR=1.00 (referent) HR=1.05 (0.98–1.13) HR=1.00 (0.85–1.17) HR=2.15 (1.23–3.73); p–trend=0.23	the identification of a dose–response relationship Limited power in the highest exposure categories Unable to evaluate breast cancer risk by histologic type

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: ES, pooled estimate; HR, hazard ratio; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; NR, not reported; NS, not significant; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for the measure of trend; RR, relative risk or risk estimate; USA, United States of America; y, year/s.

*Adjusted for socioeconomic status, age at menarche, parity, age at first birth, body mass index, alcohol intake, smoking, strenuous physical activity, family history of breast cancer, living with a partner, use of oral contraceptives, menopausal hormone therapy.

†Adjusted for benign breast disease history, family history of breast cancer, age at menarche, parity and age at first birth, height, race, body mass index (BMI), BMI at age 18, oral contraceptive use, mammography screening, menopausal status, smoking status, alternative healthy eating index, physical activity, marital status, living alone, personal income, shift work after 1989, region, particulate matter <2.5µm, census–tract median home value, income, and population density.

‡Adjusted for age (months), height (inches; continuous), body mass index (weight (kg)/height (m)2; <18.5, 18.5–24.9, 25.0–29.9, or ≥30), body mass index at age 18 years (<18.5, 18.5–24.9, 25.0–29.9, or ≥30), adolescent body size (average of diagram scores at ages 10 and 20 years; 1.0, 1.5–2.0, 2.5–3.0, 3.5–4.0, or ≥4.5), age at menarche (<12, 12–13, or ≥14 years), age at first birth and parity combined (for NHS: nulliparous, age <25 years and 1–2 children, age <25 years and ≥3 children, age 25–29 years and 1–2 children, age 25–29 years and ≥3 children, age ≥30 years and 1–2 children, or age ≥30 years and ≥3 children; for NHS II: nulliparous, parous age <25 years, parous age 25–29 years, or parous age ≥30 years), breastfeeding (for NHS: none, 1–11 months, or ≥12 months; for NHS II: none, 1–12 months, or >12 months), type of menopause and age at menopause combined (premenopausal, naturally postmenopausal at age <45 years, naturally postmenopausal at age ≥45 years, surgically postmenopausal at age <45 years, or surgically postmenopausal at age ≥45 years), menopausal hormone therapy use (never, past, or current), duration of use of menopausal hormone therapy with oestrogen alone (months; continuous), duration of use of oestrogen and progesterone menopausal hormone therapy (months; continuous), first–degree family history of breast cancer (yes or no), history of benign breast disease (yes or no), alcohol consumption (0.0, 0.1–14.0, 14.1–28.0, or >28 g/day), physical activity level (≤8.0, 8.1–16.0, 16.1–24.0, or >24 metabolic equivalent–hours/week), and current mammography use (yes or no). All categorical covariates were included in models with missing indicators.

§†In the NHS II, analyses using updated data on duration of shift work excluded participants during the cycles in which they were missing information on shift work exposure, resulting in fewer cases and person–years than in analyses using history of shift work reported at baseline in 1989.

Medical factors

Table D.59 Aspirin and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Lu et al., 2017[454] Studies published 2002–2015 Denmark, Netherlands, UK & USA	13 cohort studies	857,831 women Duration of follow–up: 4.4–14 y	Aspirin intake Overall Frequency of use 5 times/week 10 times/week 20 times/week Duration of use 5 y 10 y 20 y	Breast cancer	 RR=0.94 (0.87–1.01); I^2=51.2%, p(heter)=0.005 RR=0.97 (0.95–0.99) RR=0.95 (0.90–0.99) RR=0.90 (0.81–0.99); I^2=75.3%, p(heter)=0.000 RR=0.86 (0.77–0.95) RR=0.73 (0.59–0.91) RR=0.54 (0.35–0.82); I^2=34.9%, p(heter)=0.138	Random effects model† No publication bias (p>0.05) Limitations: Limited studies for subgroup analysis Adjustments differed between included studies
de Pedro et al., 2015[450] Studies published to 2013 Denmark, Spain, UK & USA	22 studies 13 cohort studies 9 case–control studies	Number of participants: NR	Aspirin use Users vs non–users	Breast cancer	 RR=1.00 (0.96–1.04); I^2=11.7%, p(heter)=NR OR=0.87 (0.82–0.92), I^2=4.5%, p(heter)=NR	Fixed effects model (Q>0.1)/random effects model Adjustments: NR Publication bias (p<0.1) Limitations: NSAID doses or duration of use not studied Several articles failed to define "any NSAID" NSAID not uniformly recorded

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						across studies
Zhong et al., 2015[451] Studies published 1977–2015 Denmark, UK & USA	32 cohort & case–control studies 8 cohort studies 6 case–control studies	1,350,913 participants	Aspirin use Dose–response (per 3 pills/week) Dose–response (per 1 y increment)	Breast cancer	 RR=0.96 (0.92–0.99); p=0.02 RR=0.98 (0.97–1.00); p=0.02	Random effects model Adjustments: NR Publication bias (p<0.05) Limitations: Publication bias & heterogeneity Unadjusted measured related to aspirin use Limited power for subgroup analyses Most studies conducted in western countries
Bosetti et al., 2012[444] Studies published to 2011 Canada, Denmark, Netherlands, UK & USA	22 cohort studies 10 case–control studies	52,926 cases	Aspirin use Users vs non–users Overall Duration of use < 5 y ≥5 y	Breast cancer	 RR=0.90 (0.85–0.95); p<0.001; I^2=63%, p(heter)=0.05 RR=0.96 (0.91–1.02) RR=0.93 (0.84–1.03); p(heter)=0.594	Random effects model Adjustments: NR Publication bias (p<0.05) Limitations: Measurement errors in the exposure to aspirin High variability of aspirin use definitions across studies

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Algra et al., 2012[449] Studies published 1950–2011 Canada, Denmark, UK & USA	11 cohort studies 15 case–control studies	6,720 aspirin users in 31,075 cases 87,996 aspirin users in 246,037 controls	Aspirin use Users vs non–users	Breast cancer	RR=0.88 (0.82–0.95); p=0.0007; p(heter)<0.0001	Random effects model Adjustments: Age & other baseline clinical characteristics for maximum aspirin use Publication bias: NR Limitations: NR
	11 cohort studies	Aspirin users: 5,262 events/1,357,845 total person–y Non–users: 8,233 events/2,766,903 total person–y			RR=1.04 (0.91–1.19); p=0.52; p(heter)<0.0001	
	9 cohort studies	Aspirin users: 1,363 events/295,849 total person–y Non–users: 6,350 events/1,663,347 total person–y	Maximum aspirin use		RR=0.98 (0.85–1.14); p=0.83; p(heter)<0.0001	
Zhao et al., 2009[452] Studies published to 2008 Canada, Denmark, UK & USA	20 case–control & cohort studies	23,217 cases among 241,050 NSAID users 24,539 cases among 287,655 non–NSAID users	Aspirin use (low dose of 81 mg) Users vs non–users	Breast cancer	RR=0.91 (0.85–0.98); p=0.02; I^2=85%, p(heter)=NR	Random effects model Adjustments: NR No publication bias Limitations: All studies are observational studies Self–reported exposure of NSAIDs English language only studies
Takkouche et al., 2008[453] Studies publications 1966–2008	27 cohort and case–control studies	Number of participants: NR	Aspirin use Users vs non–users	Breast cancer	RR=0.87 (0.82–0.92); Ri=0.74, p(heter)<0.001	Random effects model Adjustments: NR
	18 cohort studies				RR=0.92 (0.86–0.97); Ri=0.70, p(heter)<0.001	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Canada, Denmark, Spain, UK & USA	9 case–control studies				RR=0.79 (0.72–0.86); Ri=0.39, p(heter)=0.12	No publication bias (p>0.05) Limitations: Recall bias Behaviours that are associated with NSAID use may not be adjusted for
Cohort studies						
Clarke et al., 2017[455] USA	California Teachers Study Cohort study dates: 2005−2012 Prospective study Age at enrolment: NR Median follow–up: 7 y	133,479 women; 1,457 cases Median age at 10 y follow–up: 61 y	Aspirin use	Breast cancer		Multivariable Cox proportional hazards regression model‡ Limitations: Limited numbers available by subtype of breast cancer Residual unmeasured confounding Not generalisable to other populations
		6,387 women 338 cases	Current use of 81 mg low–dose aspirin (≥3 tablets/week) vs no NSAID past 3 years		HRR=0.84 (0.72–0.98)	
		6,387 women 230 cases		HR+/HER2–	HRR=0.80 (0.66–0.96)	
		6,387 women 170 cases	Current use of 325 mg regular–dose aspirin (≥3 tablets/week) vs no NSAID past 3 years	Breast cancer	HRR=0.97(0.80–1.18)	
Bardia et al., 2016[456] USA	Iowa Women's Health Study Cohort dates: 1992−2005	26,580 women 1,581 cases	Aspirin use	Postmenopausal breast cancer		Cox proportional hazard model§ Limitations: Type, dose, or duration of aspirin not assessed
		46 cases/7,683 person–y	Family history of breast cancer 6+ times/week vs		HR=0.62 (0.41–0.93); p–trend=0.029	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Prospective study		never use			Majority participants were Caucasian
	Age at enrolment: 55−69 y	215 cases/47,012 person–y	No family history of breast cancer 2–5 times/week vs never use		HR=0.78 (0.65–0.94); p–trend<0.001	Potential self–selection and confounding
	Duration of follow up: 307,178 person–y	412 cases/84,158 person–y	BMI of <30 kg/m^2 ≤1week vs never use		HR=0.83 (0.71–0.97); p–trend<0.001	Limited power to identify subgroup effects
		513 cases/100,705 person–y	Age at menarche 11+ years ≤1 times/week vs never use		HR=0.87 (0.76–0.99); p–trend<0.001	
		226 cases/47,270 person–y	Age at menopause <55 y 2−5 times/week vs never use		HR=0.79 (0.66–0.94); p–trend<0.001	
		444 cases/89,485 person–y	Parity/Age at first live birth 1+/≤30 years ≤1 times/week vs never use		HR=0.85 (0.74–0.99); p–trend<0.001	
		78 cases/13,451 person–y	Personal history of benign breast disease 6+ times/week) vs never use		HR=0.69 (0.50–0.95); p–trend=0.004	
Randomised controlled trials						
Cook et al., 2005[707] USA	Women's Health Study Study duration: 1993−2004	39,876 females 19,934 received aspirin: 9,966 also received vitamin E	100 mg aspirin vs placebo, every 2 days	Breast cancer (as secondary endpoint)	RR=0.98 (0.87–1.09); p=0.68	Cox proportional hazards regression model Adjustments: Stratification by confounders, including smoking

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Mean age at enrolment: 54.6 y Mean follow–up: 10.1 y	19,942 received placebo; 9,971 also received vitamin E 1,230 invasive cases: 608 in intervention group 622 in placebo group Age: ≥45 y				Limitations: NR

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BMI, body mass index; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; HR, hazard ratio; HRR, hazard rate ratio; mg, milligrams; NR, not reported; NSAID, non–steroidal anti–inflammatory drug; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; Q, Q test to evaluate the heterogeneity among studies; Ri, proportion of total variance due to between–study variance; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

†Most risk measures were adjusted for age (12 studies), health history (9 studies), body mass index (BMI) (9 studies), education (6 studies), use of hormone therapy (6 studies) or alcohol consumption (6 studies); less were adjusted for mammography (5 studies), smoking (3 studies), non–steroidal anti–inflammatory drug (NSAIDs) use (4 studies), physical activity (3 studies), contraceptive use (3 studies) or weight (3 studies).

‡Adjusted for age at menarche, parity and age at first full–term pregnancy, total months breastfeeding their offspring, history of a benign breast biopsy, family history of breast cancer (mother or sister), strenuous plus moderate physical activity, alcohol consumption, body mass index, menopausal status and hormone therapy use, and (except for "Any NSAID") all of the other NSAIDS in the table (for each type: never past 3 years, former/irregular, current 3+ tablets/week, unknown).

§Adjusted for age, use of oral contraceptives, use of hormone therapy, smoking, alcohol use, physical activity level, history of rheumatoid arthritis, history of osteoarthritis all other factors in the table.

Table D.60 Cardiac glycosides and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Karasneh et al., 2017[458] Studies published to 2015 Finland, Norway, Sweden, UK & USA	9 studies 6 cohort studies 3 case–control studies	55,157 cases 2,338,591 controls	Cardiac glycosides including digoxin Non–users Users Digitalis only Digoxin only	Breast cancer ER+ ER–	 HR=1 (referent) HR=1.34 (1.25–1.44); p<0.00001; I^2=16%, p(heter)=0.30 HR=1.42 (1.23–1.63); p<0.00001 HR=1.29 (1.11–1.51); p=0.0009 RR=1.35 (1.26–1.45) HR=1.46 (1.10–1.95) RR=1.20 (1.03–1.40) HR=1.12 (0.52–2.37)	Random effects model for HRs Adjustments: All studies adjusted for at least age (1 study did not report on confounders adjusted for) Funnel plots revealed no evidence of asymmetry which would be indicative of publication bias Limitations: Studies reported different measures of association (including ORs, HRs and RRs) Small study sample (n=2) for ER+ analysis
Osman et al., 2017[459] Studies published 1976–2016 Denmark, Finland, Norway, UK & USA	9 studies 6 cohort studies 3 case–control studies	Total study sample 2,558,108 60,543 cases	Cardiac glycosides including digoxin Digitalis only Digoxin only Duration (≥3 y) Digoxin use	Breast cancer ER+ ER–	RR=1.33 (1.25–1.42); p<0.001; I^2=23.78%, p(heter)=0.23 RR=1.42 (1.22–1.64); p<0.01 RR=1.30 (1.17–1.45); p<0.01 RR=1.28 (1.10–1.49); p=0.002 RR=1.33 (1.25–1.42); p<0.001 RR=0.98 (0.61–1.58); p=0.95	Random effects model Adjustments: Individual studies adjusted for various factors Seven studies adjusted for at least age No adjustments for one study only No publication bias (p=0.27) Limitations: Small number of studies for subgroup analyses and not all studies that were included adjusted for potential confounders

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Zhang et al., 2017[460] Studies published to 2016 Denmark, Finland, Norway, UK & USA	8 studies 5 cohort studies 3 case–control studies	9,219 cases	Digitalis	Breast cancer	RR=1.35 (1.24–1.46); I^2=0.0%, p(heter)=0.59	Random effects model. Adjustments: Individual studies adjusted for various factors, with all studies adjusting for at least age No publication bias Limitations: Limited adjustments for confounders Cardiovascular risk factors (smoking and BMI) not adjusted for in many studies Bias due to dominance of large study
Cohort studies						
Chung et al., 2017[461] Taiwan	No cohort name Database mined: Jan 2000–Dec 2000 Retrospective cohort study Age at enrolment: >18 y Follow–up: 10 y	4,161 patients with heart failure 1,219 had taken digoxin 2,942 did not take digoxin 1.43 incidence per 100 person–years	Digoxin Non–users Users	Breast cancer	 HR=1 (referent) HR=1.30 (1.05–1.62); p<0.001	Cox proportional hazard regression model† Limitations: Nationwide population–based data from Taiwan may not be generalisable No information about smoking, pregnancies, dietary habits and other stressful psychosocial events

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BMI, body mass index; ER, oestrogen receptor; HR, hazard ratio; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

†Age, gender, income, region, urbanisation and Charlson Comorbidity Index.

Table D.61 HPV and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Bae & Kim, 2016[468] Studies published 1999–2015 Australia, Brazil, China, Iran, Iraq, Italy, Japan, Korea, Mexico, Turkey & USA	22 case–control studies	1,897 cases 948 controls	HPV DNA in tissue	Breast cancer	OR=4.02 (2.42–6.68); I^2=44.7%, p(heter)=0.013	Random effects model Adjustments: NR No publication bias (p=0.165) Limitations: NR
	11 case–control studies		HPV–16		OR=5.67 (2.21–14.52); I^2=32.5%	
	10 case–control studies		HPV–18		OR=2.97 (1.64–5.38); I^2=0.0%	
	5 case–control studies		HPV–33		OR=3.64 (1.26–10.48); I^2=0.0%	
Zhou et al., 2015[469] Studies published 1989–2013 Asia, Europe, Oceania & South America	16 case–control studies	Participant characteristics: NR	HPV infection	Breast cancer	OR=3.24 (1.59–6.57); p=0.000; I^2=63.9%, p(heter)<0.001	Random effects model Adjustments: NR No publication bias (p>0.05) Limitations: The effect of clinical features such as age and oestrogen receptors on HPV detection rates in breast cancer cannot be ruled out
			DNA source			
	12 case–control studies		Fixed tissue		OR=2.23 (0.99–5.00); p(heter)=0.004	
	4 case–control studies		Fresh tissue		OR=7.88 (3.99–15.60); p(heter)=0.458	
			PCR primers			
	10 case–control studies		Broad–spectrum primers		OR=5.66 (3.40–9.45); p(heter)=0.566	
	4 case–control studies		Type–specific primers		OR=3.12 (0.29–33.52); p(heter)=0.002	
	2 case–control studies		Combined primers		OR=0.68 (0.32–1.45); p(heter)=0.614	
Simões et al., 2011[470] Studies published 1990–2011	9 case–control studies	448 cases 279 controls	HPV infection Cases vs controls	Breast cancer	OR=5.90 (3.26–10.67); I^2=19%, p(heter)=0.27	Random effects model Adjustments: NR No publication bias

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Australia, Brazil, China, Germany, Japan Mexico & Turkey						Limitations: Discrepancies in reported prevalence of HPV DNA in breast carcinomas may be explained by low viral loads and use of different primers for detecting HPV DNA
Li et al., 2011[471] Studies published 1989–2010 Australia, Brazil, China, Japan, Mexico & Turkey	9 case–control studies†	447 cases 275 controls	HPV positivity Cases vs controls	Breast cancer	pOR=3.63 (1.42–9.27); p= sig.; I^2=60.0%, p(heter)=0.010	Random effects model Adjustments: NR No publication bias (p=0.309) Limitations: Differences in PCR primers influence the detection rate of HPV DNA
Cohort studies						
Salman et al., 2017[473] UK	Data collection over 3 y Prospective study Age samples were collected: 25–82 y Follow–up: NR	110 specimens 74 samples malignant, 35 were HPV positive 36 samples normal or benign	HR–HPV	Abnormal & normal breast cases	Prevalence=42%	Model: NR Adjustments: NR Limitations: The low viral load of HPV in breast cancer means that there are challenges in the utilisation of immunoblotting techniques
Lawson et al., 2015[467]	TCGA Breast Cancers Cohort	PCR: 41 patients with benign breast biopsies 1–11 y	HPV infection in PCR cohort	Breast cancer Benign breast biopsy	Prevalence=66%; p=0.001 for normal vs breast cancer Prevalence=55%	Model: NR Adjustment: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Australia (PCR cohort) & USA (TCGA cohort)	Study dates: NR Retrospective study Mean age of patients: 50.5 y Mean age of controls: 35.7 y Follow–up: NR	before developing breast cancer 21 normal breast specimens (cosmetic surgery) Mean age at diagnosis: 56.1 y TGCA: 855 breast cancer cases		Normal breast samples	Prevalence=29%; p=0.001 for normal vs benign	Limitations: NR
			HR–HPV from TCGA database	Breast cancer	Prevalence=2.3%	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: HPV, human papillomavirus; HR–HPV, high risk human papilloma3pvirus; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; PCR, polymerase chain reaction; pOR, pooled odds ratio; RR, relative risk or risk estimate; sig., significant; TCGA, The Cancer Genome Atlas; UK, United Kingdom; USA, United States of America; y, year/s.

†The abstract reports 10 studies.

Table D.62 Hysterectomy and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Altman et al., 2016[474] Sweden	Swedish Cancer Registry Cohort dates: 1973–2009 Retrospective study Age at enrolment: ≥18 y Duration of follow–up: 122,222,958 person–y	111,595 women with hysterectomy; 2,201 cases 5,379,843 women without hysterectomy; 162,445 cases	Hysterectomy without oophorectomy vs women with no surgery	Breast cancer	HR=0.97 (0.93–1.01)	Cox proportional hazard model† Limitations: Confounding by indication (indications for hysterectomy included dysfunctional bleedings, leiomyoma and uterine prolapse) Unable to control for HT use
Gaudet et al., 2014[475] USA	Cancer Prevention Study–II Nutrition Cohort Cohort dates: 1992–2009 Prospective study Age at enrolment: 50–74 y Median follow–up: 13.9 y	66,802 postmenopausal women 9,655 women with simple hysterectomy 41,397 women with no surgery	Hysterectomy without oophorectomy vs women with no surgery (aged<55 y)	Breast cancer	RR=0.86 (0.76–0.96)	Extended Cox regression model‡ Limitations: Surgery type was self–reported Exposure misclassification Selective survival bias
Woolcott et al., 2009[476]	The MEC study	68,065 women	Simple hysterectomy Overall	Breast cancer		Cox proportional hazards model§

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
USA	Cohort dates: 1993–2002 Prospective study Age at enrolment: 45–75 y Median follow–up: 7.7 y	Hysterectomy: 344 cases No hysterectomy: 1,518 cases	No hysterectomy Hysterectomy By age of hysterectomy No hysterectomy Yes, at <45 y Yes, at 45–49 y Yes, at 50+ y		RR=1.0 (referent) RR=0.98 (0.86–1.11) RR=1.0 (referent) RR=0.94 (0.81–1.09) RR=1.10 (0.86–1.41) RR=1.03 (0.69–1.54)	Limitations: Measurement error in hysterectomy status from misreporting Specific data was not available to allow for assessment of the effects of different ages at menopause or indications for hysterectomy

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: HR, hazard ratio; HT, hormone therapy; MEC, multi–ethnic cohort; RR, relative risk or risk estimate; USA, United States of America; y, year/s.

†Partial adjustment for age and calendar year, or with full adjustment, which also included parity and education level.

‡Ethnicity, education, parity, age at first birth, age at menopause, active smoking, alcohol consumption, family history of breast cancer, recreational physical activity, body mass index, use of postmenopausal hormones, mammography screening.

§Adjusted for age, body mass index, family history in a mother or sister, education, alcohol consumption, age at menarche, age at first birth, number of children, duration of current estrogen with progestin use, duration of current oestrogen only use, and duration of past oestrogen with progestin use. For analyses including all women, additionally adjusted for ethnicity.

#Adjusted for age (continuous), race (white or black), study site (Atlanta, Detroit, Los Angeles, Philadelphia or Seattle), age at menarche (continuous), first–degree family history of breast cancer (yes, no, or unknown/adopted), number of term pregnancies (0, 1, 2, or 3), educational status (some high school or less, high school graduate, some college or technical school, or college graduate or higher), and duration of hormone therapy use (never, 0–6 months, >6 months to <5 years or 5 years).

Table D.63 Pregnancy termination and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Guo et al., 2015[478] Studies published to 2014 America, China & Europe	15 prospective cohort studies 14 studies on induced abortion 12 studies on spontaneous abortion	31,816 cases	Induced abortion Overall Number of abortions 1 ≥2 Age at first abortion <20y 20–29 y ≥30 y Spontaneous miscarriage Overall Number of abortions 1 ≥2 Age at first abortion <20 y 20–29 y ≥30 y	Breast cancer	 RR=1.00 (0.94–1.05); I^2=56.8%, p(heter)=0.003 RR=1.00 (0.91–1.10); I^2=46.5%, p(heter)=0.07 RR=0.99 (0.75–1.24); I^2=0%, p(heter)=0.75 RR=1.23 (0.80–1.66); I^2= 0%, p(heter)=0.872 RR=0.93 (0.62–1.24); I^2=0%, p(heter)=0.599 RR=1.31 (0.83–1.80); I^2=0%, p(heter)=0.858 RR=1.02 (0.95–1.09); I^2=61.6%, p(heter)=0.001 RR=0.98 (0.90–1.07); I^2=0%. p(heter)=0.479 RR=0.82 (0.59–1.05); I^2=70.7%, p(heter)=0.033 RR=0.50 (0.27–0.92) RR=NR RR=1.03 (0.70–1.36)	Random effects model No adjustments No publication bias (p>0.05) Limitations Reporting bias due to stigma of abortions

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
CGHFBC, 2004[479] Australia, China, Europe, New Zealand & North America	13 prospective studies 40 retrospective studies	83,000 breast cancer cases 44,000 cases recorded prospectively 39,000 cases recorded retrospectively Average age at diagnosis: 50.4 y Average 2.4 births	Spontaneous abortion Induced abortion	Breast cancer	RR=0.98 (0.92–1.04); χ^2=15.7%, p=0.2—prospective RR=0.98 (0.018); χ^2=55.4%, p=0.05—retrospective RR=0.93 (0.89–0.96); χ^2=27.0%, p=0.008—prospective RR=1.11 (0.025); χ^2=37.6%, p=0.5—retrospective	Mantel–Haenszel Adjustments: Results stratified by study, age, and where possible, parity and age at first birth Publication bias: NR Limitations: Differential retrospective reporting of past induced abortions

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: CGHFBC, Collaborative Group on Hormonal Factors in Breast Cancer; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; y, year/s.

Table D.64 Previous cancer other than breast cancer and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Ibrahim et al., 2012[491] Studies published 1985–2011 Canada, Europe, Germany, Italy, Netherlands, Nordic countries, Norway, UK & USA	34 cohort studies	25,305 women 957 cases Median age at diagnosis of HL: 23.7 y Median age at diagnosis of breast cancer: 35 y	Hodgkin lymphoma vs general population Overall Age at diagnosis 1–14 y 15–19 y 20–24 y 25–29 y >40 y Treatment modality Radiation only Radiotherapy & chemotherapy Chemotherapy only	Breast cancer	RR=8.23 (5.43–12.47); I^2=96%, p(heter)<0.0001 Median AER=22.9 per 10,000 person–y RR=68.70 (28.08–168.11); I^2=79% RR=22.32 (13.40–37.16); I^2=74% RR=14.43 (11.65–17.88); I^2=0% RR=6.60 (4.24–10.29); I^2=0%, RR=0.55 (0.09–3.52); I^2=0% RR=4.70 (3.28–6.75); I^2=74% RR=5.65 (2.94–10.88); I^2=91% RR=1.19 (0.50–2.82); I^2=65%	Random effects model Adjustments: NR No publication bias (p>0.05) Limitations: Hodgkin lymphoma itself carries an increased risk of second malignancy Confounding factors such as lifestyle factors, personal risk and family history Insufficient data to analyse protective effect of endogenous hormone ablation against exposure to exogenous hormones
Pirani et al., 2011[497]	12 cohort studies	235,232 women	Non–Hodgkin lymphoma vs general population	Breast cancer		Random effects model

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Studies published 1985–2008 Canada, Europe, France, Italy, Sweden, UK & USA		Median range of age at diagnosis: 10–61 y	Overall		RR=1.10 (0.88–1.37); p=NS; I^2=81.7%, p(heter)<0.001	Adjustments: NR No publication bias Limitations: Unpublished and non–English studies not included in search High heterogeneity Recruitments over extended period of time (1935–2004) Differential tumour misclassifications
Cohort studies						
Baras et al., 2017[494] Germany	Primary diagnosis: 1990−2012 Retrospective study Age at enrolment: NR Median follow–up: 5.21 y for HL & 3.13 y for NHL	8,038 women with HL 89 cases 52,731 women with NHL 705 cases Age at primary diagnosis: 15–75 y	Hodgkin lymphoma Non–Hodgkin lymphoma	Breast cancer	SIR=1.39 (1.11–1.70); p=sig. SIR=1.13 (1.05–1.21); p=sig.	Poisson regression model Adjustments: Stratified by sex, age, follow-up duration and calendar year of diagnosis Limitations: Lack of treatment data Misclassification of secondary malignancies Inadequate follow–up
Morais et al., 2017[490] Portugal	Primary diagnosis: 2000−2006	3,025 women 4 synchronous	Gastric cancer 2 months after diagnosis	Breast cancer	SIR=1.02 (0.57–1.68)	Poisson regression model Adjustments: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	End date: 31 Dec 2010 Retrospective study Age at enrolment: NR Median follow–up: 7.0 y	cases 15 metachronous cases Median age at diagnosis of primary: 68 y	6 months after diagnosis		SIR=1.01 (0.55–1.70)	Limitations: Registry information did not include family history, lifestyle factors, comorbidities and treatment; Data did not include histology or stage of gastric cancer
Lin et al., 2016[503] Taiwan	Primary diagnosis: 2000−2008 End of follow–up: 31 Dec 2011 Retrospective study Age at enrolment: >20 y Median follow–up: 6.51 y	129 breast cancer cases among thyroid cancer cases 368 breast cancer cases among controls	Thyroid cancer Overall Not treated with ^{131}I Treated with ^{131}I	Breast cancer	 HR=1.31 (1.07–1.61) HR=1.26 (0.90–1.76) HR=1.34 (1.06–1.69)	Cox proportional hazard model Adjustments: Age, all comorbidities, hormone therapy, mammography, and ultrasonography Limitations: No conclusions about lifestyle risk and genetic factors Use of non–scientifically verified registry
Chen et al., 2016[489] Taiwan	Cohort dates: 1997−2011 Retrospective study	17,314 women 57 cases Median age at	Gastric cancer vs general population	Breast cancer	SIR=1.19 (0.90–1.54); p=NS	Cox proportional hazard model Adjustments: Stratified by sex, calendar year, and age in 5–y intervals

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Age at enrolment: >20 y Follow–up: 137,798 person–y	diagnosis: 67 y				Limitations: Family history of cancer and lifestyle factors not included Disease stage not recorded
Cho et al., 2015[504] Korea	Cohort dates: 1993–2010 Retrospective study Age at enrolment: NR Elevated risk in first 10 y of follow–up	151,755 women 599 cases Median age at thyroid cancer diagnosis: 47 y	Thyroid cancer	Breast cancer	SIR=1.20 (1.10–1.30); p=sig.	Model: NR Adjustments: NR Limitations: Tumour size, stage of cancer, treatment modalities, and genetic and family history were not reported
Guan et al., 2015[487] USA	Primary diagnosis: 1992–2012 Retrospective study Age at enrolment: NR Follow–up: ≥10 y	Colon cancer: 8,496 women 1,839 cases Rectal cancer: 2,969 women 647 cases Age at primary diagnosis: >20 y	Colon cancer vs general population Overall Rectal cancer vs general population Overall	Breast cancer	SIR=0.99 (0.94–1.03) SIR=0.93 (0.86–1.00)	Poisson exact methods Adjustments: NR Limitations: No detail provided about treatment strategies, lifestyle factors, and comorbidities
Lee et al., 2015[486] Taiwan	Study dates: 1996–2011 Retrospective study	43,147 women Median age at primary diagnosis: 67 y (men & women)		Breast cancer		Poisson probability distribution Adjustments: NR Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Age at enrolment: NR Median follow–up: 4.03 y	272 cases 157 cases 118 cases	Colorectal cancer Colon cancer Rectal cancer		SIR=1.21 (1.07–1.36); p=sig. SIR=1.19 (1.01–1.39); p=sig. SIR=1.22 (1.01–1.46); p=sig.	Lifestyle factors, treatment modalities and family history data not included
Dörffel et al., 2015[495] Austria, Germany & Switzerland	Study dates: 1978–2013 Retrospective study Age at enrolment: NR Median follow–up: 14.3 y	1,124 women 31 cases Median age at primary diagnosis: 13.3 y Age at breast cancer diagnosis: 25–44 y	Paediatric Hodgkin lymphoma vs German population Overall Median Minimum Maximum	Breast cancer	 AER=14.9 per 10,000 person–y SIR=17.2 SIR=14.3 SIR=25.7	Model: NR Adjustments: NR Limitations: No adjustment for radiation treatment and family history
Schaapveld et al., 2015[492] Netherlands	Cohort dates: 1965−2000 End of follow–up: 2010 Retrospective study First received treatment 15–50 y Median follow–up: 19.1 y	1,698 women 183 cases Median age at treatment for HL: 28.6 y Women who had survived ≥5 y after HL treatment	Hodgkin lymphoma Overall Radiation Tx above diaphragm No Yes	Breast cancer	 SIR=4.7 (4.0–5.4) AER=54.3 (44.7–65.0) per 10,000 person–y SIR=1.0 (0.3–2.2) SIR=5.4 (4.6–6.2); p(heter)<0.001	Poisson regression model Adjustments: Sex, age, follow–up interval, attained age, and treatment Limitations: NR
Chen et al., 2015[498] Taiwan	Primary diagnosis: 1997–2011 Retrospective study	1,351 women 2 cases	Oesophageal cancer	Breast cancer	SIR=0.96 (0.12–3.48)	Poisson probability distribution Adjustments: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Age at enrolment: >20 y Median follow–up: 0.86 y	Median age at primary diagnosis: 71 y				Limitations: Histological types of oesophageal cancer not known Obesity, tobacco, alcohol use, genetic alteration and family malignancy history could not be analysed
Kim et al., 2013[505] USA	Primary diagnosis: 1973−2008 End of follow–up: 31 Dec 2008 Retrospective study Age at enrolment: NR Follow–up: 36 y	39,228 women 1,037 cases Thyroid cancer diagnosis: <40 to ≥70 y	Thyroid cancer Overall Histological subtype Papillary Follicular Medullary Radiation Tx None Isotypes Beam radiation Radiation, NOS Year of diagnosis 1973–1983 1984–1993 1994–2003 2004–2008	Breast cancer	SIR=1.13 (1.06–1.20) SIR=1.14 (1.06–1.22) SIR=1.07 (0.91–1.25) SIR=1.16 (0.77–1.68) SIR=1.13 (1.05–1.21) SIR=1.14 (0.98–1.31) SIR=1.02 (0.64–1.41) SIR=1.17 (0.92–1.42) SIR=1.13 (1.02–1.25) SIR=1.06 (0.95–1.18) SIR=1.21 (1.08–1.37) SIR=1.09 (0.81–1.45)	Poisson exact method Adjustments: NR Limitations: Data by size were not captured prior to 1988, limiting generalisability Some results difficult to interpret due to certain stratifications e.g. anaplastic histologic subtype
Lu et al., 2013[506] Taiwan	Primary diagnosis: 1979–2006 Retrospective study Age at enrolment: NR	14,863 women 102 cases Mean age of thyroid cancer diagnosis: 44.20 y	Thyroid cancer vs general population Overall Follow–up interval ≤5 y 5–10 y >10 y	Breast cancer	SIR=1.42 (1.16–1.72); p=sig. SIR=4.44 (3.24–5.95); p=sig. SIR=1.41 (0.96–1.98) SIR=0.64 (0.41–0.95); p=sig.	Poisson probability distribution Adjustments: NR Limitations: Lack of information regarding RAI exposure history and

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Age at diagnosis			subtypes of thyroid cancer
	Mean follow–up: 7.29 y	Mean age at SPM diagnosis: 58.62 y	<50 y		SIR=1.37 (1.06–1.74); p=sig.	
			≥50 y		SIR=1.53 (1.06–2.13); p=sig.	
Tabuchi et al., 2012[488] Japan	Primary diagnosis: 1985–2004 Retrospective study Age at enrolment: NR Median follow–up: 2.5 y	355,966 patients 1,007 breast cancer cases Age at diagnosis of primary: 0–79 y	Primary type	Breast cancer		Poisson probability distribution Adjustments: NR Limitations: SPMs are followed up in hospitals where cancer registration is higher Risk factors confounded by primary diagnosis
			Blood		SIR=0.65 (0.25–1.04)	
			Colorectal		SIR=1.22 (0.97–1.47)	
			Kidney/urinary tract/bladder		SIR=0.97 (0.42–1.52)	
			Liver		SIR=1.26 (0.75–1.76)	
			Lung		SIR=1.66 (1.10–2.21)	
			Ovary		SIR=1.43 (0.82–2.04)	
			Stomach		SIR=1.63 (1.34–1.91)	
			Thyroid		SIR=1.97 (1.34–2.61)	
			Uterus		SIR=1.40 (1.10–1.71)	
Youlden & Baade, 2011[210] Australia	Primary diagnosis: 1982–2001 Retrospective study Age at enrolment: NR Median follow–up: 5.5 y	94,001 women 2,962 cases Age at first diagnosis: >15 y	Primary cancer	Breast cancer		Poisson probability distribution Adjustments: NR Limitations: Lifestyle and genetic factors, and treatment modalities not included in data set
			All cancers		SIR=1.32 (1.27–1.37)	
			Melanoma		SIR=1.19 (1.07–1.33)	
			Colorectal		SIR=1.21 (1.07–1.36)	
Royle et al., 2011[496] Australia	Primary diagnosis: 1983–2005 Retrospective study	56,619 women Median age at primary diagnosis: 65 y	Primary cancer	Breast cancer		Poisson probability distribution Adjustments: Decade of diagnosis

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		196 cases	Non–HL		SIR=2.27 (1.97–2.61); p=sig.	
	Age at enrolment: NR	49 cases	All HL		SIR=5.45 (4.03–7.20); p=sig.	Limitations: New classifications of LHN may affect incidence numbers
		91 cases	Lymphoid Leukaemia		SIR=1.89 (1.52–2.33); p=sig.	
	Median follow–up: 2.9 y	32 cases	Myeloid leukaemia		SIR=2.24 (1.53–3.16); p=sig.	Lack of treatment information
		63 cases	Plasma cell tumours		SIR=2.18 (1.68–2.79); p=sig.	
Spanogle et al., 2010[501] USA	Primary diagnosis: 1973–2003 Retrospective study Age at enrolment: NR Follow–up: until death or end of 2003	69,853 women 1,565 cases Mean age at primary diagnosis: 54 y	Cutaneous melanoma vs general population	Breast cancer	SIR=1.07 (1.02–1.12)	Poisson probability distribution Adjustments: NR Limitations: Cutaneous melanoma is underreported Data missing for genetic or lifestyle factors or treatment modalities
Levi et al., 2009[500] Switzerland	Primary diagnosis: 1974–2006 Retrospective study Age at enrolment:	1,834 women 28 cases	Invasive ovarian cancer	Breast cancer	SIR=1.72 (1.15–2.05)	Poisson probability distribution Adjustments: NR Limitations:
			Borderline ovarian cancer		SIR=0.82 (0.30–1.79)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	NR Follow–up: 8,401 person–y					Increased diagnostic attention in women diagnosed with ovarian cancer
Levi et al., 2008[502] Switzerland	Primary diagnosis: 1974–2005 End of follow–up: end of 2005 Prospective study Age at enrolment: NR Follow–up: NR	31,377 patients 440 female cases 21,046 patients 320 cases 6,985 patients 81 cases 3,346 patients 39 cases	All skin cancers Basal cell carcinoma Squamous cell carcinoma Melanoma	Breast cancer	SIR=1.18 (1.08–1.30) SIR=1.11 (0.99–1.24) SIR=1.06 (0.85–1.32) SIR=1.04 (0.74–1.42)	Poisson probability distribution Adjustments: NR Limitations: Data did not include stage at diagnosis and lifestyle factors
Chuang et al., 2008[499] Australia, Canada, Europe & Singapore	Primary diagnosis: 1943–2000 Prospective study Age at enrolment: NR Median follow–up: 0.5 y	19,110 women 37 cases: 6 cases adenocarcinoma; 31 cases squamous cell carcinoma	Oesophageal cancer Adenocarcinoma Squamous cell carcinoma	Breast cancer	 SIR=1.03 (0.38–2.25) SIR=0.84 (0.57–1.20)	Model: NR Adjustments: Age, sex, year, and registry Limitations: Small numbers may have affected the risk estimate calculations
Case–control						

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Veit–Rubin et al., 2012[493] USA	SEER program of the National Cancer Institute First primary HL diagnosis 1973–2007 Mean age at HL diagnosis: 47.9 y	Cases: 9,620 women with HL with 316 breast cancer cases (diagnosed ≥6 months after HL diagnosis) Controls: 450,413 breast cancer cases	HL diagnosis	Breast cancer		Poisson distribution Adjustments: NR Limitations: No information on chemotherapy and the dose and type of radiation administered No information on how radiotherapy was delivered Unable to evaluate effects of different radiotherapy protocols on the risk for a second breast cancer.
		5,176 HL patients 234 breast cancer cases	Radiotherapy for HL		SIR=3.2 (2.8–3.6); p<0.001	
		4,193 patients with HL 74 breast cancer cases	No radiotherapy for HL		SIR=1.4 (1.1–1.8); p<0.01	
			Age at diagnosis of HL			
		1,526 patients with HL 69 breast cancer cases	≤19 y		SIR=13.4 (10.5–17.0); p<0.001	
		3,062 patients with HL 108 breast cancer cases	20–29 y		SIR=4.4 (3.6–5.3); p<0.001	
		1,988 patients with HL 61 breast cancer cases	30–39 y		SIR=2.0 (1.5–2.5); p<0.001	
		950 patients with HL 29 breast cancer cases	40–49 y		SIR=1.4 (0.9–2.0)	
		2,094 patients with	≥50 y		SIR=1.03 (0.8–1.4)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		HL 49 breast cancer cases				

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AER, absolute excess risk; LHN, lymphohaematopoietic neoplasm; NHL, Non–Hodgkin lymphoma; HL, Hodgkin lymphoma; HR, hazard ratio; ^{131}I, iodine–131; NOS, not otherwise specified; NR, not reported; NS, not significant; p, p–value; p(heter), p–value for the measure of heterogeneity; RAI, post–operative radioactive iodine; RR, relative risk or risk estimate; SEER, Surveillance, Epidemiology and End Results; sig., significant; SIR, standardised incidence ratio; SPM, second primary malignancy; Tx, treatment; UK, United Kingdom; USA, United States of America; y, year/s.

Table D.65 Silicone breast implants and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Noels et al., 2015[508] Studies published to 2013 Canada, Denmark, Sweden & USA	17 cohort studies	7 study populations Population info: NR	Breast implants vs no implant	Breast cancer	RR=0.63 (0.56–0.71); I^2=0%, p(heter)=0.423 SIR=0.69 (0.56–0.85); I^2=84%, p(heter)<0.001	Random effects (SIR), fixed effects (RR) model Publication bias (funnel plot) Adjustments: NR Limitations: Publication bias Confounders Applied language restriction
Balk et al., 2016[507] Studies published to 2015 Australia, Europe & North America	11 longitudinal studies Follow–up: 4–20 y	Study sample: NR Icluded women with any history of silicone gel–filled breast implants, excluding injected silicone, silicone tissue expanders, & recalled implants produced by Poly Implant Prothese, & at least one half the participants had to have silicone gel (vs saline) implants	Breast implants vs no implant	Breast cancer	ES=0.63 (0.54–0.73); I^2=0%, p(heter)=0.53, SIR=0.76 (0.64–0.91); I^2=52%, p(heter)=0.051	Random effects model Adjustments¶ Limitations: Differences across studies Inadequate adjustments among studies Findings are not specific to silicone gel implants Possible confounders

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: ES, effect size; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; SIR, standard incidence ratio; y, year/s.

¶One study adjusted only for age and year of implantation. One study adjusted for age, race, time since surgery, and "predictors of cancer". One study adjusted for "extraneous variables".

Table D.66 Stress and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Lin et al., 2013[517] Studies published 1995–2012 Australia, England, Finland, Poland, Sweden & USA	7 studies 3 cohort studies 4 case–control studies Cohort studies Case–control studies	99,807 women Number of cases & controls: NR Women aged 20–79 y	Striking life events Severe striking life events Striking life events	Breast cancer	OR=1.51 (1.15–1.97); I^2= 93% OR=2.07 (1.06–4.03); I^2= 96% RR range: 1.07–2.1 RR range: 0.9–7.08	Random effects model* Possible publication bias p<0.05 Limitations: The seven studies differed somewhat in their definition of striking life events & therefore number of events was used
Heikkilä et al., 2013[523] Studies published 1985–2008 Denmark, Finland, France, the Netherlands, Sweden & UK	12 prospective cohort studies	116,056 participants 59,695 females 1,010 cases Women aged 17–70 y Median follow–up: 12 y	Job strain Passive job Active job High strain	Breast cancer	HR=0.97 (0.82–1.14); I^2= 0%, p=0.6 HR=1.00 (0.99–1.12); I^2=0%, p=0.5 HR=1.00 (0.84–1.19); I^2=30.8%, p=0.2 HR=1.01 (0.81–1.26); I^2=49%, p=0.033	Random effects model Adjusted for age, sex socioeconomic position, BMI, smoking & alcohol intake Publication bias: NR Limitations: Length of job strain not assessed Data included fewer unemployed people compared with the general population Other potential risk factors were not adjusted for in the analysis Residual confounding

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Santos et al., 2009[518] Studies published 1982–2007 Australia, Denmark, England, Finland, Norway, Sweden, & USA	8 studies 2 cohort studies 6 case–control studies	66,612 women Number of cases & controls NR	Stressful life events Widowhood Divorce High intensity stress	Breast cancer	RR=1.04 (0.75–1.44); Q=7.634, p=0.020 RR=1.03 (0.72–1.48); Q=9.591, p=0.008 RR=1.73 (0.98–3.05); Q=24.688, p<0.001	Random effects model Adjustments† Publication bias: NR Limitations: Some studies could not be included because of lack of data The majority of studies included were on Nordic women
Duijts et al., 2003[519] Studies published 1966–2002 Australia, Europe & USA	27 studies 10 retrospective case–control studies 9 limited prospective studies 4 prospective case–control studies	Number of women NR 7,666 cases Mean age at diagnosis: 53.8 y	Stressful life events Death of spouse Death of relative/friend Change in marital status	Breast cancer	OR=1.77 (1.31–2.40); I^2=0% OR=1.37 (1.10–1.71) OR=1.35 (1.09–1.68) OR=0.88 (0.73–1.08)	Model: NR Adjustments: NR Significant publication bias Limitations: Significant publication bias & heterogeneity
Cohort studies						
Schoemaker et al., 2016[520] UK	Breakthrough Generations Study Cohort date: 2003–2012 Prospective study	106,612 women 1,783 cases	Experience of stress Never/ Occasionally Frequently Continuously Adverse life events Death of	Breast cancer	RR=1.0 (referent) RR=0.92 (0.83–1.03) RR=0.92 (0.73–1.15); p–trend=0.15	Cox proportional hazards model Adjustments‡ Limitations: Lack of information on intensity of stress on workplace stress & the extent of social support or

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Mean age at baseline: 46.6 y Follow up: 6.1 y		husband/partner Death of child/parent or other close relative Death of close friend Personal illness Loss of job Divorce/ separation Other stressful event Number of events 0 1 2 ≥3		RR=1.13 (0.88–1.46) RR=0.87 (0.78–0.97) RR=0.94 (0.83–1.08) RR=1.03 (0.87–1.22) RR=1.09 (0.91–1.30) RR=1.15 (0.96–1.38) RR=0.95 (0.86–1.05) RR=1.00 (referent) RR=0.97 (0.86–1.09) RR=0.93 (0.81–1.07) RR=0.93 (0.77–1.12); p=0.25	stress adaptive capacity 5–year time limit on stress evaluation Study did not collect information on stress during childhood or adolescence
Sawada et al., 2016[521] Japan	Japan collaborative cohort study Cohort dates: 1988–1990 Prospective study Age at baseline: 40–79 y Mean follow–up: 12.8 y, 372,156 person–y	29,098 women 209 cases	Perceived stress Disagree Neither Agree Agree strongly	Breast cancer	 HR=1.00 (referent) HR=1.21(0.80–1.82) HR=1.71 (1.02–2.85) HR=1.00 (0.56–1.78)	Cox proportional hazards regression model Adjustments§ Limitations: One item measure was used to determine perceived stress Stress was measured only at baseline & the measurement has not been scientifically validated Identification of BC in four of the studies was not based on cancer registry data

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Surtees et al., 2010[522] UK	EPIC–Norfolk study Cohort dates: 1993–1997 Prospective study Age at baseline: 41–80 y Follow–up: 102,514 person–y, median 9.1 y	11,467 women 313 cases	Social adversity Difficulties reported in childhood Life events in past 5 y Loss events in past 5 y Non–loss events in past 5 y Long term difficulties in past 5 y Perceived stress over past 10 y	Breast cancer	 HR=1.02 (0.91–1.16) HR=0.99 (0.89–1.11) HR=1.21 (0.98–1.51) HR=0.97 (0.81–1.17) HR=1.16 (0.85–1.60) HR=1.17 (0.84–1.64)	Cox proportional hazards regression model Adjustments¶ Limitations: The approach required to assess these experiences may act as a barrier to detecting the associations that may be present in the general population It may also be necessary to assess a larger cohort

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: EPIC, European prospective investigation into Cancer; HR, hazard ratio; NR, not reported; OR, odds ratio; p, p–value; p–trend, p–value for the measure of trend; Q, Q test to evaluate the heterogeneity among studies; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

*Studies included adjusted for confounding factors, including age, use of oral contraceptives, any type of hormone replacement, menopause, alcohol intake, smoking, socioeconomic status, and family history of breast cancer.

†Models adjusted for age, sex, socioeconomic position, body mass index (BMI), smoking and alcohol intake.

‡Adjusted for attained age, age at menarche, age at first birth and parity, cumulative duration of breast feeding, oral contraceptive use, postmenopausal hormone use, benign breast disease, BMI at age 20, postmenopausal BMI and time–updated menopausal status, height, physical activity, alcohol consumption, cigarette smoking, family history of breast cancer and socio–economic status.

§Adjusted for age, study area, educational level, family history of breast cancer, age at menarche, age at menopause, age at first birth, parity, use of exogenous female hormone, alcohol drinking, consumption of green leafy vegetables, daily walking, exercise, sedentary work, height, and body mass index.

¶Stratified by age and menopausal status, parity, use of menopausal hormones (HRT), age at menarche, age at first birth, family history of breast cancer, physical activity, social class, BMI, height, and alcohol intake.

Table D.67 Trauma to the breast and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Systematic review						
Song et al., 2015[526] Studies published 1972 to 2014 Australia, France, Israel, Japan, Slovenia, Turkey, UK & USA	26 studies	43 patients 5 cases Mean age 49 y	Breast injury resulting from seat–belt use	Breast cancer	Prevalence=17.2%	Model: N/A Adjustments: NR Publication bias: NR Limitations: NR
Cohort studies						
Gatta et al., 2012[528] Italy	Hospital–based cohort Cohort dates: 2001–2008† Retrospective study Age at enrolment: >23 y Duration of follow–up: NR	500 hospital patients 102 cases 9 males included in analysis General population (referent)	Breast trauma	Breast carcinoma	OR=0.84 (0.41–1.75)§; p=0.64	Logistic regression model Adjusted for age & oestrogen Progestin therapy Limitations: NR
Case–control studies						
Rigby et al., 2002[527] UK	Population screening case–control Duration: 1996–1998 Age at enrolment: 50–65 y	67 cases (confirmed by biopsy) 134 controls (women without breast cancer as reference) participating in North Lancashire	Physical trauma to the breast	Breast cancer	OR=3.3 (1.3–10.8); p<0.0001	Model: NR Adjustments: NR Limitations: Possible recall bias & question of biological plausibility

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		Breast Screening Service				

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: NR, not reported; OR, odds ratio; p, p–value; UK, United Kingdom; y, year/s.

†Cohort commenced in 2008 is noted in abstract.

§95% confidence interval 0.41–1.73 is noted in abstract.

Table D.68 Type 2 diabetes and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
De Bruijn et al., 2013[534] Studies published 2007–2012 Israel, Netherlands, Scotland, Sweden, UK & USA	6 studies	Number of patients NR Number of cases NR	Type 1 & 2 diabetes vs no diabetes	Breast cancer	HR=1.23 (1.12–1.34); p<0.001; I^2=0%, p(heter)=0.64	Random effects model Adjustments: NR No publication bias: Egger's regression intercept –0.77, p=0.197 Limitations: Not all studies distinguished between type 1 and type 2 diabetes Anti–diabetic medications and detection time were not accounted for
Boyle et al., 2012[530] Studies published to 2011 Austria, Canada, Chile, Denmark, Germany, Italy, Japan, Korea, Netherlands, Sweden, Taiwan, Thailand, Turkey, UK & USA	40 studies 22 cohort studies 18 case–control studies 36 studies investigated BC incidence 14 studies investigated type 2 diabetes 6 studies investigated postmenopausal women type 2 diabetes	Number of participants NR 56,111 cases Study size 11–7,830 cases, median 322	Type 1 & 2 diabetes Type 2 diabetes	Breast cancer (incidence only) Breast cancer (incidence & mortality) Postmenopausal breast cancer	RR=1.24 (1.12–1.36); I^2=73% RR=1.16 (1.04–1.29); I^2=72% RR=1.12 (1.03–1.21); I^2=51%	Random effects model Adjustments: NR No publication bias: Egger's test all studies –0.32, p=0.75 Limitations: Meta regression analysis had limited power due to high heterogeneity in studies that did not make adjustments

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Hardefeldt et al., 2012[535] Studies published 1990–2012 Armenia, Canada, Chile, China, Denmark, Israel, Italy, Japan, Korea, Mexico, Norway, Sweden, Switzerland, Taiwan, Thailand, Turkey, UK, Uruguay & USA	40 studies 3 cross sectional studies 21 case–control studies 16 cohort studies	Number of cases NR Number of controls NR	Diabetes mellitus (non–specific) Age, BMI and family history adjusted studies	Breast cancer	OR=1.20 (1.13–1.29); p<0.01; I^2=73.41%, p(heter)<0.001 OR=1.11 (1.01–1.22); I^2=25.02%, p(heter)=0.23	Random effects model Adjustments: 21 studies adjusted for age and BMI
	Type 2: 10 studies 6 case–control studies 4 cohort studies		Type 2 diabetes		OR=1.22 (1.07–1.40); p<0.01	Evidence of publication bias: Egger's p=0.01 Limitations: Most studies did not account for therapeutic regimes Most studies did not distinguish between types of diabetes
Liao et al., 2011[536] Studies published 2000–2010 America, Asia & Europe	12 studies 7 cohort studies 5 case–control studies	730,069 patients Number of cases: NR	Diabetes mellitus (unspecified)	Breast cancer	RR=1.23 (1.18–1.27); I^2=68.7%, p(heter)<0.001	Random effects model Adjustments: NR Publication bias: NR for breast cancer incidence studies
	5 studies			Premenopausal breast cancer	RR=1.15 (0.91–1.64); I^2=55.0%, p(heter)=0.11	Limitations: Some diabetic patients may have been misclassified
	3 studies			Postmenopausal breast cancer	RR=1.25 (1.20–1.30); I^2=51.9%, p(heter)=0.08	No distinction between type 1 & type 2 diabetes Diabetic drugs unknown Some studies did not adjust for confounders and had small sample sizes

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Gini et al., 2016[538] Italy	FVG administrative health–related database 2002–2009 Retrospective study Age at diabetes diagnosis: 40–84 y (median 65 y) Median follow–up: 3.65 y	14,420 women 93 cases	Type 2 diabetes ≥3 y between diabetes & BC diagnosis	Breast cancer	SIR=1.24 (1.00–1.52)	Model: NR Adjustments: age, sex, and year of cancer diagnosis (2002–2005, 2006–2009). Limitations: Lack of information on confounders such as BMI, smoking & obesity status Potential classification bias of diabetes type
Xu et al., 2015[539] China	No cohort name Enrolment period: 2004–2010 Retrospective study Mean age in women: 59.37 y Median follow–up: 3.78 y	20,213 women 132 cases	Type 2 diabetes	Breast cancer	SIR=1.66 (1.38–1.95)	Model: NR Adjustments: Age and gender Limitations: Short average follow–up time Potential heterogeneity in patient population Smoking, alcohol consumption, BMI, physical activity & use of diabetic medications not adjusted for

Note: Risk estimate are presented with 95% confidence intervals.

Abbreviations: BC, breast cancer; BMI, body mass index; FVG, Friuli Venezia Giulia; HR, hazard ratio; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; SIR, standardised incidence ratio; UK, United Kingdom; USA, United States of America; y, year/s.

Chemical exposures

Table D.69 Bisphenol A and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Case–control studies						
Trabert et al., 2014[543] Poland	Hospital–based In situ/invasive breast cancer diagnosis: 2000–2003 Mean age at recruitment: 59 y	1,150 women 575 incident cases 575 controls	Creatinine adjusted urinary BPA–G (ng/mg) <2.06 2.06–4.16 4.17–7.80 >7.80	Postmenopausal breast cancer	 OR=1 (referent) OR=1.70 (1.15–2.52) OR=1.02 (0.67–1.55) OR=1.09 (0.73–1.63); p–trend=0.59	Linear regression model Adjustments† Limitations: Underlying disease processes may influence biomarker levels Differences in absolute BPA–G levels Short half–life of BPA–G does not reflect long term exposure
Brophy et al., 2012[545] Canada	Population–based Recruitment dates: 2002–2008 Mean age at recruitment: 56.2 y for cases 60.0 y for controls	1,005 prevalent cases: 26 cases in plastics 30 cases in food 1,146 controls: 11 controls in plastics 10 controls in food	Carcinogens & endocrine disrupters Minor sector of longest duration (lagged 5 y) Minor sectors‡ Food Plastics (non–auto) Plastics (auto) Cumulative exposure§ Plastics	Breast cancer	 OR=1 (referent) OR=2.25 (0.97–5.26) OR=0.04 (0.00–58.0) OR=3.12 (1.29–7.55) OR=2.43 (1.39–4.22); p=0.0018	Conditional logistic regression Adjustments‡ Limitations: Misclassification due to survey instrument–derived work histories coded in NAICS and NOC categories Changing trends in technology and manufacturing
Yang et al., 2009[544]	Hospital–based	152 participants	BPA levels			Model: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Korea	Study dates: 1994–1997 Mean age at recruitment: 46.23 y for cases 48.56 y for controls	70 incident cases 82 controls	Comparison of median levels Cases (0.61 µg/L) vs controls (0.03 µg/L)		Wilcoxon test; p=0.42	Adjustments: NR Limitations: NR

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: BPA, bisphenol A; BPA–G, BPA–glucuronid; LOD, limit of detection; NAICS, North American Industry Classification System; ng/mg, nanograms per milligram; NOC, National Occupational Classification; NR, not reported; OR, odds ratio; p, p–value; µg/L, micrograms per litre; y, year/s.

†Adjusted for education (less than high school, high school education, some post high school education, college graduate), body mass index (<25, 25–29.9, >30 kg/m^2), age at menarche (≤12, 13–14, ≥15 y), parity (nulliparous, parous), years since menopause (<1, 1–5, 6–10, 11–15, ≥16 y), duration of menopausal hormone therapy use (never, <5, ≥5 y), family history of breast cancer, history of benign breast disease, and ever had a screening mammogram.

‡Model inclusions: reproductive risk factors, demographic risk factors such as smoking (pack–years and pack–years squared) calculated up to the age of diagnosis/participation, education in three levels (less than high school, high school and some college, college degree), and family income (<$40,000, >$40,000 blue collar, >$40,000 white collar). Employment duration terms (linear and squared) were statistically significant and included in all matched analyses (except the initial descriptive analysis by minor sector of longest duration).

Table D.70 DDT exposure and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Park et al., 2014[549] Studies published to 2012 USA, Canada, Europe, Asia & South America	35 studies 16 hospital–based case–control studies 11 population–based case–control studies 10 nested case–control studies	8,160 cases 9,280 controls Populations details: NR	DDT/DDE	Breast cancer	OR=1.03 (0.95–1.12); I^2=40.9%, p(heter)=0.006	Random effects model Adjustments: NR No publication bias (p=0.145) Limitations: Delay time between exposure and diagnosis Age of exposure Effect of susceptible population Combined exposure with other potential carcinogens
Ingber et al., 2013[551] Studies published to 2012 Belgium, Canada, Denmark, Egypt, India, Italy, Japan, Mexico, Poland, Slovakia, Spain, Sweden, USA & Vietnam	35 case–control 11 nested case–control studies 38 DDE & 18 DDT studies for summary ORs	14–643 cases 11–477 controls	DDE Lowest level in blood Highest level in blood DDT Lowest level in blood Highest level in blood	Breast cancer	 OR=1.00 (referent) OR=1.04 (0.94–1.15); p=NS; I^2=31.72%, p(heter)=0.020 OR= 1.00 (referent) OR=1.02 (0.92–1.13); I^2=64.49%, p(heter)=0.384	Random effects models Adjustments: Studies stratified by study design, control group, lipid adjustment and by sample type No publication bias (p>0.05) Limitations: Chemical blood burden range defining lowest and highest level group different across the studies Not many studies controlled for age at menarche

Note: Risk estimates are presented with 95% confidence intervals. Abbreviations: BMI, body mass index; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HT, hormone therapy; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; USA, United States of America.

Table D.71 Deodorant/antiperspirant and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Pooled analyses						
Allam, 2016[565] Studies published 1966–2016 Iraq & USA	2 case–control studies	737 cases 729 controls	Use of antiperspirants	Breast cancer	OR=0.40 (0.35−0.46)	Fixed effects model Adjustments: NR Publication bias: NR Limitations: Lack of quality in the primary data Insufficient number of cases Possible biases in the retrospective case–control studies In Iraq study, controls derived from an oncological department
Meta–analyses						
Hardefeldt et al., 2012[565] Studies published 1950–2012 Iraq & USA	2 case–control studies	Study sample: NR	Regular antiperspirant/ deodorant use	Breast cancer	OR=0.81 (0.51−1.28)	Random effects model Adjustments: NR Publication bias: NR Limitations: NR
Case–controls						
Linhart et al., 2017[566] Austria	Age–matched case–control study Recruitment dates: 2013–2016	209 cases 209 controls without malignant breast disease	Self–reported history of use of underarm cosmetic products when they were < 30 y Never	Breast cancer	OR=1.00 (referent)	Conditional logistic regression model Adjustments† Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Age at baseline: 20–85 y		1–4 times/month		OR=0.50 (0.20–1.26)	Possible recall bias
			2–6 times/week		OR=0.53 (0.23–1.25)	
			Daily		OR=1.03 (0.51–2.07)	Self–reporting information may be incomplete, inaccurate & differ between cases & controls
			Several times/day		OR=3.88 (1.03–14.66)	
			UCP use during past 5 years‡			
			Never		OR=1.00 (referent)	The mix of incident and prevalent cases in the study may be source of bias
			1–4 times/month		OR=1.41 (0.49–4.04)	
			2–6 times/week		OR=0.59 (0.25–1.40)	
			Daily		OR=1.22 (0.56–2.66)	
			Several times/day		OR=3.16 (0.90–11.15)	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: NR, not reported; OR, odds ratio; UCP, underarm cosmetic product; USA, United States of America; y, year/s.

†Adjusted for age at interview, age at menarche, parity, age at first live birth, menopausal status, age at menopause, menopausal hormone therapy drug therapy, history of breast cancer, history of benign breast disease, family history of other cancer, body mass index, alcohol consumption in multivariable conditional logistic regression analysis.

‡UCP use during last 5 years before breast cancer diagnosis in cases/during last 5 years before interview in controls.

Table D.72 Dioxin and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Xu et al., 2016[576] Studies published to 2015 France, international cohort & Italy	3 cohort studies	3,768 cases Number of controls: NR	External exposure to TCDD	Breast cancer	RR=0.99 (0.93–1.06); I^2=9.30%, p(heter)=0.356	Random effects model Individual studies adjusted for a range of factors No evidence of publication bias: Egger's p=0.245 Limitations: Background uncontaminated levels were lacking and could not be included in analysis Different lag times in one study
Cohort studies						
Danjou et al., 2015[581] France	E3N cohort Study period: 1993–2008 Prospective Mean age at enrolment: 53.5 (<0.98 pg/kg dietary dioxin), 53.0 (0.98–1.23), 52.5 (1.23–1.52), 51.9 (≥1.52) Median follow–up: 14.9 y	63,830 women 3,465 cases	Dietary dioxin exposure (pg/kg body weight/day) <0.98 0.98–1.23 1.23–1.52 ≥1.52	Breast cancer	HR=1 (referent) HR=0.94 (0.86–1.04) HR=0.93 (0.83–1.03) HR=0.96 (0.85–1.09); p–trend=0.9405	Cox proportional hazard model† Limitations: Dietary questionnaire could be influenced by biased recordings No contamination data for some food items on the questionnaire Occupational/ environmental exposure may affect result

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	(888,505 person–y)					
Warner et al., 2011[708] Italy	SWHS cohort 1976–2009 Retrospective study Women aged 0–40 y at explosion Follow–up: 32 y	888 women 33 cases	Environmental TCDD (10–fold increase in serum)	Breast cancer	HR=1.44 (0.89–2.33); p=0.13	Cox proportional hazard model Adjustments: Parity and family history of breast cancer in a first–degree relative Limitations: Small number of cancer cases
Warner et al., 2002[577] Italy	SWHS cohort 1996–1998 Retrospective Women aged 0–40 y at explosion Follow–up: 20 y	981 women 15 cases	Environmental TCDD (10–fold increase in serum)	Breast cancer	HR=2.1 (1.0–4.6); p=0.05	Cox proportional hazard model Adjustments: Single covariates, including parity Limitations: Small number of cancer cases
Case–control studies						
Viel et al., 2008[579] France	Population–based case–control 1996–2002	434 cases 2,170 controls	Predicted level air concentrations Women aged 20–59 y Very low	Breast cancer	OR=1 (referent)	Conditional logistic regression Adjustments: NR Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Women aged ≥20 y		Low		OR=1.06 (0.72–1.56)	Time lag in sampling for some matched sets
			Intermediate		OR=1.25 (0.82–1.89)	
			High		OR=0.88 (0.43–1.79)	Chance of misclassification
			Women aged ≥60 y			
			Very low		OR=1 (referent)	
			Low		OR=0.90 (0.63–1.29)	
			Intermediate		OR=0.96 (0.66–1.41)	
			High		OR=0.31 (0.08–0.89)	
Reynolds et al., 2005[578] USA	Hospital–based case–control Recruitment occurred to the mid–1990s Women aged: <40 y: 5 cases, 10 controls 40–49 y: 29 cases, 27 controls 50–59 y: 27 cases, 11 controls ≥60 y: 18 cases, 4 controls	131 women 79 cases 52 controls	Adipose levels of PCDD TEQ (pg/g) ≤14.0 14.1–20.9 ≥21.0	Breast cancer	OR=1 (referent) OR=0.72 (0.28–1.88) OR=0.73 (0.27–1.95); p–trend=0.99	Unconditional logistic regression Adjustments: Age and ethnicity Limitations: Over–matching Measurement of dioxin concentrations
Dai et al., 2008[580] USA	Michigan Department of Community Health register Retrospective	4,604 female breast cancer cases	Soil dioxin contamination in zip codes (ppt TEQ) 48883 48415 48457 48601	Breast cancer	OR=1 (referent) OR=1.28 (–0.11–0.60) OR=1.13 (–0.25–0.50) OR=1.25 (–0.08–0.52)	Unconditional logistic regression Adjustments: Age Limitations: Uncertainties into health

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	1985–2002			48602	OR=1.39 (0.03–0.64)	outcomes
				48603	OR=1.34 (–0.01–0.58)	
				48604	OR=1.34 (–0.04–0.63)	Zip code residence at diagnosis is inadequate to describe development of cancer location
				48611	OR=1.22 (–0.19–0.59)	
				48616	OR=1.01(–0.37–0.39)	
				48618	OR=1.35 (–0.10–0.69)	
				48623	OR=1.15 (–0.22–0.49)	Data sets lacked residential history information
				48626	OR=1.13 (–0.28–0.52)	
				48640	OR=1.86 (0.32–0.92)	
				48642	OR=0.63 (–0.80–0.14)	Unable to adjust for all confounding variables
				48650	OR=1.20 (–0.19–0.55)	
				48655	OR=1.26 (–0.15–0.61)	
				48657	OR=1.35 (–0.06–0.66)	
				48706	OR=1.2 (–0.12–0.47)	
				48708	OR=1.25 (–0.08–0.53)	
				48732	OR=1.22 (–0.13–0.53)	
				48734	OR=1.3 (–0.09–0.60)	
				48880	OR=1.88 (0.27–0.98)	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; ER, oestrogen receptor; HR, hazard ratio; NR, not reported; OR, odds ratio; p, p–value; pg/g, picograms per gram; pg/kg, picograms per kilogram; p(heter), p–value for the measure of heterogeneity; PCDD, polychlorinated dibenzo–*p*–dioxin; ppt, parts per trillion; PR, progesterone receptor; p–trend, p–value for trend; RR, relative risk or risk estimate; SWHS, Seveso Women's Health Study; TCDD, 2,3,7,8–tetrachlorodibenzo–p–dioxin; TEQ, toxic equivalents; USA, United States of America; y, year/s.

†Age, height, body mass index, energy intake, education, physical activity, smoking status, menopausal status combined with use of menopausal hormone treatment, alcohol intake, age at menarche, use of oral contraceptives, use of progestin, age at menopause, age at first full term pregnancy and number of live births, breastfeeding, family history of breast cancer, history of personal benign breast disease and mammography.

Table D.73 Ethylene oxide and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Mikoczy et al., 2011[588] Sweden	Swedish sterilant workers cohort Cohort dates: 1972–2006 Retrospective study Duration of follow–up: 58,220 person–y	Workers employed for at least 1 year 2,171 participants (862 males and 1,309 females) 41 cases	EtO exposure compared with general public No induction latency period	Breast cancer incidence 1972–2006	SIR=0.81 (0.58–1.09)	External (SIR) calculated as a normal variable Internal (IRR) calculated with Poisson regression Adjustments: IRR data adjusted for gender, age and calendar period Limitations: Information about possible confounding variables unavailable Shift work occurred in the cohort
	Duration of follow–up: 27,415 person–y	2,046 participants (males and females) 33 cases	≥15 y induction latency period		SIR=0.86 (0.59–1.20)	
	Duration of follow–up: 15,763 person–y Average age at end of follow–up: 52.4 y	615 participants (females only) 10 cases	0–0.13 ppm–y	Breast cancer incidence	IRR=1.00	
	Duration of follow–up: 8,245 person–y Average age at end of follow–up: 58.8 y	287 participants (females only) 14 cases	0.14–0.21 ppm–y		IRR=2.76 (1.20–6.33)	
	Duration of follow–up: 8,874 person–y Average age at end of follow–up: 60.6 y	295 participants (females only) 17 cases	≥0.22 ppm–y		IRR=3.55 (1.58–7.93)	

Note: Risk estimates are presented with 95% confidence intervals.
Abbreviations: EtO; ethylene oxide; IRR, incidence rate ratio; ppm–y, parts per million years; SIR, standardised incidence rate; y, year/s.

Table D.74 Land contamination and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Benedetti et al., 2017[589] Italy	SENTIERI project cohort Cohort dates: 1996–2005 Exploratory ecological study Age and follow–up: NR	14 NPCSs	Land contamination (PCBs, dioxins, heavy metals and solvents)	Breast cancer		Model: NR† Adjustments: Age, gender, and socioeconomic deprivation index Limitations: Could not adjust for confounding factors Difficult to hypothesis on substances and mechanisms that have determined the excesses of cases in some NPCs
			Geographical area			
		227 cases	Basso Bacino Fiume Chienti		SIR=117 (104–130)	
		1,187 cases	Brescia Caffaro		SIR=125 (120–132)	
		403 cases	Fidenza		SIR=102 (94–111)	
		1,097 cases	Litorale Domozio Flegreo & Agro Aversano		SIR=103 (98–108)	
		249 cases	Laguna Grado Marano		SIR=95 (85–106)	
		472 cases	Laghi Mantova		SIR=113 (105–122)	
		80 cases	Milazzo		SIR=108 (89–130)	
		966 cases	Porto Torres		SIR=125 (119–132)	
		712 cases	Priolo		SIR=111 (104–118)	
		702 cases	Sassuolo Scandiano		SIR=90 (85–96)	
		497 cases	Taranto		SIR=145 (134–156)	
		902 cases	Terni Papigno		SIR=114 (107–120)	
		876 cases	Trento Nord		SIR=98 (92–103)	
		3,045 cases	Venezia Porto Marghera		SIR=110 (107–114)	
Pirastu et al., 2013[589] Italy	SENTIERI project cohort Cohort dates: 2006–2007 Retrospective study	Taranto NPCSs 317 cases	Environmental contaminants in TA–NPCS vs remainder of Taranto province	Breast cancer	SIR=1.24 (1.13–1.36)	Model: NR† Adjustments: NR Limitations: Assumption that all residents in the area experience the same

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Age and follow–up: NR					exposures Ecological design Use of mortality data at municipal level for a short period of time
Guajardo & Oyana, 2009[591] USA	MDCH Cohort dates: 1989–2002 Retrospective study Majority of cases were in females over 45 y No follow–up	Total population: approximately 156,000 (males and females) 3,768 cases Ethnicities: Caucasian (83.5%), African–American (10.4%), Hispanic (4.8%), Asian (0.8%) & Native American (0.5%)	Environmental contamination By Michigan state zip codes	Breast cancer		Model: NR Adjustments: Age using 2000 USA census data Limitations: NR
		2,861 females 52 cases	48883		OR=1 (referent)	
		3,827 females 92 cases	48415		OR=1.33 (0.0944–1.876)	
		3,266 females 69 cases	48457		OR=1.17 (0.811–1.677)	
		19,205 females 436 cases	48601		OR=1.25 (0.939–1.677)	
		13,344 females 324 cases	48602		OR=1.34 (1.000–1.807)	
		17,399 females 516 cases	48603		OR=1.65 (1.238–2.202)‡	
		4,996 females	48604		OR=1.42 (1.026–1.967)‡	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		128 cases 2,375 females 52 cases	48611		OR=1.21 (0.820–1.783)	
		3,072 females 62 cases	48616		OR=1.11 (0.767–1.614)	
		2,074 females 58 cases	48618		OR=1.55 (1.064–2.270)‡	
		4,409 females 87 cases	48623		OR=1.09 (0.769–1.538)	
		2,324 females 45 cases	48626		OR=1.07 (0.713–1.596)	
		13,339 females 421 cases	48640		OR=1.76 (1.316–2.355)‡	
		12,610 females 178 cases	48642		OR=0.77 (0.566–1.056)	
		3,062 females 71 cases	48650		OR=1.28 (0.893–1.841)	
		2,651 females 62 cases	48655		OR=1.29 (0.891–1.877)	
		3,222 females 84 cases	48657		OR=1.45 (1.019–2.051)‡	
		17,269 females 407 cases	48706		OR=1.3 (0.974–1.745)	
		11,973 females 285 cases	48708		OR=1.32 (0.977–1.775)	
		5,201 females 143 cases	48732		OR=1.53 (1.108–2.105)‡	
		3,265 females 110 cases	48734		OR=1.88 (1.349–2.630)‡	
		2,594 females 86 cases	48880		OR=1.85 (1.307–2.625)‡	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Pesatori et al., 2009[592] Italy	Seveso cohort Cohort dates: 1977–1996 Prospective study Date of contamination: 10 July 1976 Age at enrolment: <75 y Follow–up: continual	371 females 8 cases	TCDD soil levels Zone A (high exposure) vs non–contaminated zone Overall Time since accident 0–4 y 5–9 y 10–14 y 15+ y	Breast cancer	RR=1.43 (0.71–2.87) N/A RR=0.81 (0.11–5.74) RR=1.42 (0.35–5.68) RR=2.57 (1.07–6.20)	Poisson regression model Adjustments: Gender, age category and period (five–year classes) Limitations: Low number of cases Exposure categorisation based on environmental contamination data (TCDD soil measurements) Official residence of the subjects at the time of the accident does not coincide with presence at time of incident and possible misclassification of exposure
		2,350 females 30 cases	Zone B (medium exposure) vs non–contaminated zone Overall Time since accident 0–4 y 5–9 y 10–14 y 15+ y		RR=0.85 (0.59–1.22) RR=0.70 (0.26–1.87) RR=0.79 (0.35–1.76) RR=1.09 (0.58–2.04) RR=0.78 (0.42–1.46)	
		15,928 females 249 cases	Zone R (low exposure) vs non–contaminated zone Overall Time since accident 0–4 y 5–9 y 10–14 y 15+ y		RR=1.00 (0.88–1.15) RR=1.10 (0.81–1.49) RR=1.07 (0.81–1.41) RR=0.87 (0.66–1.15) RR=1.01 (0.81–1.27)	
Dai et al., 2008[580]	MDCH Cohort dates:	378,831 women	Soil dioxin contamination ZIP code	Breast cancer		Model: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
USA	1985–2002 Retrospective study Age at enrolment: 15–75+ y Follow–up: NR	4,602 cases		48883	OR=1 (referent)	Adjustments: Age at a significance level of p≤0.05 Limitations: Lack of TEQ data for other soils from background sites/ZIP codes farther away from Midland ZIP code of residence at diagnosis not reflective of location where cancer developed Lack of residential history information Not all confounding factors could be adjusted for
				48415	OR=1.28 (–0.11–0.60); p=0.1699	
				48457	OR=1.13 (–0.25–0.50); p=0.5163	
				48601	OR=1.25 (–0.08–0.52); p=0.1526	
				48602	OR=1.39 (0.03–0.64); p=0.0309	
				48603	OR=1.34 (–0.01–0.58); p=0.0579	
				48604	OR=1.34 (–0.04–0.63); p=0.0877	
				48611	OR=1.22 (–0.19–0.59); p=0.3160	
				48616	OR=1.01 (–0.37–0.39); p=0.9657	
				48618	OR=1.35 (–0.10–0.69); p=0.1407	
				48623	OR=1.15 (–0.22–0.49); p=0.4546	
				48626	OR=1.13 (–0.28–0.52); p=0.5451	
				48640	OR=1.86 (0.32–0.92); p<0.0001	
				48642	OR=0.63 (–0.80– –0.14); p=0.0047	
				48650	OR=1.2 (–0.19–0.55); p=0.3430	
				48655	OR=1.26 (–0.15–0.61); p=0.2408	
				48657	OR=1.35 (–0.06–0.66); p=0.0982	
				48706	OR=1.2 (–0.12–0.47); p=0.2509	
				48708	OR=1.25 (–0.08–0.53); p=0.1539	
				48732	OR=1.22 (–0.13–0.53); p=0.2356	
				48734	OR=1.3 (–0.09–0.60); p=0.1438	
				48880	OR=1.88 (0.27–0.98); p=0.0006	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: MDCH, Michigan Department of Community Health; NPCS, National Priority Contaminated site; N/A, not available; NR, not reported; OR, odds ratio; p, p–value; PCB, polychlorinated biphenyl; RR, relative risk or risk estimate; SENTIERI, Italian Epidemiological Study of Residents in National Contaminated Sites; SIR, standardised incidence ratio; TA–NPCS, Taranto province excluding NPCS municipalities; TCDD, 2,3,7,8–Tetrachlorodibenzo–p–dioxin; TEQ, total toxic equivalent; USA, United States of America; y, year/s; ZIP; zone improvement plan.

†90% confidence intervals. ‡Significant positive association.

Table D.75 Outdoor air pollution and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Keramatinia et al., 2016[596] Studies published to 2014 Canada, Denmark, Saudi Arabia, USA	5 studies 3 ecological studies 1 cohort study 1 case–control study	Study sample: NR	NO_2 exposure	Breast cancer	R=1.38 (1.11–1.59)	Fixed effects model Adjustments: 1 study adjusted for only race, 2 studies adjusted for a range of factors and 2 studies did not adjust Publication bias: NR Limitations: Limited number of studies with adjusted measure of association Correlation coefficient presented as measure of association; the association may not state any risk at individual level Search did not include the grey literature that could have improved review
Cohort studies						
Hart et al., 2018[595] USA	Nurses' Health Study II Cohort dates: 1989–2011 Prospective study Nurses aged 25–42	109,239 women 3,321 invasive cases	HAPs exposure 1,2–dibromo–3–chloropropane Q4 vs Q1(referent) Diesel engine Emissions Q4 vs Q1 (referent) Arsenic compounds (Inorganic)	Breast cancer	HR=1.12 (0.98–1.29) HR=1.10 (0.99–1.22)	Multivariable proportional hazards models Adjustments* Limitations: Substantial exposure errors Inability to examine exposures

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	y at baseline Follow–up: 2,203,192 person–y		Q4 vs Q1(referent)		HR=0.96 (0.86–1.06)	early in the life of participants Findings may not be generalisable
			Biphenyl Q4 vs Q1(referent)		HR=0.99 (0.89–1.09)	
			Bis(2–Ethylhexyl) Phthalate Q4 vs Q1(referent)		HR=1.01 (0.92–1.12)	
			Dibutulphthalate Q4 vs Q1(referent)		HR=1.06 (0.96–1.17)	
			Dimethyl formamide Q4 vs Q1(referent)		HR=1.08 (0.97–1.20)	
			4–Nitrophenol Q4 vs Q1(referent)		HR=1.07 (0.96–1.19)	
			Selenium compounds Q4 vs Q1(referent)		HR=0.96 (0.86–1.07)	
			Styrene Q4 vs Q1(referent)		HR=0.97 (0.89–1.06)	
Shmuel et al., 2017[598] Puerto Rico & USA	Sister study Cohort dates: 2003–2009 Prospective study Mean age at baseline: 55.6 y Mean follow–up: 6.3 y	50,884 women 2,028 cases 36,383 Non–Hispanic, White 3,556 Non–Hispanic, Black 1,933 Hispanic 1,062 Other	Combined measure of traffic pollutants (multiple lanes, median/barrier and traffic during rush hour on intersecting road) 100ft + and/or Neither 3+ lanes nor median barrier	Breast cancer	HR=1.00 (referent)	Cox regression model Adjustments: Age, race/ethnicity, and highest level of education attained in the household at age 13 y Limitations: Exposure misclassification Recall bias
			And light traffic		HR=1.2 (0.7–2.0)	
			And Moderate traffic		HR=0.8 (0.5–1.3)	
			And Heavy traffic		HR=1.4 (1.0–1.9)	
			Combined measure of traffic pollutants (multiple lanes, median/barrier and traffic during rush hour on intersecting	Premenopausal breast cancer	HR=1.00 (referent)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			road) 100ft + and/or Neither 3+ lanes nor median barrier And light/moderate traffic		HR=1.2 (0.6–2.5)	
			And heavy traffic		HR=1.1 (0.6–2.2)	
			Combined measure of traffic pollutants (multiple lanes, median/barrier and traffic during rush hour on intersecting road) 100ft + and/or Neither 3+ lanes nor median barrier And light/moderate traffic	Postmenopausal breast cancer	HR=1.00 (referent) HR=0.9 (0.6–1.3)	
			And heavy traffic		HR=1.5 (1.1–2.0)	
			Combined measure of traffic pollutants (multiple lanes, median/barrier and traffic during rush hour on intersecting road) 100ft + and/or Neither 3+ lanes nor median barrier And light/moderate traffic	Invasive ER+	HR=1.00 (referent) HR=1.0 (0.6–1.5)	
			And heavy traffic		HR=1.1 (0.7–1.7)	
			Combined measure of traffic pollutants	Invasive ER–		

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			(multiple lanes, median/barrier and traffic during rush hour on intersecting road) 100ft + and/or Neither 3+ lanes nor median barrier		HR=1.00 (referent)	
			And light/moderate traffic		N/A	
			And heavy traffic		HR=1.3 (0.5–3.3)	
Andersen et al., 2016[597] Denmark	Danish Nurse cohort Cohort dates: 1993 or 1999 to 2013 Prospective study Mean age at baseline: 52.9 y Duration of follow–up: 16 y	22,877 women 1,145 cases 21,732 no cases 11,579 premenopausal women 11,120 postmenopausal women	Air pollution $PM_{2.5}$ (3.3 mg/m^3) PM_{10} (2.9 mg/m^3) NO_2 (7.4 mg/m^3)	Breast cancer	 RR=1.00 (0.91–1.09) RR=1.02 (0.94–1.11) RR=1.00 (0.94–1.07)	Cox proportional hazards regression model Adjustments† Limitations: NR
Hart et al., 2016[600] USA	Nurses' Health Study II Cohort dates: 1989 enrolled Data collected: 1993–2011 Mean age at baseline: 25–42 y	115,921 women	48 months exposure to PM (per 10µg/m^3) PM_{10} $PM_{2.5–10}$ $PM_{2.5}$	Breast cancer	 HR=1.00 (0.93–1.07) HR=1.06 (0.96–1.17) HR=0.90 (0.79–1.03)	Multivariable adjusted model Adjustments‡ Limitations: Information available for adult exposures, which may not be an important etiological period Findings in this cohort may not be generalisable to population
			Proximity to A1 roads 0–49m 50–199m ≥200m		 HR=1.60 (0.80–3.21) HR=1.11 (0.89–1.40) HR=1.00 (referent)	
			48 months exposure to PM (per 10µg/m^3)	Premenopausal breast cancer		

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Follow–up: 1993–2011		PM_{10}		HR=1.03 (0.93–1.13)	with more racial/ethnic diversity or a broader range of socioeconomic status
			$PM_{2.5–10}$		HR=1.07 (0.93–1.22)	
			$PM_{2.5}$		HR=0.99 (0.83–1.18)	
			Proximity to A1 roads			
			0–49m		HR=1.74 (0.72–4.21)	
			50–199m		HR=1.26 (0.94–1.67)	
			≥200m		HR=1.00 (referent)	
			48 months exposure to PM (per 10µg/m^3)	Postmenopausal breast cancer		
			PM_{10}		HR=0.97 (0.86–1.09)	
			$PM_{2.5–10}$		HR=1.07 (0.92–1.25)	
			$PM_{2.5}$		HR=0.76 (0.61–0.95)	
			Proximity to A1 roads			
			0–49m		HR=1.48 (0.47–4.62)	
			50–199m		HR=0.97 (0.65–1.45)	
			≥200m		HR=1.00 (referent)	
			48 months exposure to PM (per 10µg/m^3)	ER+PR+ invasive breast cancer		
			PM_{10}		HR=1.05 (0.95–1.15)	
			$PM_{2.5–10}$		HR=1.13 (0.99–1.29)	
			$PM_{2.5}$		HR=0.95 (0.79–1.14)	
			Proximity to A1 roads			
			0–49m		HR=1.48 (0.55–3.97)	
			50–199m		HR=1.08 (0.79–1.48)	
			≥200m		HR=1.00 (referent)	
			48 months exposure to PM (per 10µg/m^3)	ER–PR– invasive breast cancer		
			PM_{10}		HR=0.97 (0.80–1.18)	
			$PM_{2.5–10}$		HR=0.96 (0.73–1.26)	
			$PM_{2.5}$		HR=0.97 (0.68–1.40)	
			Proximity to A1 roads			
			0–49m		HR=1.52 (0.89–2.60)	
			50–199m		HR=N/A	
			≥200m		HR=1.00 (referent)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Garcia et al., 2015[601] USA	California Teacher Study Cohort established: 1995–1996 Prospective cohort study Mean age at baseline: 53–57 y Follow–up period: 1995–2011	112,378 women 5,676 cases 91,831 white ethnicity 2,894 black ethnicity 4,805 Hispanic ethnicity 3,907 Asian/Pacific Islander ethnicity 3,265 other or mixed ethnicity	Acrylamide Q1 Q2 Q3 Q4 Q5	Breast cancer	 HR=1.00 (referent) HR=N/A HR=1.02 (0.94–1.10) HR=1.09 (1.02–1.17) HR=1.08 (1.01–1.16); p–trend=0.008	Cox proportional hazard model Adjustments: Models stratified by age and adjusted for race Limitations: Potential exposure misclassification Analyses are predicated on the assumption that these modelled ambient concentrations can serve as proxies for inhalational exposure to these compounds Indoor inhalation exposures or ambient exposures outside of the census tract of baseline residence were not considered
			Acrylonitrile Q1 Q2 Q3 Q4 Q5		 HR=1.00 (referent) HR=1.03 (0.95–1.12) HR=1.02 (0.94–1.11) HR=1.05 (0.97–1.14) HR=1.06 (0.97–1.15); p–trend=0.17	
			Benzene Q1 Q2 Q3 Q4 Q5		 HR=1.00 (referent) HR=1.09 (1.00–1.18) HR=1.03 (0.95–1.12) HR=1.03 (0.95–1.12) HR=1.06 (0.98–1.16); p–trend=0.38	
			Benzidine Q1 Q2 Q3 Q4 Q5		 HR=1.00 (referent) HR=N/A HR=0.98 (0.86–1.12) HR=0.97 (0.91–1.04) HR=1.06 (0.99–1.14); p–trend=0.24	
			1,3–Butadiene Q1 Q2 Q3 Q4 Q5		 HR=1.00 (referent) HR=0.98 (0.91–1.07) HR=1.06 (0.98–1.15) HR=0.99 (0.91–1.08) HR=1.02 (0.94–1.11); p–trend=0.56	
			Carbon tetrachloride Q1		 HR=1.00 (referent)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Q2		HR=0.98 (0.90–1.07)	
			Q3		HR=1.04 (0.96–1.13)	
			Q4		HR=1.03 (0.95–1.12)	
			Q5		HR=1.08 (1.00–1.18); p–trend=0.03	
			Chloroprene			
			Q1		HR=1.00 (referent)	
			Q2		HR=N/A	
			Q3		HR=N/A	
			Q4		HR=1.05 (0.96–1.15)	
			Q5		HR=1.07 (1.00–1.14); p–trend=0.04	
			1,4–Dioxane			
			Q1		HR=1.00 (referent)	
			Q2		HR=1.04 (0.96–1.13)	
			Q3		HR=1.05 (0.96–1.14)	
			Q4		HR=1.07 (0.99–1.16)	
			Q5		HR=1.02 (0.94–1.11); p–trend=0.23	
			Ethyl carbamate			
			Q1		HR=1.00 (referent)	
			Q2		HR=N/A	
			Q3		HR=N/A	
			Q4		HR=0.97 (0.90–1.05)	
			Q5		HR=1.07 (1.00–1.14); p–trend=0.22	
			Ethylene dibromide			
			Q1		HR=1.00 (referent)	
			Q2		HR=1.05 (0.97–1.14)	
			Q3		HR=1.07 (0.99–1.16)	
			Q4		HR=1.03 (0.95–1.12)	
			Q5		HR=1.01 (0.93–1.10); p–trend=0.88	
			Ethylene dichloride			
			Q1		HR=1.00 (referent)	
			Q2		HR=1.04 (0.95–1.12)	
			Q3		HR=0.94 (0.86–1.02)	
			Q4		HR=1.04 (0.96–1.13)	
			Q5		HR=1.05 (0.97–1.14); p–trend=0.25	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Ethylene oxide			
			Q1		HR=1.00 (referent)	
			Q2		HR=0.93 (0.85–1.00)	
			Q3		HR=0.92 (0.85–1.00)	
			Q4		HR=0.97 (0.89–1.05)	
			Q5		HR=1.00 (0.92–1.08); p–trend=0.70	
			Ethylidene dichloride			
			Q1		HR=1.00 (referent)	
			Q2		HR=1.01 (0.93–1.10)	
			Q3		HR=1.09 (1.00–1.18)	
			Q4		HR=1.08 (0.99–1.17)	
			Q5		HR=1.02 (0.94–1.11); p–trend=0.19	
			Hydrazine			
			Q1		HR=1.00 (referent)	
			Q2		HR=N/A	
			Q3		HR=0.92 (0.86–0.99)	
			Q4		HR=0.98 (0.91–1.06)	
			Q5		HR=1.04 (0.97–1.12); p–trend=0.36	
			Methylene chloride			
			Q1		HR=1.00 (referent)	
			Q2		HR=0.97 (0.89–1.05)	
			Q3		HR=1.06 (0.98–1.15)	
			Q4		HR=1.01 (0.93–1.10)	
			Q5		HR=1.04 (0.96–1.13); p–trend=0.21	
			4,4'–Methylene bis(2–chloroaniline)			
			Q1		HR=1.00 (referent)	
			Q2		HR=N/A	
			Q3		HR=N/A	
			Q4		HR=1.02 (0.92–1.13)	
			Q5		HR=1.07 (1.01–1.15); p–trend=0.03	
			Nitrobenzene			
			Q1		HR=1.00 (referent)	
			Q2		HR=N/A	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Q3		HR=N/A	
			Q4		HR=1.04 (0.97–1.12)	
			Q5		HR=1.03 (0.96–1.10); p–trend=0.29	
			Propylene dichloride			
			Q1		HR=1.00 (referent)	
			Q2		HR=1.00 (0.92–1.08)	
			Q3		HR=0.92 (0.85–1.01)	
			Q4		HR=1.01 (0.93–1.09)	
			Q5		HR=1.04 (0.96–1.13); p–trend=0.20	
			Propylene oxide			
			Q1		HR=1.00 (referent)	
			Q2		HR=1.05 (0.97–1.15)	
			Q3		HR=1.11 (1.02–1.20)§	
			Q4		HR=1.05 (0.97–1.14)	
			Q5		HR=1.01 (0.93–1.10); p–trend=0.18	
			Styrene			
			Q1		HR=1.00 (referent)	
			Q2		HR=1.04 (0.96–1.13)	
			Q3		HR=1.02 (0.94–1.11)	
			Q4		HR=1.05 (0.96–1.14)	
			Q5		HR=1.04 (0.96–1.13) p–trend=0.41	
			2,4–Toluene diisocyanate			
			Q1		HR=1.00 (referent)	
			Q2		HR=1.05 (0.96–1.14)	
			Q3		HR=1.04 (0.96–1.13)	
			Q4		HR=1.03 (0.95–1.12)	
			Q5		HR=1.07 (0.98–1.16); p–trend=0.17	
			o–Toluidine			
			Q1		HR=1.00 (referent)	
			Q2		HR=N/A	
			Q3		HR=N/A	
			Q4		HR=1.10 (1.01–1.21)	
			Q5		HR=1.03 (0.97–1.10) p–trend=0.10	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Vinyl chloride			
			Q1		HR=1.00 (referent)	
			Q2		HR=1.03 (0.94–1.12)	
			Q3		HR=1.12 (1.03–1.21)§	
			Q4		HR=1.07 (0.99–1.17)	
			Q5		HR=1.06 (0.98–1.16); p–trend=0.06	
			Vinylidene chloride			
			Q1		HR=1.00 (referent)	
			Q2		HR=0.97 (0.90–1.06)	
			Q3		HR=0.98 (0.90–1.07)	
			Q4		HR=1.04 (0.96–1.13)	
			Q5		HR=1.03 (0.94–1.11); p–trend=0.27	
			Summary variable			
			Q1		HR=1.00 (referent)	
			Q2		HR=0.98 (0.90–1.07)	
			Q3		HR=0.97 (0.89–1.05)	
			Q4		HR=1.02 (0.94–1.10)	
			Q5		HR=1.05 (0.96–1.14); p–trend=0.11	
Reding et al., 2015[599] USA	Sister study Cohort dates: 2003–2009 Prospective cohort study Age at enrolment: 56.9 y cases and 55.1 y controls Mean follow–up: 4.95 y	1,749 cases 47,591 controls 947 ER+PR+ breast cancer 223 ER–PR– breast cancer 40,750 non–Hispanic white ethnicity 4,318 non–Hispanic black ethnicity 2,433 Hispanic ethnicity 1,236 other	Ambient air pollution	Breast cancer	HR=1.03 (0.96–1.11)	Cox proportional hazards model Adjustments: Models adjusted for age at diagnosis, race, educational attainment, smoking status, menopausal hormone therapy Limitations: Air pollution exposure earlier in life could impact breast cancer risk
			$PM_{2.5}$	ER+PR+	RR=1.00 (0.91–1.09)	
				ER–PR–	RR=0.99 (0.81–1.20); p=0.99	
			PM_{10}	Breast cancer	HR=0.99 (0.98–1.00)	
				ER+PR+	RR=1.02 (0.96–1.09)	
				ER–PR–	RR=0.96 (0.83–1.10); p=0.69	
			NO_2	Breast cancer	HR=1.02 (0.97–1.07)	
				ER+PR+	RR=1.10 (1.02–1.19)	
				ER–PR–	RR=0.92 (0.77–1.09); p=0.04	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		ethnicity 7 unknown ethncity				

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: ER, oestrogen receptor; HR, hazard ratio; HAPs, hazardous air pollutants; N/A, not available; NO, nitrogen oxide; NR, not reported; p, p–value; p(trend), p–value for trend; PM, particulate matter; PR, progesterone receptor; Q, quintile; RR, relative risk or risk estimate; USA, United States of America; y, year/s.

*All models adjusted for age, calendar period, race, family history of breast cancer, history of aspiration or biopsy confirmed benign breast disease, age at menarche, parity and age at first birth, menopausal status and postmenopausal hormone use, oral contraception use, recent mammogram, height, body mass index (BMI) at age 18, difference between current BMI and BMI at age 18, smoking status, physical activity, overall diet quality (including alcohol consumption), alcohol consumption at age 15 and age 18, shift work, individual–level socioeconomic status (marital status, living arrangements, household income), area–level socioeconomic status (census tract median home value and median income) and census region of residence.

†Also adjusted for parity, age at first birth, age at menarche, hormone therapy use, oral contraceptive use, and menopausal status.

‡HR adjusted for age, race calendar period , history of benign breast disease, family history, age at menarche, parity, age at first birth, height, BMI at age 18, current BMI, alcohol consumption at ages 15–17 and 18–22, overall diet quality (AHEI–2010), oral contraceptive use, menopausal status and hormone use, smoking status, physical activity, individual level socioeconomic status (marital status, living arrangements, household income) and area level socioeconomic status (census tract level median income and median home value) and census region of residence.

§Remains statistically significant ($p < 0.05$) after adjustment for multiple comparisons.

Table D.76 Polychlorinated biphenyls risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Leng et al., 2016[599] Studies published to 2014 Belgium, Canada, Denmark, Japan, Mexico, Spain, Sweden & USA	16 studies 5 nested case–control studies 11 case–control studies	3,438 cases	PCB PCB 187 PCB 118 PCB 138 PCB 156 PCB 170 PCB 99 PCB 183 PCB 153 PCB 180	Breast cancer	OR=1.18 (1.01–1.39); I^2=26.8%, p=0.224 OR=1.32 (0.98–1.78); I^2=74.5% OR=1.08 (0.99–1.17); I^2=27.8% OR=1.19 (0.85–1.67); I^2=65.3% OR=1.28 (0.89–1.86); I^2=61.6% OR=1.36 (1.02–1.80); I^2=0.0%, p=0.609 OR=1.56 (1.25–1.95); I^2=0.0%, p=0.647 OR=1.04 (0.81–1.34); I^2=70.3% OR=1.02 (0.81–1.29); I^2=56.6%	Random effects model (p<0.10)/ fixed effects model (p>0.10) Adjustments: Age No publication bias Limitations: Inappropriate definition of cases or controls Bias with selection of study population Potential confounders Dose–response effect not properly evaluated Interaction of individual chemicals to mixtures or to similar chemicals
Zhang et al., 2015[612] Studies published 1994–2013 Belgium, Canada, China, Denmark, Japan, Mexico, Norway & USA	25 case–control studies	12,866 participants 6,088 cases 6,778 controls	PCB exposure Total Potentially oestrogenic PCBs Potentially anti–oestrogenic and immunotoxic, dioxin–like PCBs Phenobarbital, CYP1A & CYP2B inducers		pOR=1.09 (0.97–1.22); I^2=55.4%, p(heter)<0.0001 pOR=1.10 (0.97–1.24); I^2=0.0%, p(heter)=0.506 pOR=1.23 (1.08–1.40); I^2=48.0%, p(heter)=0.002 pOR=1.25 (1.09–1.43); I^2=40.2%, p(heter)=0.023	Random effects model (I^2<25%)/ fixed effects model (I^2 of 25–50%) Adjustments: NR No publication bias (p>0.05) Limitations: One of the included studies is an unpublished thesis Six studies did not adjust lipid as a main confounder The definite dose for PCB exposure differed slightly across

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						the studies Exposure to mixtures of PCBs and other chemicals with oestrogenic properties and other organochlorine pesticides may also affect breast cancer risk
Cohort studies						
Donat–Vargas et al., 2016[615] Sweden	Swedish Mammography Cohort Cohort dates: 1997−2012 Prospective study Mean age at enrolment per median PCB exposure (ng/d): 62 y for <139 60 y for 139–193 63 y for >193 Duration of follow–up: 14 y	36,777 participants 1,593 cases	Dietary PCB exposure <139 ng/d 139–195 ng/d >195 ng/d	Breast cancer	HR=1.00 (referent) HR=0.98 (0.83–1.17) HR=0.96 (0.75–1.24); p–trend=0.77	Cox proportional hazard regression models† Limitations: Measurement error and misclassification of PCB exposure Limited number of cases in some stratified analyses

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: HR, hazard ratio; OR, odds ratio; ng/d, nanograms per day; NR, not reported; pOR, pooled odds ratios; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for the measure of trend; PCB, polychlorinated biphenyl; USA, United States of America; y, year/s.

†Adjusted for attained age, postsecondary education, family history of breast cancer, oophorectomy (only for breast and endometrial cancer), history of diabetes, body mass index, weight loss >5 kg within one year, age at menarche ≤12 years, use of oral contraceptives, parity, age at first birth ≥30 years, age at menopause ≥51 years, ever use of postmenopausal hormones, smoking habits, leisure time inactivity, time spent walking or bicycling, alcohol consumption, total energy intake and dietary eicosapentaenoic acid–docosahexaenoic acid intake.

Table D.77 Occupation as a hairdresser and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Takkouche et al., 2009[618] Studies published 1966–2009 14 countries: Individual countries NR	12 incidence–only studies 7 cohort studies 5 hospital & population based case–control studies	Cohort studies: 6652 cases Case–control studies: 2,165 cases 3,582 controls	Being a hairdresser or related worker	Breast cancer	RR=1.03 (0.98–1.08); p=0.95	Random effects model Adjustments: Individual studies adjusted for various factors, with all adjusting for age & sex No publication bias Limitations: Studies included used information systems that may present incomplete information on confounders & occupational exposure
Cohort studies						
Ekenga et al., 2015[620] Puerto Rico & USA	Sister study Population based Cohort dates: 2 003–2009 Prospective cohort study Age at interview: 60+ y = 14,840 non–	47,640 participants 1,966 cases 45,674 non–cases	Lifetime exposure to dyes or inks Ever use vs never use	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	HR=1.2 (1.0–1.6); p–trend=0.30 HR=1.4 (0.9–2.1); p–trend=0.69 HR=1.0 (0.8–1.3); p–trend=0.18	Multivariable Cox proportional hazards regression model Adjustments† Limitations: Results might not be generalisable to women without family history of breast cancer Self–reported exposure
			>1,560 days 520–≤1,560 days 130–≤520 days <130 days	Breast cancer	HR=1.2 (0.8–1.8) HR=1.2 (0.8–1.8) HR=1.0 (0.7–1.5) HR=1.1 (0.7–1.5)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	cases & 771 cases 55–59 y = 9,114 non–cases & 379 cases 50–54 y =8,862 non–cases & 351 cases <50 y= 12,858 non–cases & 465 cases Mean follow–up: 5.2 y		Never used		HR=1.00 (referent); p–trend=0.47	Linear exposure–response model may not have been the most appropriate approach for studying chemical exposures Low prevalence of exposure to some agents & the small number of breast cancer diagnoses in some exposure limited the statistical power of study Findings may have been due to chance alone
Pukkala et al., 2009[619] Denmark, Finland, Iceland, Norway & Sweden	NOCCA Population based Cohort dates: 1961–2005 Retrospective study Age at baseline: 30–64 Follow–up: 1,059,586 person–y	1,983 cases	Female hairdresser vs all occupational categories	Breast cancer	SIR=1.06 (1.01–1.10)	Model: NR Adjustments: NR Limitations: The occupation at one point in time may not always correspond to the lifelong occupational history of a person

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: HR, hazard ratio; NOCCA, Nordic Occupational Cancer project; NR, not reported; p, p–value; p–trend, p–value for trend; RR, relative risk or risk estimate; SIR, standard incidence ratio; USA, United States of America; y, year/s.

†HRs adjusted for race/ethnicity, education, income, parity and age at first birth.

Table D.78 Personal use hair dyes/relaxers and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Gera et al., 2018[623] Studies published 1980–2017 Finland, Iran & USA	8 case–control studies	38,037 participants	Hair dyes Never use Ever use	Breast cancer	 RR=1.00 (referent) RR=1.19 (1.03–1.37)	Random effects model (Duval and Tweedie's Trim and Fill procedure) No severe publication bias Adjustments: NR Limitations: Lack of accurate information regarding exposure characteristics Heterogeneity among studies No uniform adjustment for confounding factors Variation between different populations Limited combined sample size and statistical power
Takkouche et al., 2005[622] Studies published 1966–2005	2 cohort studies 12 case–control studies	Cohort studies: 665,993 women 1,135 cases Case–control	Any personal use of hair dye All studies Permanent dye use	Breast cancer	 RR=1.06 (0.95–1.18); p(heter)<0.001 RR=0.98 (0.91–1.07);	Random effects model Adjustments† Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Jordan, UK & USA		studies: 5,019 cases 8,486 controls	Intensive exposure (>200 lifetime exposures)		p(heter)=0.13 RR=0.99 (0.89–1.11); p(heter)=0.45	Several case–control studies use the same comparison group for different outcomes Failure to control for potential or unknown confounders
Cohort studies						
Mendelsohn et al., 2009[624] China	Shanghai Women's Health Study cohort End of follow–up: Dec 2005 Prospective study Age at enrolment: 40–70 y Mean follow–up: 7 y	70,366 women 592 cases 358 non–user cases 42,739 non–user controls 234 user cases 28,166 user controls	Hair dye use Ever vs never Duration of use 1–2 y 3–4 y 5–9 y ≥10 y	Breast cancer	RR=0.93 (0.78–1.09) RR=0.90 (0.72–1.12) RR=0.87 (0.66–1.13) RR=0.91 (0.65–1.29) RR=1.00 (0.67–1.50)	Cox proportional hazards model Adjustments: Age, education, and smoking duration in pack/years Limitations: Questions about colour or type of hair dye not asked in the baseline questionnaire Possible misclassification of non–users Small number of cases
Rosenberg et al., 2007[621] USA	Black Women's Health Study Cohort dates: 1995–2003 Prospective study Age at enrolment:	48,167 women 574 cases	Hair straightener use Ever use vs no use Duration of hair straightener use No use 1–4 5–9 10–14	Breast cancer	IRR=1.04 (0.78–1.39) IRR=Reference IRR=1.17 (0.79–1.71) IRR=1.02 (0.69–1.50) IRR=0.85 (0.59–1.23)	Age–stratified Cox regression model Adjustments: NR Limitations: Random misclassification of use tended to dilute associations

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	21–69 y Follow–up: 266,298 person–y		15–19 ≥20 Frequency of hair straightener use (times per y) No use 1 2 3–4 5–6 ≥7		IRR=1.19 (0.85–1.67) IRR=1.03 (0.76–1.39) IRR=Reference IRR=1.44 (0.89–2.32) IRR=0.98 (0.65–1.46) IRR=1.03 (0.75–1.40) IRR=1.06 (0.77–1.46) IRR=1.04 (0.75–1.44)	No information on individual brands

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: IRR, incidence rate ratios; NR, not reported; Q, test for heterogeneity among studies; RR, relative risk or risk estimate; UK, United Kingdom; USA, United States of America; y, year/s.

†Studies adjusted for various factors, including: age, marital status, social class, duration of hair dye use, county of residence, smoking, family history of cancer, age at first birth, religion, education, birthplace, race, history of receiving Medicaid, age at menarche, menopause, first birth, family history of breast cancer, parity, weight, income, education, alcohol consumption, history of lactation, fat intake and history of benign breast disease.

Radiation exposure

Table D.79 Electromagnetic field radiation—low frequency and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Zhang et al., 2016[631] Studies published to 2015 Asia, Europe, North America & Oceania	23 case–control studies	42 studies in total: 13,259 cases 100,882 controls Population details: NR	Extremely low EMFs All studies	Breast cancer	OR=1.07 (1.00–1.15); p=0.06; p(heter)<0.00001	Fixed effects model/random effects model for p(heter)<0.1 No publication bias (p>0.05) Adjustments: NR Limitations: Cohort studies not included due to differences in methods Genetic & environmental factors were not combined Some heterogeneity evident
				Premenopausal breast cancer	OR=1.57 (0.95–2.59); p=0.08; p(heter)=0.0002	
				Postmenopausal breast cancer	OR=1.00 (0.88–1.14); p=0.97; p(heter)=0.43	
			Device measured studies	Breast cancer	OR=1.05 (0.95–1.16), p=0.39; p(heter)=0.88	
				Premenopausal breast cancer	OR=1.23 (1.01–1.49); p=0.04; p(heter)=0.18	
				Postmenopausal breast cancer	OR=0.96 (0.81–1.14); p=0.63; p(heter)=0.79	
Zhao et al., 2014[632] Studies published 2000–2007 Canada, Norway, Sweden & USA	16 case–control studies 4 studies 5 studies	Cases: 7,838 exposed 36,902 unexposed Controls: 9,027 exposed 122,875 unexposed	Extremely low EMFs (0–300 Hz)	Breast cancer	OR=1.10 (1.01–1.20); p=0.04; I^2=56%, p(heter)=0.003	Random effects model Small publication bias Adjustments: Race, family history, age of menarche, menopause, & use of oestrogen after menopause Limitations: NR
				Premenopausal breast cancer	OR=1.25 (1.05–1.49); p=0.01; I^2=0.0%, p(heter)=0.55	
				Menopausal breast cancer	OR=1.04 (0.93–1.18); p=0.48; I^2=0.0%, p(heter)=0.62	
Chen et al., 2013[633] Studies published 1990–2010	23 case–control studies 9 studies	24,338 cases 60,628 controls 14 studies selected	Extremely low EMFs	Breast cancer	OR=1.07 (1.02–1.13); p<0.05; I^2=39%, p(heter)=0.03	Quality effects model Adjustments: NR
				Premenopausal breast cancer	OR=1.11 (1.00–1.23); p<0.05; I^2=22%, p(heter)=0.24	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Canada, Norway, Sweden, Taiwan & USA	9 studies	cases from cancer registry Other studies selected from hospitals or other cohort studies Controls from 19 studies were randomly selected residents		Postmenopausal breast cancer	OR=1.02 (0.95–1.09); p=NS; I^2=0.0%, p(heter)=0.60	Small publication bias (funnel plot) Limitations: Exposure assessment was limited
	7 studies			ER+	OR=1.11 (1.03–1.20); p<0.05; I^2=0.0%, p(heter)=0.85	
	7 studies			ER–	OR=0.96 (0.84–1.10); p=NS; I^2=0.0%, p(heter)=0.54	
Chen et al., 2010[634] Studies published 2000–2009 Canada, Norway, Sweden & USA	15 case–control studies	24,338 cases 60,628 controls Age at enrolment: ≥15 y 7 studies selected cases from cancer registry & others based on clinical examination Controls were healthy population–based individuals matched for age, ethnicity and years of resident	Extremely low EMFs (0–300 Hz) Overall	Breast cancer	OR=0.99 (0.90–1.09); I^2=75.8%, p(heter)=0.000	Random effects model Adjustments: Most studies adjusted for age & menopausal status No publication bias (p=0.026) Limitations: Relying on results and figures presented in publications Information lacking on ER and menopausal status Controls not uniformly defined
	10 studies		Residential exposure		OR=1.02 (0.92–1.12); I^2=39.9%, p(heter)=0.092	
	5 studies		Occupational exposure		OR=0.93 (0.79–1.10); I^2=86.3, p(heter)=0.000	
Cohort studies						
Koeman et al.,	Netherlands Cohort Study on diet and	62,573 women	Extremely low EMFs (occupational	Postmenopausal		Cox proportional hazards model

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
2014[635] Netherlands	cancer Prospective cohort Cohort dates: 1986–2003 Age at enrolment: 55–69 Follow–up: 17.3 y	2,077 cases 1,379 ductal cases 378 lobular cases 815 ER+ cases Analyses performed for women with information on age at menopause only	exposure) Ever exposed Background Low High Cumulative exposure 1st tertile (>0–6.5 unit–y) 2nd tertile (>6.5–11 unit–y) 3rd tertile (>11–136 unit/y)	breast cancer	 HR=1 (referent) HR=1.07 (0.94–1.23) HR=1.24 (0.59–2.58) HR=1.28 (1.06–1.56) HR=0.92 (0.75–1.12) HR=1.03 (0.85–1.25); p–trend=0.88	Adjustments† Limitations: Only few women were employed in high–exposed jobs
Li et al., 2013[636] China	Nested case–cohort study Shanghai Textile Industry Bureau Retrospective study Recruitment dates: 1989–1991 Age at entry into follow–up: 30–66 y Follow–up: 5.2–10.9 y	267,400 workers 1,687 incident cases diagnosed 1989–2000 4,702 non–cases Active & retired female employees that are permanent residents of Shanghai	Cumulative magnetic field exposure (μT–years) Entire employment period >0–2.70 μT–years >2.70–4.13 μT–years >4.13–6.24 μT–years >6.24 μT–years	Breast cancer	 HR=1.00 (referent) HR=1.13 (0.97–1.33) HR=1.01 (0.86–1.18) HR=1.03 (0.87–1.21); p–trend=0.858	Cox proportional hazards model Adjustments: Age at baseline, number of live births, age at first live birth, lifetime duration of breastfeeding & alcohol consumption Limitations: Exposure misclassification

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: EMF, electromagnetic field; ER, oestrogen receptor; HR, hazard ratio; Hz, hertz; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; USA, United States of America; μT, micro–Tesla; y, year/s.

†The following covariates were considered for all cancer outcomes: smoking (current vs former and ex–smokers, average number of cigarettes smoked daily, number of years smoking cigarettes), passive smoking by the partner (current, former, or non–smoker), level of education as an indicator of social economic status (primary, lower, secondary and medium, and higher vocational), body mass index (in kg/m^2), alcohol consumption (g/day), vegetable, legume, fruit, fish and seafood, and meat consumption (each in g/day), and total energy intake (kcal/day). Breast cancer HRs corrected for alcohol intake, body mass index, fruit intake, age at menarche, age at menopause, parity, age at first child, number of children, benign breast growth, and family history of breast cancer.

Table D.80 Electromagnetic field radiation—radiofrequency and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Hallberg, 2016[642] 23 European countries	Cohort dates: NR Prospective / retrospective study: NR Age at enrolment: NR Follow–up: NR	Number of participants: NR	Number of main frequency modulation FM transmitters (87.5–108 MHz) FM transmitter density Locally covering FM transmitters in Sweden	Breast cancer	R^2=0.21; p=0.03 R^2=0.64; p<0.001	Model: NR Adjustments: NR Limitations: NR
Case–control studies						
Davis et al., 2002[643] USA	Population–based Study duration: 1992–1995 Age at recruitment: 20–74 y	1,606 women 813 cases 793 controls	Night time bedroom broadband magnetic field (continuous)	Breast cancer Premenopausal breast cancer Postmenopausal breast cancer	OR=1.04 (0.97–1.12) OR=1.00 (0.90–1.10) OR=1.00 (0.90–1.10)	Multivariable adjusted model Adjustments† Limitations: Possible selection bias Possible exposure misclassification

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: FM, frequency modulation; MHz, megahertz; NR, not reported; OR, odds ratio; p, p–value; R^2, correlation coefficient; USA, United States of America; y, year/s.

†Odds ratios were adjusted for parity, age at first pregnancy, mother/sister breast cancer, early double oophorectomy, oral contraceptive use, ever upper gastrointestinal series, and ever smoker (all subjects); mother/sister breast cancer at younger than age 45 years and alcohol intake (if premenopausal); and hormone therapy (if postmenopausal).

Table D.81 Occupation as a flight attendant (cosmic radiation) and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Liu et al., 2016[646] Studies published to 2016 Denmark, Finland, Iceland, Norway, Sweden & USA	9 cohort studies 1 pooled analysis	31,697 participants 821 cases Follow–up: 511,926 person–y	Female flight attendant	Breast cancer	SIR=1.40 (1.30–1.50); I^2=0.0%, p(heter)=0.744	Model: NR Adjustments† No publication bias (p>0.05) Limitations: Confounding factors Underestimation of the risk of cancer Potential clinical heterogeneity Limited number of qualified studies
Tokumaru et al., 2006[647] Studies published 1966–2005 Finland, Iceland, Norway, Sweden & USA	5 cohort studies	8 studies in total: 15,433 women 148,658 person–y at risk	Female flight attendant	Breast cancer	RR=1.41 (1.22–1.62); p<0.0001	Fixed effects model No adjustments Publication bias: NR due to small number of studies included Limitations: Failure to identify all relevant studies Varied population among the studies Test for heterogeneity statistically negative, potential variability should be noted

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
						Possible publication bias
Buja et al., 2006[648] Studies published to 2004 Denmark, Finland, Iceland, Norway, Sweden & USA	7 cohort studies	16,635 female flight attendants Follow–up: average 19.3 years	Female flight attendant	Breast cancer	SIR=1.40 (1.19–1.65); τ=0.07‡	Bayesian hierarchical model No adjustments No publication bias (p>0.05) Limitations: The 'healthy worker effect', missing data & reproductive history were potential sources of bias
Cohort studies						
Pinkerton et al., 2016[650] USA	Mortality cohort of former flight attendants employed by Pan American World Airways Employment from 1 Jan 1953 Retrospective study Follow–up: NR	6,093 participants 344 cancer cases 5,749 controls	Cumulative cosmic radiation Per 10mGy	Breast cancer	ERR=−0.021 (−0.14–0.17)¶ ERR=1.6 (0.14−6.6)††; p=0.02‡‡	Cox regression model Adjustments§ Limitations: Low cumulative exposure, potential exposure misclassification Potential recall bias Relatively low participation
Schubauer–Berigan et al., 2015[651] USA	Mortality cohort of former flight attendants employed by Pan American World Airways Employment from 1 January 1953	6,093 women enrolled 344 breast cancer cases Ethnicity: >90% white Median year of	Female flight attendant Cosmic radiation Overall cohort 10 y lagged results (absorbed dose) 0 to <1.55mGy 1.55 to <3.57mGy 3.57 to <6.61mGy 6.61 to <13.9mGy	Breast cancer	SIR=1.37 (1.23–1.52) SIR=1.35 (1.05, 1.71) SIR=1.32 (1.03, 1.67) SIR=1.54 (1.20, 1.96) SIR=1.21 (0.94, 1.54)	Model: NR Adjustments: Age, race and calendar year Limitations: Results observed might not be representative of current levels of breast cancer risk in this cohort

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Retrospective study	birth: 1947	13.9+ mGy		SIR=1.48 (1.15, 1.87); p(trend)=0.13	Correlation exposure metrics make interpretation of positive findings difficult Misclassification in exposure estimates Possible underestimation of SIRs for breast cancer
	Follow–up: NR		Effect modification of trend slope for 10–year lagged exposure variable parity: Absorbed dose (mGy)††			
			Effect modification of trend slope for 10–year lagged exposure variable : Absorbed dose (mGy)			
			0 births		Slope (SE)=−2.95E−05 (1.75E−05)	
			1 birth		Slope (SE)=−3.90E−05 (1.37E−05); p<0.01	
			2 births		Slope (SE)=2.17E−05 (6.39E−05)	
			3 births		Slope (SE)=2.62E−04 (1.23E−04); p<0.05	
			Effect modification of trend slope for 10–year lagged exposure variable by age at first birth: Absorbed dose (mGy)			
			14–<15 y		Slope (SE)=1.02E−05 (8.00E−05)	
			25–<30 y		Slope (SE)=4.42E−05 (1.00E−04)	
			30–<35 y		Slope (SE)=−7.83E−05**	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			35+ y		(3.41E–05); p<0.05 Slope (SE)=−2.39E–05 (5.06E–05)	
Pukkala et al., 2012[652] Finland, Iceland, Norway & Sweden	Retrospective study Mean follow–up: 23.6 y	8,507 women 263 cases Finnish crew working 1947–1993 Icelandic crew working 1947–1997 Norwegian crew working 1950–1994 Swedish crew working 1957–1994	Female airline crew member	Breast cancer	SIR=1.50 (1.32−1.69)	Conditional logistic regression model Adjustments: Age at first birth, parity & number of children Limitations: Lack of data on work at night

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: ERR, excess relative risk; FFA, female flight attendant; NR, not reported; NS, not significant; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; SIR, standard incidence ratio; USA, United States of America; y, year/s.

†Age, sex, calendar year. A number of studies also adjusted for age at first birth, parity, number of children, length of employment, flight assignment, years of service and/or age at entry.

‡Posterior mean of heterogeneity.

§Results are adjusted for age (since risk sets were created based on attained age), age at menarche, height, alcohol status, age at first birth, menopausal status, use of hormone therapy and family history of breast cancer.

¶Parity (0, 1, 2).

††Parity (≥3).

‡‡P–value for model with two way interaction for exposure and parity compared to model without an interaction term.

Table D.82 Sun exposure and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Estébanez et al., 2018[662] Studies published 1998–2018 Australia, Brazil, Canada, China, Denmark, Europe, France, Germany, India, Iran, Italy, Japan, Korea, Mexico, Norway, Saudi Arabia, Sweden, Switzerland, Taiwan, UK, USA	68 studies overall 17 cohort studies 21 NCC studies 30 case–control studies	NCC studies: 32,181 women Case–control studies: 35,167 women	25(OH)D (highest vs lowest category)	Breast cancer		Fixed and random effects models Individual studies adjusted for a range of factors Publication bias or heterogeneity observed Limitations: Different cut off points to serum levels used by studies Variability within the literature Case–control studies prone to methodological issues Vitamin D might affect only certain subtypes of breast cancer
	4 studies	Cohort studies: 24,606 women, 3,502 cases	Cohort studies		RR=0.85 (0.74–0.98); I^2=3.56%,	
	29 studies		Case–control studies		OR=0.65 (0.56–0.76); I^2=40.87%,	
	14 studies		NCC studies		OR=0.92 (0.83–1.01); I^2=15.87%,	
	9 studies		Case–control studies	Premenopausal breast cancer	OR=0.63 (0.49–0.80)	
	4 studies		NCC studies		OR=0.67 (0.49–0.92)	
	19 studies		Case–control studies	Postmenopausal breast cancer	OR=0.74 (0.59–0.93)	
	12 studies		NCC studies		OR=0.97 (0.82–1.14)	
Gandini et al., 2011[663] Studies published to 2009 Denmark,	10 studies 1 cohort study 4 NCC studies 5 case–control	6,175 cases 23,595 controls	Serum 25–hydroxyvitamin D (per 10 ng/ml) All studies	Breast cancer	Summary RR=0.89 (0.81−0.98); I^2=88%, p(heter)<0.001	Mixed effects model Adjustments: BMI and physical exercise No publication bias (p>0.05)
		3,030 cases	Case–control studies		Summary RR=0.83 (0.79−0.87); I^2=NR	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Germany, UK & USA	studies	3,145 cases	NCC & cohort studies		Summary RR=0.97 (0.92−1.03); I^2=54%, p(heter)=0.07	Limitations: Case–control studies had major limitations, with the potential for reverse causation
Cohort studies						
Zamoiski et al., 2016[659] USA	USRT study cohort Cohort dates: 2003–05 to 2012–13 Prospective study Mean age at enrolment: 55.8 y (no breast cancer) & 57.5 y (breast cancer cases) Follow–up: from baseline 2003–05 until primary cancer diagnosis or 2012–13	36,725 female radiologic technologists 716 cases	UVR exposure Time outdoors (hour/day) <1 1–1.9 2–2.9 3–3.9 ≥4 Ambient UVR 0–97.0 97.0–104.8 104.8–117.9 117.9–140.4 >140.4 Combined UVR 0–149.6 149.6–213.9 213.9–280.1 280.1–369.1 >369.1	Breast cancer	 HR=1 (referent) HR=0.88 (0.70–1.10) HR=0.96 (0.76–1.20) HR=0.95 (0.76–1.20) HR=0.87 (0.68–1.10); p–trend=0.46 HR=1 (referent) HR=1.41 (1.11–1.79) HR=1.21 (0.94–1.54) HR=1.26 (0.99–1.61) HR=1.22 (0.95–1.56); p–trend=0.36 HR=1 (referent) HR=0.96 (0.77–1.21) HR=0.92 (0.73–1.16) HR=1.06 (0.85–1.33) HR=0.85 (0.67–1.08); p–trend=0.49	Cox proportional hazard model† Limitations: NR
Lin et al., 2012[660] USA	NIH–AARP cohort Cohort dates: 1995−1996 to 2006 Prospective study	178,138 women 8,681 cases Ethnicity: non–Hispanic Caucasian	Ambient UVR exposure July erythemal exposure (J/m^2) ≤186.3	Breast cancer	 HR=1 (referent)	Multivariate Cox regression model‡ Limitations: No information on sun–related behaviours

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
		women	>186.3–236.8		HR=0.99 (0.93–1.05)	Residential UVR exposure based on TOMS dataset, which does not account for aerosols
	Mean age at enrolment: 62.07 y		>236.8–253.7		HR=1.05 (0.99–1.12)	
			>253.7		HR=1.03 (0.97–1.09); p–trend=0.198	Residence at baseline does not account for mobility
	Mean follow–up: 9.07 y					Results may not be generalisable to younger age groups
Yang et al., 2011[661]	SWLH cohort	49,261 women	UVR exposure	Breast cancer		Cox proportional hazard model§
			Annual number of sunburns			
Sweden	Cohort dates: 1991–1992 to 2006	1,053 cases	≤1			Limitations:
			10–19,20–29 & 30–39 y		HR=1 (referent)	Non–differential misclassification of UVR exposure and dietary vitamin D intake may have biased the results toward zero
	Prospective study	Mean age at breast cancer diagnosis: 51.6 y	≥2			
	Age at enrolment: 30–49 y		10–19 y		HR=0.90 (0.70–1.16)	
			10–19 & 20–29 y		HR=1.11 (0.89–1.38)	Limited information on seasonal variations, variations in stratospheric ozone, atmospheric aerosols and pollution, cloud cover and surface reflection
	Mean follow–up: 14.9 y		10–19, 20–29 & 30–39 y		HR=1.02 (0.81–1.27)	
			20–29 &/or 30–39 y		HR=0.91 (0.71–1.16); p–trend=NS	
			Annual number of weeks on sunbathing vacations			
			Never			
			10–19, 20–29 & 30–39 y		HR=1 (referent)	
			≥1			
			10–19 y		HR=0.81 (0.49–1.33)	
			10–19 & 20–29 y		HR=0.56 (0.36–0.89)	

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			10–19, 20–29 & 30–39 y		HR=0.65 (0.46–0.93)	
			20–29 &/or 30–39 y		HR=0.87 (0.70–1.07); p–trend=NS	

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: 25(OH)D, 25–hydihydroxyvitamin D; BMI, body mass index; HR, hazard ratio; J/m^2, joule per square metre; NCC, nested case–control studies; ng/ml, nanograms per millilitre; NIH–AARP, National Institutes of Health–American Association of Retired Persons [Diet and Health Study]; NR, not reported; NS, not significant; OR, odds ratio; p, p–value; p, p–value; p(heter), p–value for the measure of heterogeneity; p–trend, p–value for trend; RR, relative risk or risk estimate; SWLH, Swedish Women's Lifestyle & Health; TOMS, Total Ozone Mapping Spectrometer; USRT, United States Radiologic Technologists; UVR, ultraviolet radiation; UK, United Kingdom; USA, United States of America; y, year/s.

†Adjusted for birth cohort (before 1930, 1930–1939–1940–1944–1945–1949–1950–1954–1955–1961), ethnicity (white, black, Asian or Pacific Islander, American Indian or Alaska native, other), BMI (<18.5, 18.5–25, 25–30, >30 kg/m2), ever given birth (yes/no), age at first birth (<20,20–24, 25–29, 30–34, ≥35), age at menarche (under 11, 11–12, 13–14, 15 and older), ever taken hormone therapy (yes/no) family history of breast cancer (yes/no), exercise (0, 1–3, 4–7, 7–14, 15 and higher hours/week), menopausal status (pre– or post–menopausal), number of births (0, 1–2, 3–4, 5 and higher), use of oral contraceptives (ever/never), alcohol consumption (0, 1–2, 3–10, 11 and higher drinks/week), and ionizing radiation exposure to the breast (continuous). Trend tests were conducted by modelling categorical values as ordinal.

‡Adjusted for age at baseline, sex, BMI, caloric intake, intake of fruit, vegetables, and red and white meat, alcohol consumption, tobacco smoking, education, physical activity, median household income.

§Adjusted for education, smoking, alcohol drinking, body mass index, physical activity, parity, age at first birth, age at menarche, oral contraceptive use, breast feeding, and family history of breast cancer. Attained age was used as the time scale in the models.

Table D.83 Diagnostic ionising radiation and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Cohort studies						
Matthews et al., 2013[673] Australia	Cohort dates: 1985– 2007 Retrospective study Age at enrolment: 0–19 y Mean follow-up: 9.5 y (exposed) & 17.3 y (unexposed)	10,939,680 participants 680,211 exposed to CT scan 60,674 cases of cancer 145 breast cancer cases	CT scan exposure Exposed vs. unexposed	Breast cancer	IRR=0.99 (0.83–1.17) EIR per 100,000 person-y= –0.03 (–0.39–0.34)	Poisson regression model Adjustments: values stratified by age, sex and year of birth. Limitations: Misclassification of some participants in unexposed group; Unable to estimate individual doses; Records of repeat scans were not available.
Ronckers et al. 2008[665] USA	Cohort dates: 1992–1993 Retrospective study Age at enrolment: NR Median follow-up: 35.5 y	3,010 female scoliosis patients 78 cases Median age at end of follow-up: 47.6 y Scoliosis diagnosis: 1912–1965	Diagnostic radiograph exposure Linear dose response (ERR per unit dose) Overall Any family history of breast cancer No Yes	Breast cancer	 ERR per GY=2.86 (-0.07–8.62); p=0.058 ERR per Gy= −0.16 (<0−4.41) ERR per Gy=8.37 (1.50−28.16); p=0.03	Linear radiation dose-response model† Limitations: NR

Note. Risk estimates are presented with 95% confidence intervals.

*Abbreviations: EIR, excess incidence rate; ERR, excessive relative risk; IRR, incident rate ratio; p, p-value; USA, United States of America; y, year/s.

†Stratified by attained age (<35, 35-39, 40-44, 45-49, 50-54, 55-59, 60-69, and 70+ years) and calendar year (1925-1929, 1930-1934, …, 1990-1995) and adjusted for total number of X-rays (minimally exposed, <10, 10-19, 20-39, 40-59, and ≥60), where appropriate. Also adjusted for age at first birth, menopausal status at questionnaire completion, household income, and family history of breast cancer.

Table D.84 Therapeutic exposure to ionising radiation and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Doi et al., 2014[683] Studies published 1950–2009 Canada, France, Netherlands, Sweden, UK & USA	4 cohort & case–control studies	22,276 patients Age at primary cancer diagnosis: 0–20 y	RT for childhood cancer including HL (radiation dose range 0.1–<20)	Breast cancer	ERR per Gy=0.31 (0.16–0.59); Q=351.48, p(heter)<0.001	Random effects model Adjustments: NR Publication bias (p<0.001) Limitations: Follow–up duration not reported
Ibrahim et al., 2012[491] Studies published 1985–2011 Canada, France, Italy, Netherlands, Norway, Sweden, UK & USA	34 cohort studies	25,305 women 957 cases Median age at primary cancer diagnosis: 23.7 y Median age at breast cancer diagnosis: 35 y	RT for HL RT vs no RT RT≤ 30 years of age	Breast cancer	RR=4.70 (3.28–6.75); I^2=74%, p(heter)<0.00001 RR=14.08 (9.93–19.98)	Random effects model Adjustments: NR No publication bias (p>0.05) Limitations: Lifestyle and family history not adjusted for HL may increase risk of secondary malignancies independent of RT
Cohort studies						
Teepen et al., 2017[692] Netherlands	Cohort dates: 1963–2001 End of study: Jan 2013	6,165 women Mean age at diagnosis of primary cancer: ≤17 y	RT for childhood cancers	Breast cancer		Multivariable Cox proportional hazards model Adjustments: Ifosfamide and doxorubicin dose
	Retrospective study	183 women 13 cases	Chest RT vs no RT		HR=2.5 (1.3–4.9)	Limitations:

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
	Median follow–up: 20.7 y	77 women 5 cases	TBI vs no RT		HR=10.6 (3.7–30.2)	Number of breast cancer events Confounding factors
Sud et al., 2017[690] Sweden	Cohort dates: 1965–2012 Retrospective study Median follow–up: 12.6 y	9,522 participants Mean age at diagnosis of HL: 49 y	RT for HL Age at diagnosis <35 y >35 y	Breast cancer	 SIR=6.00 (4.91–7.33), p<0.001 SIR=1.14 (0.85–1.51)	Poisson regression model Adjustments: NR Limitations: Reliance on year of treatment as surrogate for type of treatment Smoking not included in the analysis
Moskowitz et al., 2017[694] USA	Child Cancer Survivor Study Cohort dates: 1994–2012 Primary cancer diagnosis: 1970–1986 Retrospective study Median follow–up: 26 y	1,108 women 195 cases Age at primary cancer diagnosis: ≤20 y Age at breast cancer diagnosis: 23–58 y	RT for childhood cancers RT within 1 year of menarche vs >1 year from menarche vs no RT	Breast cancer	HR=1.80 (1.19–2.72)	Cox proportional hazard regression model Adjustments: Chest radiation field, delivered dose, anthracycline exposure and age at childhood cancer estimated risk Limitations: Self–reported data on hormonal factors and medication use Differences by age at breast cancer diagnosis not tested
Moskowitz et al., 2015[695]	Child Cancer Survivor Study	363 patients	Spinal RT for leukaemia & CNS tumours	Breast cancer		Model: NR

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
USA	Cohort dates: 1970–1986 Retrospective study Age at enrolment: ≥20 y Median follow–up: 27 y	3 cases Median age at primary cancer diagnosis: 5 y	Overall Leukaemia only		SIR=2.4 (0.8–7.5) SIR=3.8 (1.2–11.7)	Adjustments: NR Limitations: Small sample size and young age of the cohort
Moskowitz et al., 2014[687] USA	Child Cancer Survivor Study Cohort dates: 1970–1986 Retrospective study Median follow–up: 25.9 y	1,230 women 203 cases Median age at last follow–up: 37.3 y Median age at primary cancer diagnosis: 13 y	RT for childhood cancers Primary field of chest radiation Mantle (5−54 Gy) Mediastinal (3−54 Gy) Whole lung (2−20 Gy) Total body (4−16 Gy) Abdominal (4−40 Gy) Posterior chest (6−54 Gy) Other one–sided anterior (10−61 Gy) Dose of radiation to chest 10−19 Gy ≥20 Gy	Breast cancer	 SIR=24.2 (20.7−28.3) SIR=13.0 (8.4−20.2) SIR=43.6 (27.1−70.1) SIR=19.3 (7.3−51.5) SIR=10.8 (2.7−43.2) SIR=0.0 SIR=9.9 (3.2−30.6) SIR=30.6 (18.4−50.7) SIR=21.2 (18.3−24.5)	Poisson regression model Adjustments: Delivered radiation dose Limitations: Young cohort may under estimate breast cancer incidence Small incidence of women treated with TBI and women treated with WLI after 45 y of age

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Elkin et al., 2011[686] USA	Hospital–based cohort, from 8 hospitals Breast cancer diagnosis: 1980–2006 Retrospective study Follow–up: 42 y	253 cases with history of HL 741 controls with no history of HL Age at HL diagnosis: 11–67 y Age at breast cancer diagnosis: 24–84 y	RT HL survivor vs patient with sporadic breast cancer	Metachronous CBC	HR=4.3 (1.7–11.0); p<0.01	Cox proportional hazards regression model Adjustments† Limitations: Cohorts were selected from tertiary academic medical centres rather than community–based settings.
Adams et al., 2010[693] USA	Cohort dates: 1985–1987 & 2003–2008 Retrospective study Mean age at enrolment: 37 y Median follow–up: 56.8 y	1,120 treated females 96 treated cases 2,382 untreated female siblings 57 untreated cases	RT for enlarged thymus	Breast cancer	RR=3.05 (2.15–4.36), p<0.001 ERR per Gy=1.10 (0.61–1.86)	Multivariate Poisson regression model Adjustments: Treatment, birth cohort and attained age Limitations: Lower–than–desired response rate and non–response bias
De Bruin et al., 2009[709] Netherlands	HL treatment: 1965–1995 Prospective study Median follow–up: 17.8 y	1,122 women 120 cases Age at HL treatment: <51 y	sRT for HL vs general population Overall sRT Mediastinal RT	Breast cancer (invasive + DCIS)	SIR=5.6 (4.6–6.8) AER=57 (45–72) cases per 10,000 persons/y HR=1 (referent)	Multivariate Cox regression model Adjustments‡ Limitations: Inability to assess radiation dose effects

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
			Mantle field		HR=3.0 (1.2–7.6)	Missing data regarding age at menopause
Case–control studies						
Cooke et al., 2013[691] UK	Nested case–control Source of population: NR Study duration: 2003−2010 Primary treatment: 1956–2003 Age at recruitment: ≥53 y	5,002 women 260 cases Age at breast cancer diagnosis: <30–69 y	sRT for HL Duration between sRT & menarche ≤5 y before 2–5 y before 0.5–2 y before Within 0.5 y 0.5–2 y after 2–5 y after 5–10 y after	Breast cancer	OR=0.94 (0.10–8.46) OR=4.08 (1.27–13.14) OR=4.90 (1.60–14.98) OR=5.52 (1.97–15.46) OR=3.47 (1.40–8.58) OR=2.38 (1.43–3.97); p–trend<0.001 OR=1.33 (0.89–1.98)	Unconditional logistic regression Adjustments§ Limitations: HL treatment, family history of breast cancer, reproductive history and use of HT

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: AER, absolute excess risk; CBC, contralateral breast cancer; CNS, central nervous system; DCIS, ductal carcinoma in situ; ERR, excess relative risk (per Gy); HL, Hodgkin lymphoma; HR, hazard ratio; HT, hormone therapy; Gy, Gray; IRR, incident rate ratio; NR, not reported; OR, odds ratio; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; RT, radiation therapy; SIR, standardised incidence ratio; sRT, supradiaphragmatic radiation therapy; TBI, total body irradiation; UK, United Kingdom; USA, United States of America; WLI, whole lung irradiation; y, year/s.

†Breast cancer stage at diagnosis, axillary lymph node involvement, laterality at diagnosis, type of surgery, surgical margin status, menopausal status, family history of breast cancer in a first–degree relative, whether breast cancer was screen detected, receipt of radiation therapy for breast cancer, receipt of chemotherapy for breast cancer, and receipt of hormonal therapy for breast cancer

‡HRs adjusted for other types of sRT, age at first RT to the breast, and time since first RT to the breast; calendar time was used as the time scale. Time at risk for RT started five years after first treatment with RT. Analysis was restricted to patients from Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Erasmus MC/Daniel den Hoed Kliniek, Leiden University Medical Center, Emma Children's Hospital/Academic Medical Center (n=715).

§Year of treatment, duration between treatment and questionnaire completion, date of birth, sRT field, ovarian–toxic treatment; age at menarche and treatment.

Table D.85 Radioactive treatment for thyroid cancer and risk of breast cancer

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Meta–analyses						
Zhang et al., 2016[699] Studies published to 2014 America, East Asia & Europe	6 cohort studies	17,914 participants 96 cases in experimental group 144 cases in control group Age at diagnosis: 42–50 y Mean follow–up: 7.8–12 y	Radioactive iodine for treatment of thyroid cancer	Breast cancer	RR=0.61 (0.47–0.79); I^2= 46%, p(heter)=0.10 .	Fixed–effects model Adjustments: NR Publication bias: NR Limitations: Inaccessibility of detailed data on age in the six cohorts, an age–adjusted subgroup analysis was not carried out The follow–up times of the current studies were not long enough
Sawka et al., 2009[698] Studies published to 2008 Europe & North America	2 cohort studies	37,119 participants Number of cases: NR Median follow–up: 8.6 y & 13 y	Radioactive thyroid treatment of thyroid cancer	Breast cancer	RR=0.86 (0.64–1.16); p=0.324	Fixed–effects model Adjustments: NR Publication bias: NR Limitations: Limited follow–up period of primary studies & relatively large losses to follow–up in the European cohorts A formal meta–regression analysis of cumulative RAI dose activity & the risk of second primary malignancies could not be conducted
Cohort studies						

Authors	Study details	Study sample	Exposures	Outcomes	Risk estimates	Author comments
Lin et al., 2016[503] Taiwan	Taiwan National Health Insurance Database Cohort dates: 2000−2008 Retrospective study Age at enrolment: most patients ≤49 y Follow–up: 6.51 y	10,361 women with thyroid cancer 3,292 women with thyroid cancer without ^{131}I treatment 7,069 women with thyroid cancer with ^{131}I treatment 41,444 controls 479 cases of breast cancer	^{131}I Treatment for thyroid cancer vs no treatment Overall Cumulative ^{131}I dose Without treatment ≤4.44 (GBq) >4.44 (GBq)	Breast cancer	HR=1.34 (1.06–1.69) HR=1.00 (referent) HR=1.18 (0.79–1.77) HR=0.90 (0.56–1.46)	Cox proportional hazard model Adjustments: Age, all comorbidities, hormone therapy, mammography & ultrasonography Limitations: Database provides no detailed information on patients Evidence from retrospective cohort study is lower in statistical quality Registries in the National Health Insurance not verified for scientific purposes No individual patient's medical chart & data could be directly checked

Note: Risk estimates are presented with 95% confidence intervals.

Abbreviations: GBq, gigabecquerel; HR, hazard ratio; NR, not reported; p, p–value; p(heter), p–value for the measure of heterogeneity; RR, relative risk or risk estimate; y, year/s.

Glossaries

Glossary 1—General and epidemiological terms

Absolute risk	Is a measure of the risk of a certain event happening, or a person's chance of developing a specific disease over a specified time period. In cancer research, it is the likelihood that a person who is free of a specific type of cancer at a given age will develop that cancer over a certain period of time
Attributable risk	Also known as absolute risk difference. This absolute measure of effect represents the difference between the absolute risks in two groups, usually between an exposed and unexposed group. The excess number of cases that could be explained by or could be attributed to that factor increases with the proportion of the population exposed to the factor and with the incidence rate of the disease in the population (i.e. absolute risk).
Ashkenazi	Ashkenazi is the term used to refer to Jews who have ancestors from Eastern or Central Europe, such as Germany, Poland, Hungary, Lithuania, Ukraine or Russia. As Ashkenazi Jews descend from a small population group, they have more genes in common than the general population. In Australia, most Jewish families are of Ashkenazi ancestry.
Confidence intervals	A range of values that has a specified probability of containing the true point estimate of effect. The most common specified probability is 95%, akin to p=0.05. The narrower the interval the more precise the estimate of the risk and the less likely that the risk would be subject to chance variation. A relative risk is generally considered statistically significant when the value of 1.0 is not in the 95% confidence interval.
Confounding	Confounding occurs when an exposure and an outcome are associated with each other simply because both are acted on by a third variable (confounder), not because the exposure has a causal effect on the outcome.
Heterogeneity	Differences between studies that impact on the interpretation of the results and the ability to draw any legitimate or meaningful conclusions. Heterogeneity can be quantified using the I^2 statistic, which describes the percentage of total variation across studies in a meta–analysis that is due to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% can be considered as low, moderate,

	and high. Other measures of heterogeneity include Tau which is a measure of the dispersion of true effect sizes between studies when fitting a random–effects model in terms of the scale of the effect size, i.e. it is in the same 'units' as the results measure.
Odds ratio (OR)	Uses the odds of developing a disease in both groups to calculate a relative measure between two groups rather than the risk. As a rule, retrospective study designs will only report odds ratios (ORs), whereas prospective study designs, like the cohort study, will generally report a relative risk (RR) estimate.
Point estimation (size of effect)	Refers to the measure of effect or point estimate provided in the results of each study (e.g. mean difference, relative risk, odds ratio, hazard ratio, sensitivity, specificity). In the case of a meta–analysis it is the summary or pooled measure of effect from the studies included in the systematic review (e.g. weighted mean difference, summary or pooled relative risk). These point estimates are calculated in comparison to either doing nothing or versus an active control.
Progesterone	Naturally-occurring progestogen; predominantly produced by the ovaries in cycling premenopausal women and in low doses by the adrenal glands in women of all ages.
Progestins	Synthetic progestogens including compounds such as medtrocyprogesterone acetate (MPA), levonorgestrel, and norethindrone acetate (NETA).
Progestogen	Any substance, natural or artificial (that is, synthetic), that exerts progesterone-like activity via the activation of progesterone receptors.
Relative risk (RR)	Relative risk (RR) is the most common metric of comparative risk reported throughout this report, and it compares the absolute risk of a group of people who are exposed to a risk factor with the absolute risk of a group of people who are not exposed to the risk factor. It is sometimes referred to as the 'risk ratio'. Depending on the study design and statistical method used, the relative risk can be presented using different measures of effect, such as the incidence rate ratio (also called the standardised incidence ratio) and hazard ratio.

Standardised incidence ratio	Standardised incidence ratio is the disease incidence in a cohort compared to in the general population, i.e. the ratio of the observed number of cases compared to the expected number of cases. The expected number of cases is computed using age–specific rates from a reference population, weighted according to the age structure of the study population.

Glossary 2—Study types

Case–control studies	Case–control studies are one of the most basic study designs for epidemiological research. In case–control studies, people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and the information obtained about their previous exposure/non–exposure to the factor under study, such as reproductive history or diet. It is a retrospective design.
Cohort studies	Cohort designs are widely used in epidemiological research. Participants do not have the disease of interest, such as breast cancer, at the start of the study, but are followed prospectively through time. The occurrence or incidence of the disease is compared between groups of people exposed to the factor under study and groups of people not exposed.
Meta–analysis (following systematic review)	In a meta–analysis similar studies that address the same research question are identified through systematic review and the results are statistically combined and analysed, and the overall result interpreted as if derived from one large study. This method gives greater statistical power to detect important associations. It allows the detection of less obvious associations as well as the examination of dose–response relationships often not possible in individual studies.
Nested case–control studies	Nested case–control studies are carried out within an existing cohort study. All the cases in the cohort are compared with a matched sample of the participants who have not developed cancer by the time of disease occurrence in the cases (controls). It has many of the strengths of the cohort study including minimising selection bias compared with a case–control study and having exposure information collected at inception and/or during the course of follow–up.
Pooled analysis	Pooled analyses are a type of meta–analysis but in pooled analyses individual–level data from various published or unpublished epidemiological studies of a similar type – usually prospective cohort studies – are combined and re–analysed as a 'single study'. This creates a larger data set and increased statistical power.
Prospective cohort studies	A type of cohort study that follows a group of similar people (a cohort) and studies them over time to determine how certain factors affect rates of a certain outcome. They are often referred to as the gold standard of observational epidemiological designs as they are less prone to bias, recall error and have higher validity than other observational study designs.

Randomised controlled trials	Randomised controlled trials (RCTs) are well–controlled, experimental studies in humans. In RCTs the unit of experimentation (e.g. people, or a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a random mechanism (such as a coin toss, random number table, computer–generated random numbers) and the outcomes from each group are compared. RCTs are considered the gold standard in clinical trials as they are the most rigorous and reliable.
Retrospective cohort studies	A type of cohort study whereby cohorts (groups of people exposed and no exposed) are defined at a point of time in the past and information collected on subsequent outcomes. All of the events – exposure to the risk factor, latent period, and subsequent development of the disease – have already occurred in the past. Data are simply collected in the present.

Glossary 3—Breast cancer terms

Basal–like or triple negative breast cancer	A subtype of breast cancer. Prevalence approximately 10–20% Aggressive, fast growing, more common in younger women, high recurrence rates ER–/PR–/HER2–, often has higher grade and tends to metastasise. Increased incidence in patients with a germline *BRCA1* mutation.
Ductal carcinoma in situ (DCIS)	Non–invasive breast cancer where abnormal cells are in the ducts, but have not spread to surrounding tissues.
Epigenetic changes	Epigenetic changes involve changes in gene expression (what genes, and by how much genes are turned on in a cell to make RNA and proteins) that are due to mechanisms other than changes in the underlying DNA sequence. Epigenetic changes can be transmitted across cell generations or inherited.
Genomic changes	There are different genetic changes, or 'drivers' of cancer, for example changes in oncogenes (cancer–causing genes), tumour suppressor genes (genes that usually protect cells from abnormal proliferation) or DNA repair genes. These changes can be inherited, or can arise during a person's lifetime due to errors as cells divide, or due to damage to DNA caused by certain environmental exposures.
HER2–overexpressing breast cancer	A subtype of breast cancer. Prevalence approximately10–20% More aggressive, poor short–term prognosis, more common in younger women, high recurrence rates ER–/PR–/HER2+ Sensitive to anti–HER2 treatments.
In situ breast cancer	Also called non–invasive breast cancer that has not spread from the tissue in the breast where the cancer started.
Inflammatory breast cancer	A rare form of invasive breast cancer that affects the lymph vessels in the skin of the breast, causing the breast to be red and swollen.
Invasive breast cancer	Invasive cancers are cancers that have spread from the tissue where the cancer started, to surrounding tissue.
Invasive ductal carcinoma	Also known as infiltrating ductal carcinoma, is cancer that has spread from the duct to surrounding tissues.
Lobular carcinoma in situ (LCIS)	A non–invasive breast cancer where abnormal cells are in the lobules, but have not spread to surrounding tissues.
Lumina B breast cancer	A subtype of breast cancer. Prevalence approximately10–20%

	More aggressive, poor–prognosis, high recurrence rates ER+ and/or PR+/HER2+, or ER+ and/or PR+/HER2–/high grade, high proliferation (high Ki–67) Less oestrogen sensitive than luminal A.
Luminal A breast cancer	A subtype of breast cancer. Prevalence approximately 50–60% Less aggressive, more slowly growing, low recurrence rates ER+ and/or PR+, HER2–, low grade, low proliferation (low Ki–67) Endocrine treatment sensitive.
Paget's disease of the nipple	A rare form of breast cancer affecting the nipple and the areola around the nipple. It is commonly associated with invasive cancer elsewhere in the breast.

Abbreviations

Abbreviations

ACR	average cumulative risks
ADA	absolute dense area
ADH	atypical ductal hyperplasia
AER	absolute excess risk
AH	atypical hyperplasia
AhR	aryl hydrocarbon receptor
AICR	American Institute for Cancer Research
AIHW	Australian Institute of Health and Welfare
AJ	Ashkenazi Jew
ALCL	anaplastic large cell lymphoma
ALH	atypical lobular hyperplasia
aMED	alternate Mediterranean Diet score
APBIb	accelerated partial breast irradiation through brachytherapy
AR	absolute risk
ART	assisted reproductive technology
A–T	ataxia–telangiectasia
ATM	ataxia–telangiectasia mutated
BBD	benign breast disease
BC	breast cancer
BCAC	Breast Cancer Association Consortium
BCFR	Breast Cancer Family Registry
BCIS	breast cancer in situ
BCRAT	Breast Cancer Risk Assessment Tool
BCS	breast conserving surgery
BGS	Breakthrough Generations Study

BIA–ALCL	breast implant–associated anaplastic large cell lymphoma
BI–RADs	Breast Imaging Reporting and Data System
BMI	body mass index
BOADICEA	Breast and Ovarian Cancer Disease Incidence and Carrier Estimation Algorithm
BPA	bisphenol A
BPA–G	BPA–glucuronid
BRCA1/2	BReast CAncer 1/2 gene mutation
BRCA1+	BRAC1 gene mutation carrier
BRCAPRO	BRCA probability
BSSA	South Australian breast cancer screening programme
CARE	Contraceptive and Reproductive Experiences
CBC	contralateral breast cancer
CCSS	Childhood Cancer Survivor Study
CDH1	Cadherin 1
CEE	conjugated equine oestrogens
CHANCES	Consortium on Health and Ageing; network of Cohorts in Europe and the United States
CHK2	checkpoint kinase 2
CI	confidence interval
CIMBA	Consortium of Investigators of Modifiers of BRCA1/2
CSI	carcinoma in situ
CIR	cumulative incidence rate
cm	centimetre
COGS	Collaborative Oncology Gene–environment Study
combined MHT	combined oestrogen–progestogen menopausal hormone therapy
COX	cyclooxygenase
CPSII	Cancer Prevention Study II
CR	cumulative risk

CT	chemotherapy
CUP Breast SLR	Continuous Update Project Systematic Literature Review
DA	dense area
DCIS	ductal carcinoma in situ
DEHP	bis(2–ethylhexyl) phthalate
DEP	diethyl phthalate
DES	diethylstilboestrol
DET	dichloro–diphenyl–trichloroethane
DESAD	Diethylstilbestrol and Adenosis
DHEAS	dehydroepiandrosterone sulphate
DNA	deoxyribonucleic acid
DOB	date of birth
DRMR	dose–response meta–regression
E3N	Étude épidémiologique auprés des femmes de la mutuelle générale de l'éducation nationale
E3N–EPIC	Etude Epidémiologique auprès des femmes de la mutuelle générale de l'éducation nationale – European Prospective Investigation into Cancer and Nutrition
E–cadherin	epithelial cadherin
ECR	estimated cumulative risk
EHBCCG	Endogenous Hormones and Breast Cancer Collaborative Group
ELF–EMF	extremely low frequency electromagnetic field
EMBRACE	Epidemiological Study of BRCA1 and BRCA2 mutation carriers
EORTC	European Organisation for Research and Treatment Centre
EPA–DHA	eicosapentaenoic acid–docosahexaenoic acid
EPIC	European Prospective Investigation into Cancer and Nutrition
EPIC–Italy	European Prospective Investigation into Cancer and Nutrition (cohort in Italy: Florence, Milan, Ragusa province, Turin and Naples)
ER	oestrogen receptor
ER–	oestrogen receptor negative

ERR	excess relative risk
ES	Effect size
EtO	ethylene oxide
ETS	environmental tobacco smoke
EVOO	extra virgin olive oil
FDA	Food and Drug Administration
FM	frequency modulation
FFTP	first full term pregnancy
FFQ	food frequency questionnaire
FVG	Friuli Venezia Giulia
GBq	gigabecuerel
g/d	grams per day
GHz	gigaHertz
GI	glycaemic index
GL	glycaemic load
GnRH	gonadotropin–releasing hormone
GP	general practitioner
GWAS	genome–wide association study
Gy	Gray
HAA	heterocyclic aromatic amine
HAP	hazardous air pollutant
HBOC	Hereditary Breast and Ovarian Cancer Syndrome
HCA	hetrocyclic amine
HDGC	hereditary diffuse gastric cancer
HER	human epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2
HER2–	human epidermal growth factor receptor 2 negative
HF	high frequency
HL	Hodgkin lymphoma

HPHC	Harvard Pilgrim Health Care
HPV	human papillomavirus
HR	hazard ratio (also used for hormone receptor in places)
HRR	hazard rate ratio
HR+	hormone receptor positive
HR–HPV	high risk human papillomavirus
HT	hormone therapy
Hz	Hertz
IARC	International Agency for Research on Cancer
IBC	ipsilateral breast cancer
IBCCS	International BRCA1/2 Carrier Cohort Study
IBIS	International Breast Intervention Study
IDC	invasive ductal carcinoma
IGCLC	International Gastric Cancer Linkage Consortium
IGF1	insulin–like growth factor 1
ILC	invasive lobular carcinoma
IQR	interquartile range
IRR	incident rate ratio
IVF	in vitro fertilisation
JACC	Japan Collaborative Cohort study
J/m^2	joules per square metre
JPHC	Japan Public Health Centre
kcal/day	kilocalories per day
kConFab	Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer
kg/m^2	kilograms per square metre
kHz	kiloHertz
km	kilometres
KPNC	Kaiser Permanente Northern California

KPSC	Kaiser Permanente Southern California
LAN	light at night
LCIS	lobular carcinoma in situ
LF	low frequency
LFS	Li–Fraumeni Syndrome
LIFE	Learning the Influence of Family and Environment
LOD	limit of detection
LRT	likelihood ratio test
m	metre
MDACC	MD Anderson Cancer Centre
MDCH	Michigan Department of Community Health
MEC	multiethnic cohort
MedD	Mediterranean Diet
MET	metabolic equivalent
MF	medium frequency
mg	milligrams
MGC	mammary gland carcinogen
MHT	menopausal hormone therapy
MHz	megaHertz
mMED	modified Mediterranean Diet score
MPA	medroxyprogesterone acetate
MSKCC	Memorial Sloan–Kettering Cancer Centre
mSv	millisieverts
µg/d	micrograms per day
µg/L	micrograms per litre
µmol/L	micromoles per litre
MW	microwave
n	number
N/A	not available

NAICS	North American Industry Classification System
NAT2	N–acetyltransferase 2
NBOCC	National Breast and Ovarian Cancer Centre
NCC	nested case–control studies
NCI	National Cancer Institute
NCI LSF	National Cancer Institute Li–Fraumeni Syndrome
NDA	non–dense area
ng/d	nanograms per day
ng/mg	nanograms per milligram
Ng/ml	nanograms per millilitre
NHL	non–Hodgkin lymphoma
NHMRC	National Health and Medical Research Council
NHS	Nurses' Health Study (Refers to first study not NHSII or Nurses' Health Studies (NHS and NHSII)
NHSII	Nurses' Health Study II
NIH–AARP	National Institutes of Health–American Association of Retired Persons (Diet and Health Study)
NIOSH	National Institute for Occupational Safety and Health
NLCS	Netherlands Cohort Study
nmol/L	nanomoles per litre
NO	nitrogen oxide
NO_2	nitrogen dioxide
NOC	National Occupational Classification
NOCCA	Nordic Occupation Cancer Project
NP	non–proliferative
NPCS	National Priority Contaminated Site
NR	not reported
NS	not significant
NSABP	National Surgical Adjuvant Breast Project

NSAID	non–steroidal anti–inflammatory drugs
NSW	New South Wales
OC	oral contraceptive
25(OH)D	25–hydihydroxyvitamin D
OR	odds ratio
ORDET	Hormones and Diet in the Aetiology of Breast Cancer Risk
PAH	polycyclic aromatic hydrocarbons
PALB2	partner and localier of BRAC2
PCB	polychlorinated biphenyl
PCOS	polycystic ovarian syndrome
PCR	polymerase chain reaction
PDA	percent dense area
PDWA	proliferative disease without atypia
pg/g	picograms per gram
pg/kg	picograms per kilogram
PHBA	p–hydroxybenzoic acid
PHTS	PTEN Hamartoma Tumour Syndrome
PJS	Peutz–Jeghers Syndrome
PM	phthalate metabolite
$PM_{2.5, 10}$	particulate matter 2.5, 10
PMH	postmenopausal hormone
pOR	pooled odds ratio
ppm–y	parts per million years
PPRC	Professional and Public Relations Committee
ppt	parts per trillion
PR	progesterone receptor
PREDIMED	Prevención con Dieta Mediterránea (Prevention with Mediterranean Diet)
PRS	polygenic risk score

PTEN	phosphatase and tensin homolog
Q	Q test to evaluate the heterogeneity among studies
RAI	radioactive iodine (also known as ^{131}I)
RCT	randomised controlled trial
RF–EMF	radiofrequency electromagnetic field
RNA	ribonucleic acid
RR	relative risk, or risk estimate
RT	radiation therapy
SD	standard deviation
SE	standard error
SEER	Surveillance, Epidemiology and End Results program
SENTIERI	Italian Epidemiological Study of Residents I National Contaminated Sites
SES	socioeconomic status
SHBG	sex hormone binding globulin
SIR	standardised incidence ratio
SLR	systematic literature review
SNP	single nucleotide polymorphism
SO_2	sulphur dioxide
SRR	summary relative risk
sRT	supradiaphragmatic radiation therapy
STK11	serine threonine kinase 11
SweDCIS	Swedish randomised DCIS trial
SWHS	Seveso Women's Health Study
SWLH	Swedish Women's Lifestyle and Health
TA–NPCS	Taranto province excluding NPCS municipalities
TBI	total body irradiation
TCDD	tetracholorodibenzo–p–dioxin
TCGA	The Cancer Genome Atlas

TEQ	total toxic equivalent
TNBC	triple negative breast cancer
TOMS	Total Ozone Mapping Spectrometer
TP53	tumour protein 53
TP53+	TP53 mutation carriers
TWAS	transcriptome–wide association studies
UHF	ultra high frequency
UK	United Kingdom
UKCCCR	United Kingdom Coordinating Committee on Cancer Research
UKCCCR/ANZ	United Kingdom Coordinating Committee on Cancer Research Ductal Carcinoma in situ Working Party
US	United States
USA	United States of America
USRT	United States Radiologic Technologists
UV	ultraviolet
UVR	ultraviolet radiation
UVRd	ultraviolet radiation doses
VBD	volumetric breast density
VEC	vaginal epithelial changes
WBI	whole body irradiation
WCRF	World Cancer Research Fund
WHI	Women's Health Initiative
WHICT	Women's Health Initiative Clinical Trial
WHO	World Health Organization
WHR	waist to hip ratio
WLI	whole lung irradiation
y	year/s
ZIP	zone improvement plan

References

1 Cancer Australia. Breast cancer statistics. https://breast-cancer.canceraustralia.gov.au/statistics. Accessed: June 2018

2 Australian Institute of Health and Welfare. Cancer in Australia 2017. Canberra, Australia, 2017

3 Tamimi RM. Epidemiology of breast cancer. Springer International Publishing, Switzerland, 2017

4 PDQ Screening and Prevention Editorial Board. Breast Cancer Prevention (PDQ®): Health Professional Version. https://www.cancer.gov/types/breast/hp/breast-prevention-pdq. Accessed: November 2017

5 Report of the Interagency Breast Cancer and Environmental Research Coordinating Committee. Breast Cancer and the Environment: Prioritizing Prevention. Bethesda, MD, 2013

6 World Health Organization. The world health report 2002: reducing risks, promoting healthy life. World Health Organization, Geneva, Switzerland, 2002

7 Gray JM, Rasanayagam S, Engel C, et al. State of the evidence 2017: an update on the connection between breast cancer and the environment. Environ Health. 2017;16 (1):94

8 Institute of Medicine. Breast cancer and the environment: a life course approach. The National Academies Press, Washington, DC, 2012

9 Fineout-Overholt E and Johnston L. Teaching EBP: asking searchable, answerable clinical questions. Worldviews Evid Based Nurs. 2005;2 (3):157-160

10 World Cancer Research Fund. Continuous Update Project Systematic Literature Review: The associations between food, nutrition and physical activity and the risk of breast cancer. London, UK, 2017

11 World Cancer Research Fund and American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and breast cancer. London, UK, 2018

12 National Breast and Ovarian Cancer Centre. Breast cancer risk factors: a review of the evidence. Surry Hills, NSW, 2009

13 World Cancer Research Fund and American Institute for Cancer Research. Judging the evidence. https://www.wcrf.org/sites/default/files/judging-the-evidence.pdf. Accessed: August 2018

14 Cancer Australia. What is cancer? https://canceraustralia.gov.au/affected-cancer/what-cancer. Accessed: November 2017

15 Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144 (5):646-674

16 Brisken C, Hess K and Jeitziner R. Progesterone and overlooked endocrine pathways in breast cancer pathogenesis. Endocrinology. 2015;156 (10):3442-3450

17 Obr AE and Edwards DP. The biology of progesterone receptor in the normal mammary gland and in breast cancer. Mol Cell Endocrinol. 2012;357 (1-2):4-17

18 Carroll JS, Hickey TE, Tarulli GA, et al. Deciphering the divergent roles of progestogens in breast cancer. Nat Rev Cancer. 2017;17 (1):54-64

19 Scalbert A and Romieu I. Metabolic change and metabolomics. International Agency for Research on Cancer, Lyon, France, 2014

20 Trinchieri G. Immunology and immunotherapy. International Agency for Research on Cancer, Lyon, France, 2014

21 Herceg Z and Varga HH. Stem cells and cancer stem cells. International Agency for Research on Cancer, Lyon, France, 2014

22 Howell A, Anderson AS, Clarke RB, et al. Risk determination and prevention of breast cancer. Breast Cancer Res. 2014;16 (5):446

23 Colditz GA, Bohlke K and Berkey CS. Breast cancer risk accumulation starts early: prevention must also. Breast Cancer Res Treat. 2014;145 (3):567-579

24 Dall GV and Britt KL. Estrogen effects on the mammary gland in early and late life and breast Cancer risk. Front Oncol. 2017;7 110
25 Shapira N. The potential contribution of dietary factors to breast cancer prevention. Eur J Cancer Prev. 2017;26 (5):385
26 Ries L, Eisner M, Kosary C, et al. SEER Cancer Statistics Review, 1973–1997. National Cancer Institute, Bethesda, MD., 2000
27 Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. https://www.aihw.gov.au/reports/cancer/acim-books/contents/acim-books. Accessed: June 2018
28 Singletary SE. Rating the risk factors for breast cancer. Ann Surg. 2003;237 (4):474-482
29 Cancer Australia. National Cancer Control Indicators: Cancer incidence. https://ncci.canceraustralia.gov.au/diagnosis/cancer-incidence/cancer-incidence. Accessed: August 2018
30 The Lancet. GLOBOCAN 2018: counting the toll of cancer. Lancet. 2018;392 (10152):985
31 Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand challenge in global health. Lancet. 2017;389 (10071):847-860
32 Feletto E and Sitas F. Quantifying disparities in cancer incidence and mortality of Australian residents of New South Wales (NSW) by place of birth: an ecological study. BMC Public Health. 2015;15 823
33 Moore SP, Antoni S, Colquhoun A, et al. Cancer incidence in indigenous people in Australia, New Zealand, Canada, and the USA: a comparative population-based study. Lancet Oncology. 2015;16 (15):1483-1492
34 Teng AM, Atkinson J, Disney G, et al. Ethnic inequalities in cancer incidence and mortality: census-linked cohort studies with 87 million years of person-time follow-up. BMC Cancer. 2016;16 (1):755
35 Akinyemiju T, Wiener H and Pisu M. Cancer-related risk factors and incidence of major cancers by race, gender and region; analysis of the NIH-AARP diet and health study. BMC Cancer. 2017;17 (1):597
36 Tapia KA, Garvey G, Mc Entee M, et al. Breast cancer in Australian Indigenous women: incidence, mortality, and risk factors. Asian Pac J Cancer Prev. 2017;18 (4):873
37 Australian Institute of Health and Welfare. BreastScreen Australia monitoring report 2014–2015. Canberra, Australia, 2017
38 Akinyemiju TF, Genkinger JM, Farhat M, et al. Residential environment and breast cancer incidence and mortality: a systematic review and meta-analysis. BMC Cancer. 2015;15 (1):191
39 Lyle G, Hendrie GA and Hendrie D. Understanding the effects of socioeconomic status along the breast cancer continuum in Australian women: a systematic review of evidence. Int J Equity Health. 2017;16 (1):182
40 Singh GK and Jemal A. Socioeconomic and racial/ethnic disparities in cancer mortality, incidence, and survival in the United States, 1950–2014: over six decades of changing patterns and widening inequalities. J Environ Public Health. 2017;2017
41 Akinyemiju TF, Pisu M, Waterbor JW, et al. Socioeconomic status and incidence of breast cancer by hormone receptor subtype. Springerplus. 2015;4 (1):508
42 Troisi R, Potischman N and Hoover RN. Exploring the underlying hormonal mechanisms of prenatal risk factors for breast cancer: a review and commentary. Cancer Epidemiol Biomarkers Prev. 2007;16 (9):1700-1712
43 dos Santos Silva I, De Stavola B and McCormack V. Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. PLoS Med. 2008;5 (9):e193
44 Dartois L, Fagherazzi G, Baglietto L, et al. Proportion of premenopausal and postmenopausal breast cancers attributable to known risk factors: estimates from the E3N-EPIC cohort. Int J Cancer. 2016;138 (10):2415-27
45 Xue F, Rosner B, Eliassen H, et al. Body fatness throughout the life course and the incidence of premenopausal breast cancer. Int J Epidemiol. 2016;45 (4):1103-1112

46 Sandvei MS, Lagiou P, Romundstad PR, et al. Size at birth and risk of breast cancer: update from a prospective population-based study. Eur J Epidemiol. 2015;30 (6):485-492
47 Zhang B, Shu X-O, Delahanty RJ, et al. Height and breast cancer risk: evidence from prospective studies and Mendelian randomization. J Natl Cancer Inst. 2015;107 (11):djv219
48 Bandera EV, Fay SH, Giovannucci E, et al. The use and interpretation of anthropometric measures in cancer epidemiology: a perspective from the world cancer research fund international continuous update project. Int J Cancer. 2016;139 (11):2391-2397
49 Elands RJ, Simons CC, Riemenschneider M, et al. A systematic SNP selection approach to identify mechanisms underlying disease aetiology: linking height to post-menopausal breast and colorectal cancer risk. Sci Rep. 2017;7 41034
50 Horn-Ross PL, Canchola AJ, Bernstein L, et al. Lifetime body size and estrogen-receptor-positive breast cancer risk in the California Teachers Study cohort. Breast Cancer Res. 2016;18 (1):132
51 Nitta J, Nojima M, Ohnishi H, et al. Weight gain and alcohol drinking associations with breast cancer risk in Japanese postmenopausal women-results from the Japan Collaborative Cohort (JACC) Study. Asian Pac J Cancer Prev. 2016;17 (3):1437-1443
52 Wise LA and Titus LJ. Exposure to Breast Milk in Infancy and Risk of Adult Breast Cancer: A Summary of the Evidence. Humana Press, Totowa, NJ, 2013
53 Martin RM, Middleton N, Gunnell D, et al. Breast-feeding and cancer: the Boyd Orr cohort and a systematic review with meta-analysis. J Natl Cancer Inst. 2005;97 (19):1446-57
54 Michels KB, Trichopoulos D, Rosner BA, et al. Being breastfed in infancy and breast cancer incidence in adult life: results from the two nurses' health studies. Am J Epidemiol. 2001;153 (3):275-283
55 Wise LA, Titus-Ernstoff L, Newcomb PA, et al. Exposure to breast milk in infancy and risk of breast cancer. Cancer Causes Control. 2009;20 (7):1083-1090
56 Pettersson A, Graff RE, Ursin G, et al. Mammographic density phenotypes and risk of breast cancer: a meta-analysis. J Natl Cancer Inst. 2014;106 (5):dju078
57 Wang AT, Vachon CM, Brandt KR, et al. Breast density and breast cancer risk: a practical review. Mayo Clin Proc. 2014;89 (4):548-57
58 Melnikow J, Fenton JJ, Whitlock EP, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the US Preventive Services Task Force. Ann Intern Med. 2016;164 (4):268-278
59 American College of Radiology. The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS). American College of Radiology, Reston, VA, USA, 2003
60 Sickles E, D'Orsi C and Bassett L. ACR BI-RADS Atlas: Breast imaging reporting and data system. Reston, VA. J Am Coll Radiol. 2013;23 123-6
61 Moshina N, Sebuødegård S, Lee CI, et al. Automated volumetric analysis of mammographic density in a screening setting: worse outcomes for women with dense breasts. Radiology. 2018;288 (2):343-352
62 Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. J Natl Cancer Inst. 2014;106 (10):
63 Wanders JO, Holland K, Veldhuis WB, et al. Volumetric breast density affects performance of digital screening mammography. Breast Cancer Res Treat. 2017;162 (1):95-103
64 BreastScreen Australia. Breast Density and Screening: Position Statement http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/br-policy-breast-density. Accessed: November 2018
65 Boyd NF, Greenberg C, Lockwood G, et al. Effects at two years of a low-fat, high-carbohydrate diet on radiologic features of the breast: results from a randomized trial. J Natl Cancer Inst. 1997;89 (7):488-496

66 Boyd NF, Dite GS, Stone J, et al. Heritability of mammographic density, a risk factor for breast cancer. N Engl J Med. 2002;347 (12):886-894
67 Yaghjyan L, Mahoney M, Succop P, et al. Relationship between breast cancer risk factors and mammographic breast density in the Fernald Community Cohort. Br J Cancer. 2012;106 (5):996
68 Zhu W, Huang P, Macura KJ, et al. Association between breast cancer, breast density, and body adiposity evaluated by MRI. Eur Radiol. 2016;26 (7):2308-2316
69 Boyd NF, Martin LJ, Sun L, et al. Body size, mammographic density, and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2006;15 (11):2086-2092
70 McTiernan A, Martin C, Peck J, et al. Women's Health Initiative Mammogram Density Study Investigators. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. J Natl Cancer Inst. 2005;97 (18):1366-1376
71 McCormack VA and dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15 (6):1159-1169
72 Bae JM and Kim EH. Breast Density and Risk of Breast Cancer in Asian Women: A Meta-analysis of Observational Studies. J Prev Med Public Health. 2016;49 (6):367-375
73 Chiu SY-H, Duffy S, Yen AM-F, et al. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. Cancer Epidemiol Biomarkers Prev. 2010;19 (5):1219-1228
74 Jansen L, Backstein R and Brown M. Breast size and breast cancer: a systematic review. J Plast Reconstr Aesthet Surg. 2014;67 (12):1615-1623
75 Chen L, Malone KE and Li CI. Bra Wearing Not Associated with Breast Cancer Risk: A Population-Based Case–Control Study. Cancer Epidemiol Biomarkers Prev. 2014;23 (10):2181-2185
76 Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. Lancet. 2001;358 (9291):1389-1399
77 Pharoah PD, Day NE, Duffy S, et al. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer. 1997;71 (5):800-809
78 Bevier M, Sundquist K and Hemminki K. Risk of breast cancer in families of multiple affected women and men. Breast Cancer Res Treat. 2012;132 (2):723-728
79 National Cancer Institute (NCI). Genetics of Breast and Gynecologic Cancers (PDQ)–Health Professional Version. www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq Accessed: March 2018
80 Turati F, Edefonti V, Bosetti C, et al. Family history of cancer and the risk of cancer: a network of case–control studies. Ann Oncol. 2013;24 (10):2651-2656
81 Kharazmi E, Chen T, Narod S, et al. Effect of multiplicity, laterality, and age at onset of breast cancer on familial risk of breast cancer: a nationwide prospective cohort study. Breast Cancer Res Treat. 2014;144 (1):185-192
82 Beebe-Dimmer JL, Yee C, Cote ML, et al. Familial clustering of breast and prostate cancer and risk of postmenopausal breast cancer in the Women's Health Initiative Study. Cancer. 2015;121 (8):1265-1272
83 Colditz GA, Kaphingst KA, Hankinson SE, et al. Family history and risk of breast cancer: nurses' health study. Breast Cancer Res Treat. 2012;133 (3):1097-1104
84 Bethea TN, Rosenberg L, Castro-Webb N, et al. Family history of cancer in relation to breast cancer subtypes in African American women. Cancer Epidemiol Biomarkers Prev. 2016;25 (2):366-373
85 Evans DG and Howell A. Breast cancer risk-assessment models. Breast Cancer Res. 2007;9 (5):213
86 Sutcliffe S, Pharoah PD, Easton DF, et al. Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer. Int J Cancer. 2000;87 (1):110-7

87 Slattery ML and Kerber RA. A comprehensive evaluation of family history and breast cancer risk: the utah population database. JAMA. 1993;270 (13):1563-1568
88 Claus EB, Risch N and Thompson WD. The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. Breast Cancer Res Treat. 1993;28 (2):115-120
89 Valeri A, Fournier G, Morin V, et al. Early onset and familial predisposition to prostate cancer significantly enhance the probability for breast cancer in first degree relatives. Int J Cancer. 2000;86 (6):883-887
90 Holter S, Borgida A, Dodd A, et al. Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma. J Clin Oncol. 2015;33 (28):3124-9
91 Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer. 2008;98 (8):1457-66
92 Turati F, Negri E and Vecchia CL. Family history and the risk of cancer: genetic factors influencing multiple cancer sites. Expert Rev Anticancer Ther. 2014;14 (1):1-4
93 Kurian AW, Hughes E, Handorf EA, et al. Breast and Ovarian Cancer Penetrance Estimates Derived From Germline Multiple-Gene Sequencing Results in Women. JCO Precis Oncol. 2017;1 1-12
94 van Os N, Roeleveld N, Weemaes C, et al. Health risks for ataxia-telangiectasia mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline. Clin Genet. 2016;90 (2):105-117
95 Goldgar DE, Healey S, Dowty JG, et al. Rare variants in the ATM gene and risk of breast cancer. Breast Cancer Res. 2011;13 (4):R73
96 National Institutes of Health (NIH) and U.S. National Library of Medicine (NLM). Ataxia-telangiectasia. https://ghr.nlm.nih.gov/condition/ataxia-telangiectasia. Accessed: May 2018
97 Renwick A, Thompson D, Seal S, et al. ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. Nat Genet. 2006;38 (8):873
98 Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. 2015;372 (23):2243-2257
99 Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17 (5):405-424
100 Aloraifi F, McCartan D, McDevitt T, et al. Protein-truncating variants in moderate-risk breast cancer susceptibility genes: a meta-analysis of high-risk case-control screening studies. Cancer Genet. 2015;208 (9):455-463
101 Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncol. 2017;3 (9):1190-1196
102 Decker B, Allen J, Luccarini C, et al. Rare, protein-truncating variants in ATM, CHEK2 and PALB2, but not XRCC2, are associated with increased breast cancer risks. J Med Genet. 2017;54 (11):732-741
103 National Institutes of Health (NIH) and U.S. National Library of Medicine (NLM). Genetics Home Reference. BRCA1 gene. https://ghr.nlm.nih.gov/gene/BRCA1. Accessed: June 2018
104 Janavičius R. Founder BRCA1/2 mutations in the Europe: implications for hereditary breast-ovarian cancer prevention and control. EPMA J. 2010;1 (3):397-412
105 Graffeo R, Livraghi L, Pagani O, et al. Time to incorporate germline multigene panel testing into breast and ovarian cancer patient care. Breast Cancer Res Treat. 2016;160 (3):393-410
106 Bahar AY, Taylor PJ, Andrews L, et al. The frequency of founder mutations in the BRCA1, BRCA2, and APC genes in Australian Ashkenazi Jews: implications for the generality of US population data. Cancer. 2001;92 (2):440-445

107 Risch HA, McLaughlin JR, Cole DE, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin–cohort study in Ontario, Canada. J Natl Cancer Inst. 2006;98 (23):1694-1706
108 Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317 (23):2402-2416
109 Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72 (5):1117-1130
110 Chen S and Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25 (11):1329
111 Suthers GK. Cancer risks for Australian women with a BRCA1 or a BRCA2 mutation. ANZ J Surg. 2007;77 (5):314-319
112 Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. 2013;105 (11):812-822
113 National Institutes of Health (NIH) and U.S. National Library of Medicine (NLM). Genetics Home Reference. BRCA2 gene. https://ghr.nlm.nih.gov/gene/BRCA2. Accessed: June 2018
114 Van Asperen C, Brohet R, Meijers-Heijboer E, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 2005;42 (9):711-719
115 Hansford S, Kaurah P, Li-Chang H, et al. Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. JAMA Oncol. 2015;1 (1):23-32
116 Lowstuter K, Espenschied CR, Sturgeon D, et al. Unexpected CDH1 mutations identified on multigene panels pose clinical management challenges. JCO Precis Oncol. 2017;1 1-12
117 Huynh JM and Laukaitis CM. Panel testing reveals nonsense and missense CDH1 mutations in families without hereditary diffuse gastric cancer. Mol Genet Genomic Med. 2016;4 (2):232-6
118 National Institutes of Health (NIH) and U.S. National Library of Medicine (NLM). CDH1 gene. https://ghr.nlm.nih.gov/gene/CDH1. Accessed: July 2018
119 Pharoah PD, Guilford P, Caldas C, et al. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology. 2001;121 (6):1348-1353
120 Kaurah P, MacMillan A, Boyd N, et al. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. JAMA. 2007;297 (21):2360-2372
121 Yang Y, Zhang F, Wang Y, et al. CHEK2 1100delC variant and breast cancer risk in Caucasians: a meta-analysis based on 25 studies with 29,154 cases and 37,064 controls. Asian Pac J Cancer Prev. 2012;13 (7):3501-3505
122 Zhang B, Beeghly-Fadiel A, Long J, et al. Genetic variants associated with breast-cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. Lancet Oncol. 2011;12 (5):477-488
123 Weischer M, Bojesen SE, Ellervik C, et al. CHEK2* 1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. J Clin Oncol. 2008;26 (4):542-548
124 Meijers-Heijboer H, van den Ouweland A, Klijn J, et al. Low-penetrance susceptibility to breast cancer due to CHEK2* 1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet. 2002;31 (1):55
125 National Institutes of Health (NIH) and U.S. National Library of Medicine (NLM). Li Fraumeni Syndrome. https://ghr.nlm.nih.gov/condition/li-fraumeni-syndrome#genes. Accessed: July 2018
126 National Institutes of Health (NIH) and US National Library of Medicine (NLM). CHEK2 gene. https://ghr.nlm.nih.gov/gene/CHEK2. Accessed: July 2018

127 Liu C, Wang Y, Wang Q-S, et al. The CHEK2 I157T variant and breast cancer susceptibility: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2012;13 (4):1355-60
128 Southey MC, Goldgar DE, Winqvist R, et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. J Med Genet. 2016;53 800-811
129 Tischkowitz M and Xia B. PALB2/FANCN: recombining cancer and Fanconi anemia. Cancer Res. 2010;0008-5472. CAN-10-1012
130 Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371 (6):497-506
131 Cybulski C, Kluźniak W, Huzarski T, et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. Lancet Oncol. 2015;16 (6):638-644
132 National Institutes of Health (NIH) and US National Library of Medicine (NLM). PALB2 gene. https://ghr.nlm.nih.gov/gene/PALB2. Accessed: July 2018
133 Wesoła M and Jeleń M. The risk of breast cancer due to PALB2 gene mutations. Adv Clin Exp Med. 2017;26 (2):339-342
134 Nieuwenhuis MH, Kets CM, Murphy-Ryan M, et al. Cancer risk and genotype–phenotype correlations in PTEN hamartoma tumor syndrome. Fam Cancer. 2014;13 (1):57-63
135 National Institutes of Health (NIH) and US National Library of Medicine (NLM). PTEN gene. https://ghr.nlm.nih.gov/gene/PTEN. Accessed: June 2018
136 Ngeow J, Sesock K and Eng C. Breast cancer risk and clinical implications for germline PTEN mutation carriers. Breast Cancer Res Treat. 2017;165 (1):1-8
137 Kirk J, Barlow-Stewart KK, Poplawski NK, et al. Medicare-funded cancer genetic tests: a note of caution. Med J Aust. 2018;209 (5):193-196
138 Tan M-H, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18 (2):400-407
139 Bubien V, Bonnet F, Brouste V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet. 2013;50 (4):255-263
140 Michailidou K, Lindström S, Dennis J, et al. Association analysis identifies 65 new breast cancer risk loci. Nature. 2017;551 (7678):92
141 Mavaddat N, Pharoah PD, Michailidou K, et al. Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst. 2015;107 (5):
142 National Institutes of Health (NIH) and US National Library of Medicine (NLM). What are single nucleotide polymorphisms (SNPs)? https://ghr.nlm.nih.gov/primer/genomicresearch/gwastudies. Accessed: June 2018
143 Milne RL, Kuchenbaecker KB, Michailidou K, et al. Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. Nat Genet. 2017;49 (12):1767
144 Lilyquist J, Ruddy KJ, Vachon CM, et al. Common genetic variation and breast cancer risk-past, present, and future. Cancer Epidemiol Biomarkers Prev. 2018;27 (4):380-394
145 Michailidou K, Beesley J, Lindstrom S, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet. 2015;47 (4):373
146 Li H, Feng B, Miron A, et al. Breast cancer risk prediction using a polygenic risk score in the familial setting: a prospective study from the Breast Cancer Family Registry and kConFab. Genet Med. 2017;19 (1):30
147 Kuchenbaecker KB, McGuffog L, Barrowdale D, et al. Evaluation of polygenic risk scores for breast and ovarian cancer risk prediction in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 2017;109 (7):
148 Cuzick J, Brentnall AR, Segal C, et al. Impact of a panel of 88 single nucleotide polymorphisms on the risk of breast cancer in high-risk women: results from two randomized tamoxifen prevention trials. J Clin Oncol. 2017;35 (7):743-750
149 Dite GS, MacInnis RJ, Bickerstaffe A, et al. Breast cancer risk prediction using clinical models and 77 independent risk-associated SNPs for women aged under 50 years:

Australian Breast Cancer Family Registry. Cancer Epidemiol Biomarkers Prev. 2016;25 (2):359-365
150 Shieh Y, Hu D, Ma L, et al. Breast cancer risk prediction using a clinical risk model and polygenic risk score. Breast Cancer Res Treat. 2016;159 (3):513-525
151 Vachon CM, Pankratz VS, Scott CG, et al. The contributions of breast density and common genetic variation to breast cancer risk. J Natl Cancer Inst. 2015;107 (5):dju397
152 Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz–Jeghers syndrome. Gastroenterology. 2000;119 (6):1447-1453
153 Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12 (10):3209-3215
154 Resta N, Pierannunzio D, Lenato GM, et al. Cancer risk associated with STK11/LKB1 germline mutations in Peutz–Jeghers syndrome patients: results of an Italian multicenter study. Dig Liver Dis. 2013;45 (7):606-611
155 Papp J, Kovacs ME, Solyom S, et al. High prevalence of germline STK11 mutations in Hungarian Peutz-Jeghers Syndrome patients. BMC Med Genet. 2010;11 169
156 Van Lier M, Wagner A, Mathus-Vliegen E, et al. High cancer risk in Peutz–Jeghers syndrome: a systematic review and surveillance recommendations. The American journal of gastroenterology. 2010;105 (6):1258
157 Cancer Institute NSW. Genetic testing for heritable mutations in the STK11 gene. https://www.eviq.org.au/cancer-genetics/genetic-testing-for-heritable-mutations/744-genetic-testing-for-heritable-mutations-in-the. Accessed: October 2018
158 Beggs AD, Latchford AR, Vasen HF, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010;59 (7):975-86
159 National Institutes of Health (NIH) and US National Library of Medicine (NLM). STK11 gene. https://ghr.nlm.nih.gov/gene/STK11#. Accessed: July 2018
160 Connolly DC, Katabuchi H, Cliby WA, et al. Somatic mutations in the STK11/LKB1 gene are uncommon in rare gynecological tumor types associated with Peutz-Jegher's syndrome. Am J Pathol. 2000;156 (1):339-45
161 Schon K and Tischkowitz M. Clinical implications of germline mutations in breast cancer: TP53. Breast Cancer Res Treat. 2017;1-7
162 National Institutes of Health (NIH) and US National Library of Medicine (NLM). TP53 gene. https://ghr.nlm.nih.gov/gene/TP53. Accessed: June 2018
163 Mouchawar J, Korch C, Byers T, et al. Population-based estimate of the contribution of TP53 mutations to subgroups of early-onset breast cancer: Australian Breast Cancer Family Study. Cancer Res. 2010;0008-5472. CAN-09-0851
164 McCuaig JM, Armel SR, Novokmet A, et al. Routine TP53 testing for breast cancer under age 30: ready for prime time? Fam Cancer. 2012;11 (4):607-613
165 Hwang S-J, Lozano G, Amos CI, et al. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. Am J Hum Genet. 2003;72 (4):975-983
166 Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer. 2016;122 (23):3673-3681
167 Bougeard G, Renaux-Petel M, Flaman J-M, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol. 2015;33 (21):2345-2352
168 Dyrstad SW, Yan Y, Fowler AM, et al. Breast cancer risk associated with benign breast disease: systematic review and meta-analysis. Breast Cancer Res Treat. 2015;149 (3):569-575
169 Zhou W-B, Xue D-Q, Liu X-A, et al. The influence of family history and histological stratification on breast cancer risk in women with benign breast disease: a meta-analysis. J Cancer Res Clin Oncol. 2011;137 (7):1053-1060
170 Hoogerbrugge N, Bult P, de Widt-Levert L, et al. High prevalence of premalignant lesions in prophylactically removed breasts from women at hereditary risk for breast cancer. J Clin Oncol. 2003;21 (1):41-45

171 Rohan TE, Negassa A, Chlebowski RT, et al. Estrogen plus progestin and risk of benign proliferative breast disease. Cancer Epidemiol Biomarkers Prev. 2008;17 (9):2337-2343
172 Tan-Chiu E, Wang J, Costantino JP, et al. Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. J Natl Cancer Inst. 2003;95 (4):302-307
173 Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005;353 (3):229-237
174 Visscher DW, Frank RD, Carter JM, et al. Breast cancer risk and progressive histology in serial benign biopsies. J Natl Cancer Inst. 2017;109 (10):djx035
175 Radisky DC, Visscher DW, Frank RD, et al. Natural history of age-related lobular involution and impact on breast cancer risk. Breast Cancer Res Treat. 2016;155 (3):423-430
176 Said SM, Visscher DW, Nassar A, et al. Flat epithelial atypia and risk of breast cancer: a Mayo cohort study. Cancer. 2015;121 (10):1548-1555
177 Hartmann LC, Radisky DC, Frost MH, et al. Understanding the premalignant potential of atypical hyperplasia through its natural history: a longitudinal cohort study. Cancer Prev Res. 2014;
178 Degnim AC, Dupont WD, Radisky DC, et al. Extent of atypical hyperplasia stratifies breast cancer risk in 2 independent cohorts of women. Cancer. 2016;122 (19):2971-2978
179 Cancer Australia. Clinical guidance for the management of lobular carcinoma in situ. https://canceraustralia.gov.au/publications-and-resources/clinical-practice-guidelines/clinical-guidance-management-lobular-carcinoma-situ. Accessed: August 2018
180 King TA, Pilewskie M, Muhsen S, et al. Lobular carcinoma in situ: a 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk. J Clin Oncol. 2015;33 (33):3945
181 Chuba PJ, Hamre MR, Yap J, et al. Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. J Clin Oncol. 2005;23 (24):5534-5541
182 Ginter PS and D'Alfonso TM. Current Concepts in Diagnosis, Molecular Features, and Management of Lobular Carcinoma In Situ of the Breast With a Discussion of Morphologic Variants. Arch Pathol Lab Med. 2017;141 (12):1668-1678
183 Jean-Louis CJ, Masdon J, Smith B, et al. The Pathologic Finding of Combined Lobular Carcinoma In Situ and Invasive Lobular Cancer May Indicate more than Just a High-Risk Marker Role of Lobular Carcinoma In Situ. Am Surg. 2017;83 (5):482-485
184 Li CI, Malone KE, Saltzman BS, et al. Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988-2001. Cancer. 2006;106 (10):2104-2112
185 Lo LL, Milne RL, Liao Y, et al. Validation of the IBIS breast cancer risk evaluator for women with lobular carcinoma in-situ. Br J Cancer. 2018;119 (1):36-39
186 Mao K, Yang Y, Wu W, et al. Risk of second breast cancers after lobular carcinoma in situ according to hormone receptor status. PLoS One. 2017;12 (5):e0176417
187 Levi F, Randimbison L, Te VC, et al. Invasive breast cancer following ductal and lobular carcinoma in situ of the breast. Int J Cancer. 2005;116 (5):820-823
188 Rosen PP, Kosloff C, Lieberman PH, et al. Lobular carcinoma in situ of the breast. Detailed analysis of 99 patients with average follow-up of 24 years. Am J Surg Pathol. 1978;2 (3):225-51
189 Rawal R, Bermejo JL and Hemminki K. Risk of subsequent invasive breast carcinoma after in situ breast carcinoma in a population covered by national mammographic screening. Br J Cancer. 2005;92 (1):162
190 Bodian CA, Perzin KH and Lattes R. Lobular neoplasia. Long term risk of breast cancer and relation to other factors. Cancer. 1996;78 (5):1024-34
191 Wärnberg F, Yuen J and Holmberg L. Risk of subsequent invasive breast cancer after breast carcinoma in situ. Lancet. 2000;355 (9205):724-725

192 Soerjomataram I, Louwman WJ, van der Sangen MJ, et al. Increased risk of second malignancies after in situ breast carcinoma in a population-based registry. Br J Cancer. 2006;95 (3):393-7
193 Robinson D, Holmberg L and Moller H. The occurrence of invasive cancers following a diagnosis of breast carcinoma in situ. Br J Cancer. 2008;99 (4):611-5
194 Franceschi S, Levi F, La Vecchia C, et al. Second cancers following in situ carcinoma of the breast. Int J Cancer. 1998;77 (3):392-5
195 Page DL, Kidd Jr TE, Dupont WD, et al. Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. Hum Pathol. 1991;22 (12):1232-1239
196 Andersen JA. Lobular carcinoma in situ of the breast. An approach to rational treatment. Cancer. 1977;39 (6):2597-602
197 Wong SM, King T, Boileau J-F, et al. Population-Based Analysis of Breast Cancer Incidence and Survival Outcomes in Women Diagnosed with Lobular Carcinoma In Situ. Ann Surg Oncol. 2017;24 (9):2509-2517
198 To T, Wall C, Baines CJ, et al. Is carcinoma in situ a precursor lesion of invasive breast cancer? Int J Cancer. 2014;135 (7):1646-52
199 Australian Institute of Health and Welfare & National Breast and Ovarian Cancer Centre. Risk of invasive breast cancer in women diagnosed with ductal carcinoma in situ in Australia between 1995 and 2005. Canberra, ACT, 2010
200 Gorringe KL and Fox SB. Ductal carcinoma in situ biology, biomarkers, and diagnosis. Front Oncol. 2017;7 248
201 Virnig BA, Wang S-Y, Shamilyan T, et al. Ductal carcinoma in situ: risk factors and impact of screening. J Natl Cancer Inst Monogr. 2010;2010 (41):113-116
202 Buckley ES, Sullivan T, Farshid G, et al. The utility of linked cancer registry and health administration data for describing system-wide outcomes and research: a BreastScreen example. J Eval Clin Pract. 2016;22 (5):755-760
203 Falk RS, Hofvind S, Skaane P, et al. Second events following ductal carcinoma in situ of the breast: a register-based cohort study. Breast Cancer Res Treat. 2011;129 (3):929
204 Innos K and Horn-Ross PL. Risk of second primary breast cancers among women with ductal carcinoma in situ of the breast. Breast Cancer Res Treat. 2008;111 (3):531-540
205 Elshof LE, Schaapveld M, Schmidt MK, et al. Subsequent risk of ipsilateral and contralateral invasive breast cancer after treatment for ductal carcinoma in situ: incidence and the effect of radiotherapy in a population-based cohort of 10,090 women. Breast Cancer Res Treat. 2016;159 (3):553-563
206 Cheung S, Booth ME, Kearins O, et al. Risk of subsequent invasive breast cancer after a diagnosis of ductal carcinoma in situ (DCIS). The Breast. 2014;23 (6):807-811
207 Zhang X, Dai H, Liu B, et al. Predictors for local invasive recurrence of ductal carcinoma in situ of the breast: a meta-analysis. Eur J Cancer Prev. 2016;25 (1):19
208 Liu Y, Schloemann DT, Lian M, et al. Accelerated partial breast irradiation through brachytherapy for ductal carcinoma in situ: factors influencing utilization and risks of second breast tumors. Breast Cancer Res Treat. 2015;151 (1):199-208
209 Yi M, Meric-Bernstam F, Kuerer HM, et al. Evaluation of a breast cancer nomogram for predicting risk of ipsilateral breast tumor recurrences in patients with ductal carcinoma in situ after local excision. J Clin Oncol. 2012;30 (6):600
210 Youlden DR and Baade PD. The relative risk of second primary cancers in Queensland, Australia: a retrospective cohort study. BMC Cancer. 2011;11 (1):83
211 Bazire L, De Rycke Y, Asselain B, et al. Risks of second malignancies after breast cancer treatment: long-term results. Cancer Radiother. 2017;21 (1):10-15
212 Ricceri F, Fasanelli F, Giraudo MT, et al. Risk of second primary malignancies in women with breast cancer: results from the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer. 2015;137 (4):940-948
213 Rusner C, Wolf K, Bandemer-Greulich U, et al. Risk of contralateral second primary breast cancer according to hormone receptor status in Germany. Breast Cancer Res. 2014;16 (5):452

214 Cluze C, Delafosse P, Seigneurin A, et al. Incidence of second cancer within 5 years of diagnosis of a breast, prostate or colorectal cancer: a population-based study. Eur J Cancer Prev. 2009;18 (5):343-348
215 Kurian AW, McClure LA, John EM, et al. Second primary breast cancer occurrence according to hormone receptor status. J Natl Cancer Inst. 2009;101 (15):1058-1065
216 Schaapveld M, Visser O, Louwman W, et al. The impact of adjuvant therapy on contralateral breast cancer risk and the prognostic significance of contralateral breast cancer: a population based study in the Netherlands. Breast Cancer Res Treat. 2008;110 (1):189-197
217 Soerjomataram I, Louwman W, de Vries E, et al. Primary malignancy after primary female breast cancer in the South of the Netherlands, 1972–2001. Breast Cancer Res Treat. 2005;93 (1):91-95
218 Vichapat V, Garmo H, Holmqvist M, et al. Tumor stage affects risk and prognosis of contralateral breast cancer: results from a large Swedish-population–based study. J Clin Oncol. 2012;30 (28):3478-3485
219 Bouchardy C, Benhamou S, Fioretta G, et al. Risk of second breast cancer according to estrogen receptor status and family history. Breast Cancer Res Treat. 2011;127 (1):233-241
220 Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012;13 (11):1141-1151
221 Chang-Claude J, Andrieu N, Rookus M, et al. Age at menarche and menopause and breast cancer risk in the International BRCA1/2 Carrier Cohort Study. Cancer Epidemiol Biomarkers Prev. 2007;16 (4):740-6
222 Endogenous Hormones and Breast Cancer Collaborative Group, Key T, Appleby P, et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer. 2011;105 (5):709
223 Bodicoat DH, Schoemaker MJ, Jones ME, et al. Timing of pubertal stages and breast cancer risk: the Breakthrough Generations Study. Breast Cancer Res. 2014;16 (1):R18
224 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease. Lancet. 2002;360 (9328):187-195
225 Russo J, Moral R, Balogh GA, et al. The protective role of pregnancy in breast cancer. Breast Cancer Res. 2005;7 (3):131
226 Nelson HD, Zakher B, Cantor A, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med. 2012;156 (9):635-648
227 Lambertini M, Santoro L, Del Mastro L, et al. Reproductive behaviors and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis of epidemiological studies. Cancer Treat Rev. 2016;49 65-76
228 Ritte R, Tikk K, Lukanova A, et al. Reproductive factors and risk of hormone receptor positive and negative breast cancer: a cohort study. BMC Cancer. 2013;13 (1):584
229 Sisti JS, Collins LC, Beck AH, et al. Reproductive risk factors in relation to molecular subtypes of breast cancer: results from the nurses' health studies. Int J Cancer. 2016;138 (10):2346-2356
230 Lambe M, Hsieh C-c, Chan H-w, et al. Parity, age at first and last birth, and risk of breast cancer: a population-based study in Sweden. Breast Cancer Res Treat. 1996;38 (3):305-311
231 World Health Organization. Indicators for assessing infant and young child feeding practices: conclusions of a consensus meeting held 6-8 November 2007 in Washington DC, USA. World Health Organization (WHO),, Geneva, Switzerland, 2008
232 World Cancer Research Fund and American Institute for Cancer Research. Food, Nutrition, Physical activity, and the Prevention of Cancer: A Global Perspective. Washington, DC, USA, 2007

233 Zhou Y, Chen J, Li Q, et al. Association between breastfeeding and breast cancer risk: evidence from a meta-analysis. Breastfeed Med. 2015;10 (3):175-182
234 Islami F, Liu Y, Jemal A, et al. Breastfeeding and breast cancer risk by receptor status—a systematic review and meta-analysis. Ann Oncol. 2015;26 (12):2398-2407
235 Ma H, Ursin G, Xu X, et al. Reproductive factors and the risk of triple-negative breast cancer in white women and African-American women: a pooled analysis. Breast Cancer Res. 2017;19 (1):6
236 Do K-A, Treloar SA, Pandeya N, et al. Predictive factors of age at menopause in a large Australian twin study. Hum Biol. 1998;1073-1091
237 Li H, Sun X, Miller E, et al. BMI, reproductive factors, and breast cancer molecular subtypes: a case-control study and meta-analysis. J Epidemiol. 2017;27 (4):143-151
238 Endogenous Hormones and Breast Cancer Collaborative Group. Steroid hormone measurements from different types of assays in relation to body mass index and breast cancer risk in postmenopausal women: reanalysis of eighteen prospective studies. Steroids. 2015;99 49-55
239 Endogenous Hormones and Breast Cancer Collaborative Group. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol. 2010;11 (6):530
240 Endogenous Hormones and Breast Cancer Collaborative Group. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncology. 2013;14 (10):1009-1019
241 Fortner RT, Eliassen AH, Spiegelman D, et al. Premenopausal endogenous steroid hormones and breast cancer risk: results from the Nurses' Health Study II. Breast Cancer Res. 2013;15 (2):R19
242 Schernhammer ES, Sperati F, Razavi P, et al. Endogenous sex steroids in premenopausal women and risk of breast cancer: the ORDET cohort. Breast Cancer Res. 2013;15 (3):R46
243 Kaaks R, Tikk K, Sookthai D, et al. Premenopausal serum sex hormone levels in relation to breast cancer risk, overall and by hormone receptor status—results from the EPIC cohort. Int J Cancer. 2014;134 (8):1947-1957
244 Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst. 2002;94 (8):606-616
245 James RE, Lukanova A, Dossus L, et al. Postmenopausal serum sex steroids and risk of hormone receptor-positive and -negative breast cancer: a nested case-control study. Cancer Prev Res. 2011;4 (10):1626-35
246 Sieri S, Krogh V, Bolelli G, et al. Sex hormone levels, breast cancer risk, and cancer receptor status in postmenopausal women: the ORDET cohort. Cancer Epidemiol Biomarkers Prev. 2009;18 (1):169-176
247 Farhat GN, Cummings SR, Chlebowski RT, et al. Sex hormone levels and risks of estrogen receptor–negative and estrogen receptor–positive breast cancers. J Natl Cancer Inst. 2011;103 (7):562-570
248 Kaaks R, Johnson T, Tikk K, et al. Insulin-like growth factor I and risk of breast cancer by age and hormone receptor status—A prospective study within the EPIC cohort. Int J Cancer. 2014;134 (11):2683-2690
249 National Cancer Institute (NCI). Breast Cancer Prevention (PDQ®)–Health Professional Version. https://www.cancer.gov/types/breast/hp/breast-prevention-pdq. Accessed: June 2018
250 Bernichtein S, Touraine P and Goffin V. New concepts in prolactin biology. J Endocrinol. 2010;206 (1):1-11
251 Tworoger SS, Eliassen AH, Zhang X, et al. A 20-year prospective study of plasma prolactin as a risk marker of breast cancer development. Cancer Res. 2013;73 (15):4810-9

252 Tikk K, Sookthai D, Johnson T, et al. Circulating prolactin and breast cancer risk among pre-and postmenopausal women in the EPIC cohort. Ann Oncol. 2014;25 (7):1422-1428
253 Teede HJ, Misso ML, Boyle JA, et al. Translation and implementation of the Australian-led PCOS guideline: clinical summary and translation resources from the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Med J Aust. 2018;209 (7):S3-S8
254 Harris HR and Terry KL. Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: a systematic review. Fertil Res Pract. 2016;2 14
255 Shobeiri F and Jenabi E. The association between polycystic ovary syndrome and breast cancer: a meta-analysis. Obstet Gynecol Sci. 2016;59 (5):367-372
256 Chittenden BG, Fullerton G, Maheshwari A, et al. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod Biomed Online. 2009;19 (3):398-405
257 Zhu H, Lei X, Feng J, et al. Oral contraceptive use and risk of breast cancer: a meta-analysis of prospective cohort studies. Eur J Contracept Reprod Health Care. 2012;17 (6):402-414
258 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. Lyon, France, 2007
259 Pike MC, Spicer DV, Dahmoush L, et al. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev. 1993;15 (1):17-30
260 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Pharmaceuticals. International Agency for Research on Cancer, Lyon, France, 2012
261 Vessey M and Painter R. Oral contraceptive use and cancer. Findings in a large cohort study, 1968–2004. Br J Cancer. 2006;95 385
262 Hannaford PC, Selvaraj S, Elliott AM, et al. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. BMJ. 2007;335 (7621):651
263 Rosenblatt KA, Gao DL, Ray RM, et al. Oral contraceptives and the risk of all cancers combined and site-specific cancers in Shanghai. Cancer Causes Control. 2008;20 (1):27-34
264 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet. 1996;347 (9017):1713-27
265 Iversen L, Sivasubramaniam S, Lee AJ, et al. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. Am J Obstet Gynecol. 2017;216 (6):580. e1-580. e9
266 Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2013;22 (11):1931-1943
267 Anothaisintawee T, Wiratkapun C, Lerdsitthichai P, et al. Risk factors of breast cancer: a systematic review and meta-analysis. Asia Pac J Public Health. 2013;25 (5):368-387
268 Hunter DJ, Colditz GA, Hankinson SE, et al. Oral contraceptive use and breast cancer: a prospective study of young women. Cancer Epidemiol Biomarkers Prev. 2010;19 (10):2496-2502
269 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Hormonal contraception and post-menopausal hormonal therapy. Lyon, France, 1999
270 Fabre A, Fournier A, Mesrine S, et al. Oral progestagens before menopause and breast cancer risk. Br J Cancer. 2007;96 (5):841

271 Kumle M, Weiderpass E, Braaten T, et al. Use of oral contraceptives and breast cancer risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study. Cancer Epidemiol Biomarkers Prev. 2002;11 (11):1375-1381
272 Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med. 2002;346 (26):2025-2032
273 Backman T, Rauramo I, Jaakkola K, et al. Use of the levonorgestrel-releasing intrauterine system and breast cancer. Obstet Gynecol. 2005;106 (4):813-817
274 Shapiro S, Rosenberg L, Hoffman M, et al. Risk of breast cancer in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen contraceptives. Am J Epidemiol. 2000;151 (4):396-403
275 Strom BL, Berlin JA, Weber AL, et al. Absence of an effect of injectable and implantable progestin-only contraceptives on subsequent risk of breast cancer. Contraception. 2004;69 (5):353-360
276 Munsell MF, Sprague BL, Berry DA, et al. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. Epidemiol Rev. 2014;36 (1):114-136
277 Beral V, Reeves G, Bull D, et al. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst. 2011;103 (4):296-305
278 Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310 (13):1353-1368
279 Chlebowski RT, Rohan TE, Manson JE, et al. Breast cancer after use of estrogen plus progestin and estrogen alone: analyses of data from 2 women's health initiative randomized clinical trials. JAMA Oncol. 2015;1 (3):296-305
280 Jones ME, Schoemaker MJ, Wright L, et al. Menopausal hormone therapy and breast cancer: what is the true size of the increased risk? Br J Cancer. 2016;115 (5):607
281 Román M, Sakshaug S, Graff-Iversen S, et al. Postmenopausal hormone therapy and the risk of breast cancer in Norway. Int J Cancer. 2015;138 (3):584-593
282 Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med. 2009;360 (6):573-87
283 Fournier A, Mesrine S, Dossus L, et al. Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort. Breast Cancer Res Treat. 2014;145 (2):535-543
284 Collins JA, Blake JM and Crosignani PG. Breast cancer risk with postmenopausal hormonal treatment. Hum Reprod Update. 2005;11 (6):545-560
285 Shah NR, Borenstein J and Dubois RW. Postmenopausal hormone therapy and breast cancer: a systematic review and meta-analysis. Menopause. 2005;12 (6):668-78
286 Lee S, Kolonel L, Wilkens L, et al. Postmenopausal hormone therapy and breast cancer risk: the Multiethnic Cohort. Int J Cancer. 2006;118 (5):1285-91
287 Bakken K, Fournier A, Lund E, et al. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2011;128 (1):144-156
288 Prentice RL, Chlebowski RT, Stefanick ML, et al. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. Am J Epidemiol. 2008;167 (10):1207-16
289 Prentice RL, Manson JE, Langer RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. Am J Epidemiol. 2009;170 (1):12-23
290 Fournier A, Mesrine S, Boutron-Ruault MC, et al. Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? J Clin Oncol. 2009;27 (31):5138-43
291 Porch JV, Lee I-M, Cook NR, et al. Estrogen–progestin replacement therapy and breast cancer risk: the Women's Health Study (United States). Cancer Causes Control. 2002;13 (9):847-854

292 Greiser CM, Greiser EM and Dören M. Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. Hum Reprod Update. 2005;11 (6):561-573
293 Sergentanis TN, Diamantaras A-A, Perlepe C, et al. IVF and breast cancer: a systematic review and meta-analysis. Hum Reprod Update. 2014;20 (1):106-123
294 van den Belt-Dusebout AW, Spaan M, Lambalk CB, et al. Ovarian stimulation for in vitro fertilization and long-term risk of breast cancer. JAMA. 2016;316 (3):300-312
295 Gennari A, Costa M, Puntoni M, et al. Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. Breast Cancer Res Treat. 2015;150 (2):405-413
296 Lundberg FE, Iliadou AN, Rodriguez-Wallberg K, et al. Ovarian stimulation and risk of breast cancer in Swedish women. Fertil Steril. 2017;108 (1):137-144
297 Luke B, Brown MB, Spector LG, et al. Cancer in women after assisted reproductive technology. Fertil Steril. 2015;104 (5):1218-1226
298 Reigstad MM, Storeng R, Myklebust TÅ, et al. Cancer risk in women treated with fertility drugs according to parity status—a registry-based cohort study. Cancer Epidemiol Biomarkers Prev. 2017;
299 Troisi R, Hatch EE, Titus L, et al. Prenatal diethylstilbestrol exposure and cancer risk in women. Environ Mol Mutagen. 2017;0 (0):
300 Verloop J, van Leeuwen FE, Helmerhorst TJ, et al. Cancer risk in DES daughters. Cancer Causes Control. 2010;21 (7):999-1007
301 Professional and Public Relations Committee of the DESAD (Diethylstilbestrol and Adenosis) Project of the Division of Cancer Control and Rehabilitation. Exposure in utero to diethylstilbestrol and related synthetic hormones: association with vaginal and cervical cancers and other abnormalities. JAMA. 1976;236 (10):1107-1109
302 Herbst AL, Ulfelder H and Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med. 1971;284 (15):878-81
303 Fickling D. Australia recognises cancer risk for "DES daughters". Lancet. 2004;363 (9426):2059
304 National Cancer Institute (NCI). Diethylstilbestrol (DES) and cancer. https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/des-fact-sheet. Accessed:
305 Hilakivi-Clarke L and De Assis S. Fetal origins of breast cancer. Trends Endocrinol Metab. 2006;17 (9):340-348
306 Hatch EE, Palmer JR, Titus-Ernstoff L, et al. Cancer risk in women exposed to diethylstilbestrol in utero. JAMA. 1998;280 (7):630-4
307 Troisi R, Hatch EE, Titus-Ernstoff L, et al. Cancer risk in women prenatally exposed to diethylstilbestrol. Int J Cancer. 2007;121 (2):356-360
308 Palmer JR, Wise LA, Hatch EE, et al. Prenatal diethylstilbestrol exposure and risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 2006;15 (8):1509-1514
309 Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. N Engl J Med. 2011;365 (14):1304-1314
310 Titus-Ernstoff L, Hatch EE, Hoover RN, et al. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. Br J Cancer. 2001;84 (1):126
311 Bibbo M, Haenszel WM, Wied GL, et al. A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. N Engl J Med. 1978;298 (14):763-767
312 Greenberg E, Barnes A, Resseguie L, et al. Breast cancer in mothers given diethylstilbestrol in pregnancy. N Engl J Med. 1984;311 (22):1393-1398
313 Colton T, Greenberg ER, Noller K, et al. Breast cancer in mothers prescribed diethylstilbestrol in pregnancy: further follow-up. JAMA. 1993;269 (16):2096-2100
314 World Health Organization. Physical status: the use and interpretation of anthropometry. Geneva, Switzerland, 1995
315 Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer—viewpoint of the IARC Working Group. N Engl J Med. 2016;375 (8):794-798

316 International Agency for Research on Cancer (IARC) and World Health Organization (WHO). IARC Handbooks Volume 16 – Questions and Answers. http://www.iarc.fr/en/media-centre/iarcnews/pdf/Q&AHandbook16.pdf. Accessed: April 2018
317 Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371 (9612):569-578
318 The Premenopausal Breast Cancer Collaborative Group. Association of body mass index and age with subsequent breast cancer risk in premenopausal women. JAMA Oncol. 2018;e181771
319 Freisling H, Arnold M, Soerjomataram I, et al. Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: meta-analysis of individual participant data of seven prospective cohorts in Europe. Br J Cancer. 2017;116 (11):1486
320 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. Lancet. 1997;350 (9084):1047-1059
321 Neuhouser ML, Aragaki AK, Prentice RL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the women's health initiative randomized clinical trials. JAMA Oncol. 2015;1 (5):611-621
322 Endogenous Hormones Breast Cancer Collaborative Group. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst. 2003;95 (16):1218-1226
323 International Agency for Research on Cancer and World Health Organization. Weight control and physical activity. International Agency for Research on Cancer, Lyon, France, 2002
324 Campbell KL, Foster-Schubert KE, Alfano CM, et al. Reduced-calorie dietary weight loss, exercise, and sex hormones in postmenopausal women: randomized controlled trial. J Clin Oncol. 2012;30 (19):2314
325 Byers T and Sedjo R. Does intentional weight loss reduce cancer risk? Diabetes Obes Metab. 2011;13 (12):1063-1072
326 Birks S, Peeters A, Backholer K, et al. A systematic review of the impact of weight loss on cancer incidence and mortality. Obes Rev. 2012;13 (10):868-891
327 Winder AA, Kularatna M and MacCormick AD. Does bariatric surgery affect the incidence of breast cancer development? A systematic review. Obes Surg. 2017;27 (11):3014-3020
328 Chlebowski R, Luo J, Anderson G, et al. Abstract GS5-07: Weight change in postmenopausal women and breast cancer risk in the women's health initiative observational study. Cancer Res. 2018;78 (4 Supplement):GS5-07-GS5-07
329 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Alcohol consumption and ethyl carbamate. Lyon, France, 2010
330 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Personal habits and indoor combustions. Lyon, France, 2012
331 Wu D and Cederbaum AI. Alcohol, oxidative stress, and free radical damage. Alcohol Res Health. 2003;27 277-284
332 Seitz HK, Pelucchi C, Bagnardi V, et al. Epidemiology and pathophysiology of alcohol and breast cancer: update 2012. Alcohol Alcohol. 2012;47 (3):204-212
333 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. A review of human carcinogens: personal habits and indoor combustions. Part E. International Agency for Research on Cancer, Lyon, France, 2012
334 Allen NE, Beral V, Casabonne D, et al. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst. 2009;101 (5):296-305

335 Hamajima N, Sanjosé Llongueras S, Hirose K, et al. Alcohol, tobacco and breast cancer-collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. Br J Cancer. 2002;87 1234-1245
336 Chen J-Y, Zhu H-C, Guo Q, et al. Dose-Dependent Associations between Wine Drinking and Breast Cancer Risk-Meta-Analysis Findings. Asian Pac J Cancer Prev. 2016;17 (3):1221-1233
337 Jayasekara H, MacInnis RJ, Room R, et al. Long-term alcohol consumption and breast, upper aero-digestive tract and colorectal cancer risk: a systematic review and meta-analysis. Alcohol Alcohol. 2016;51 (3):315-330
338 Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. Ann Oncol. 2013;24 (2):301-8
339 Jung S, Wang M, Anderson K, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol. 2016;45 (3):916-28
340 Hirko KA, Chen WY, Willett WC, et al. Alcohol consumption and risk of breast cancer by molecular subtype: Prospective analysis of the nurses' health study after 26 years of follow-up. Int J Cancer. 2016;138 (5):1094-1101
341 Fagherazzi G, Vilier A, Boutron-Ruault M-C, et al. Alcohol consumption and breast cancer risk subtypes in the E3N-EPIC cohort. Eur J Cancer Prev. 2015;24 (3):209-214
342 Romieu I, Scoccianti C, Chajes V, et al. Alcohol intake and breast cancer in the European Prospective investigation into Cancer and Nutrition (EPIC) study. Cancer Causes Control. 2015;18 (4):361-73
343 Chhim A-S, Fassier P, Latino-Martel P, et al. Prospective association between alcohol intake and hormone-dependent cancer risk: modulation by dietary fiber intake. Am J Clin Nutr. 2015;102 (1):182-189
344 Gansler T and Jemal A. Axillary lymphatic disruption does not increase risk of breast carcinoma. Breast J. 2009;15 (4):438-439
345 So WK, Chan DN, Lou Y, et al. Brassiere wearing and breast cancer risk: a systematic review and meta-analysis. World J Metaanal. 2015;
346 Hsieh CC and Trichopoulos D. Breast size, handedness and breast cancer risk. Eur J Cancer. 1991;27 (2):131-5
347 Lafranconi A, Micek A, De Paoli P, et al. Coffee intake decreases risk of postmenopausal breast cancer: a dose-response meta-analysis on prospective cohort studies. Nutrients. 2018;10 (2):112
348 Food Standards Australia & New Zealand (FSANZ). Caffeine. http://www.foodstandards.gov.au/consumer/generalissues/Pages/Caffeine.aspx. Accessed: May 2018
349 Grosso G, Godos J, Galvano F, et al. Coffee, caffeine, and health outcomes: an umbrella review. Annu Rev Nutr. 2017;37 131-156
350 Hashibe M, Galeone C, Buys SS, et al. Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. Br J Cancer. 2015;113 (5):809
351 Oh JK, Sandin S, Strom P, et al. Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden. Int J Cancer. 2015;137 (8):1979-89
352 Bhoo-Pathy N, Peeters PH, Uiterwaal CS, et al. Coffee and tea consumption and risk of pre- and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Breast Cancer Res. 2015;17 15
353 Lukic M, Licaj I, Lund E, et al. Coffee consumption and the risk of cancer in the Norwegian Women and Cancer (NOWAC) Study. Eur J Epidemiol. 2016;31 (9):905-916
354 Jiang W, Wu Y and Jiang X. Coffee and caffeine intake and breast cancer risk: an updated dose–response meta-analysis of 37 published studies. Gynecol Oncol. 2013;129 (3):620-629
355 Li XJ, Ren ZJ, Qin JW, et al. Coffee consumption and risk of breast cancer: an up-to-date meta-analysis. PLoS One. 2013;8 (1):e52681

356 Hidayat K, Chen G-C, Zhang R, et al. Calcium intake and breast cancer risk: meta-analysis of prospective cohort studies. Br J Nutr. 2016;116 (1):158-166
357 National Institutes of Health (NIH). Calcium. https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/. Accessed: July 2018
358 Zang J, Shen M, Du S, et al. The association between dairy intake and breast cancer in western and Asian populations: a systematic review and meta-analysis. J Breast Cancer. 2015;18 (4):313-322
359 Missmer SA, Smith-Warner SA, Spiegelman D, et al. Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. Int J Epidemiol. 2002;31 (1):78-85
360 Wu J, Zeng R, Huang J, et al. Dietary protein sources and incidence of breast cancer: a dose-response meta-analysis of prospective studies. Nutrients. 2016;8 (11):730
361 Lunn J and Buttriss JL. Carbohydrates and dietary fibre. Nutr Bull. 2007;32 (1):21-64
362 Aune D, Chan D, Greenwood D, et al. Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. Ann Oncol. 2012;23 (6):1394-1402
363 Chen S, Chen Y, Ma S, et al. Dietary fibre intake and risk of breast cancer: a systematic review and meta-analysis of epidemiological studies. Oncotarget. 2016;7 (49):80980
364 Narita S, Inoue M, Saito E, et al. Dietary fiber intake and risk of breast cancer defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective Study. Cancer Causes Control. 2017;28 (6):569-578
365 Emaus MJ, Peeters PH, Bakker MF, et al. Vegetable and fruit consumption and the risk of hormone receptor–defined breast cancer in the EPIC cohort, 2. Am J Clin Nutr. 2016;103 (1):168-177
366 Farvid MS, Chen WY, Michels KB, et al. Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: population based cohort study. BMJ. 2016;353 i2343
367 Steinmetz KA and Potter JD. Vegetables, fruit, and cancer prevention: a review. J Am Diet Assoc. 1996;96 (10):1027-1039
368 World Cancer Research Fund and American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer. Washington, DC, USA, 2010
369 Jung S, Spiegelman D, Baglietto L, et al. Fruit and vegetable intake and risk of breast cancer by hormone receptor status. J Natl Cancer Inst. 2013;105 (3):219-236
370 Fabiani R, Minelli L and Rosignoli P. Apple intake and cancer risk: a systematic review and meta-analysis of observational studies. Public Health Nutr. 2016;19 (14):2603-2617
371 Farvid MS, Chen WY, Rosner BA, et al. Fruit and vegetable consumption and breast cancer incidence: Repeated measures over 30 years of follow-up. Int J Cancer. 2018;[Epub ahead of print]
372 Zhang X, Spiegelman D, Baglietto L, et al. Carotenoid intakes and risk of breast cancer defined by estrogen receptor and progesterone receptor status: a pooled analysis of 18 prospective cohort studies. Am J Clin Nutr. 2012;95 (3):713-25
373 Elliott R. Mechanisms of genomic and non-genomic actions of carotenoids. Biochim Biophys Acta Mol Basis Dis. 2005;1740 (2):147-154
374 Gong X, Smith JR, Swanson HM, et al. Carotenoid lutein selectively inhibits breast cancer cell growth and potentiates the effect of chemotherapeutic agents through ROS-mediated mechanisms. Molecules. 2018;23 (4):
375 Bakker MF, Peeters PH, Klaasen VM, et al. Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort, 2. Am J Clin Nutr. 2016;103 (2):454-464
376 Wang Y, Gapstur SM, Gaudet MM, et al. Plasma carotenoids and breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. Cancer Causes Control. 2015;26 (9):1233-1244

377 Schwingshackl L, Schwedhelm C, Galbete C, et al. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis. Nutrients. 2017;9 (10):1063
378 van den Brandt PA and Schulpen M. Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis. Int J Cancer. 2017;140 (10):2220-2231
379 Bloomfield HE, Koeller E, Greer N, et al. Effects on health outcomes of a Mediterranean diet with no restriction on fat intake: a systematic review and meta-analysis. Ann Intern Med. 2016;165 (7):491-500
380 Toledo E, Salas-Salvadó J, Donat-Vargas C, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. JAMA Intern Med. 2015;175 (11):1752-1760
381 Bilal I, Chowdhury A, Davidson J, et al. Phytoestrogens and prevention of breast cancer: the contentious debate. World J Clin Oncol. 2014;5 (4):705
382 Dagdemir A, Durif J, Ngollo M, et al. Breast cancer: mechanisms involved in action of phytoestrogens and epigenetic changes. In Vivo. 2013;27 (1):1-9
383 Grosso G, Godos J, Lamuela-Raventos R, et al. A comprehensive meta-analysis on dietary flavonoid and lignan intake and cancer risk: level of evidence and limitations. Mol Nutr Food Res. 2017;61 (4):1600930
384 Rietjens I, Louisse J and Beekmann K. The potential health effects of dietary phytoestrogens. Br J Pharmacol. 2017;174 (11):1263-1280
385 Baglia ML, Zheng W, Li H, et al. The association of soy food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. Int J Cancer. 2016;139 (4):742-748
386 Sieri S, Agnoli C, Pala V, et al. Dietary glycemic index, glycemic load, and cancer risk: results from the EPIC-Italy study. Sci Rep. 2017;7 (1):9757
387 Schlesinger S, Chan DSM, Vingeliene S, et al. Carbohydrates, glycemic index, glycemic load, and breast cancer risk: a systematic review and dose–response meta-analysis of prospective studies. Nutr Rev. 2017;75 (6):420-441
388 Makarem N, Bandera EV, Lin Y, et al. Carbohydrate nutrition and risk of adiposity-related cancers: results from the Framingham Offspring cohort (1991–2013). Br J Nutr. 2017;117 (11):1603-1614
389 Sue LY, Schairer C, Ma X, et al. Energy intake and risk of postmenopausal breast cancer: an expanded analysis in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort. Cancer Epidemiol Biomarkers Prev. 2009;1055-9965
390 Hartman TJ, Gapstur SM, Gaudet MM, et al. Dietary energy density and postmenopausal breast cancer incidence in the Cancer Prevention Study II Nutrition Cohort, 2. J Nutr. 2016;146 (10):2045-2050
391 Thomson CA, Crane TE, Garcia DO, et al. Association between dietary energy density and obesity-associated cancer: results from the Women's Health Initiative. J Acad Nutr Diet. 2018;118 (4):617-626
392 Hodge AM, Bassett JK, Milne RL, et al. Consumption of sugar-sweetened and artificially sweetened soft drinks and risk of obesity-related cancers. Public Health Nutr. 2018;21 (9):1618-1626
393 Boyle P, Koechlin A and Autier P. Sweetened carbonated beverage consumption and cancer risk: meta-analysis and review. Eur J Cancer Prev. 2014;23 (5):481-490
394 Khodarahmi M and Azadbakht L. The association between different kinds of fat intake and breast cancer risk in women. Int J Prev Med. 2014;5 (1):6
395 Cao Y, Hou L and Wang W. Dietary total fat and fatty acids intake, serum fatty acids and risk of breast cancer: A meta-analysis of prospective cohort studies. Int J Cancer. 2016;138 (8):1894-1904
396 Chlebowski RT, Aragaki AK, Anderson GL, et al. Low-fat dietary pattern and breast cancer mortality in the Women's Health Initiative randomized controlled trial. J Clin Oncol. 2017;35 (25):2919-2926

397 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Red meat and processed meat. Lyon, France, 2015
398 World Health Organization. Q&A on the carcinogenicity of the consumption of red meat and processed meat. http://www.who.int/features/qa/cancer-red-meat/en/. Accessed: April 2018
399 Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. Lancet Oncol. 2015;16 (16):1599-1600
400 Guo J, Wei W and Zhan L. Red and processed meat intake and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat. 2015;151 (1):191-198
401 Farvid MS, Stern MC, Norat T, et al. Consumption of red and processed meat and breast cancer incidence: A systematic review and meta-analysis of prospective studies. Int J Cancer. 2018;
402 Anderson JJ, Darwis NDM, Mackay DF, et al. Red and processed meat consumption and breast cancer: UK Biobank cohort study and meta-analysis. Eur J Cancer. 2018;90 73-82
403 Diallo A, Deschasaux M, Latino-Martel P, et al. Red and processed meat intake and cancer risk: results from the prospective NutriNet-Santé cohort study. Int J Cancer. 2017;142 (2):230-237
404 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. International Agency for Research on Cancer, Lyon, France, 2004
405 Lee PN and Hamling JS. Environmental tobacco smoke exposure and risk of breast cancer in nonsmoking women. An updated review and meta-analysis. Inhal Toxicol. 2016;28 (10):431-454
406 Macacu A, Autier P, Boniol M, et al. Active and passive smoking and risk of breast cancer: a meta-analysis. Breast Cancer Res Treat. 2015;154 (2):213-224
407 Chen C, Huang YB, Liu XO, et al. Active and passive smoking with breast cancer risk for Chinese females: a systematic review and meta-analysis. Chin J Cancer. 2014;33 (6):306-16
408 Yang Y, Zhang F, Skrip L, et al. Lack of an association between passive smoking and incidence of female breast cancer in non-smokers: evidence from 10 prospective cohort studies. PLoS One. 2013;8 (10):e77029
409 Phillips DH, Martin FL, Grover PL, et al. Toxicological basis for a possible association of breast cancer with smoking and other sources of environmental carcinogens. J Womens Cancer. 2001;3 9-16
410 Thompson PA, DeMarini DM, Kadlubar FF, et al. Evidence for the presence of mutagenic arylamines in human breast milk and DNA adducts in exfoliated breast ductal epithelial cells. Environ Mol Mutagen. 2002;39 (2-3):134-142
411 Chen C, Wang X, Wang L, et al. Effect of environmental tobacco smoke on levels of urinary hormone markers. Environ Health Perspect. 2005;113 (4):412
412 Michnovicz JJ, Hershcopf RJ, Naganuma H, et al. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. N Engl J Med. 1986;315 (21):1305-1309
413 Albanes D, Jones DY, Micozzi MS, et al. Associations between smoking and body weight in the US population: analysis of NHANES II. Am J Public Health. 1987;77 (4):439-444
414 Gaudet MM, Carter BD, Brinton LA, et al. Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies. Int J Epidemiol. 2017;46 (3):881-893
415 Jones ME, Schoemaker MJ, Wright LB, et al. Smoking and risk of breast cancer in the Generations Study cohort. Breast Cancer Res. 2017;19 (1):118
416 World Health Organization. Global recommendations on physical activity for health. GENEVA, 2010

417 Tremblay MS, Aubert S, Barnes JD, et al. Sedentary behavior research network (SBRN)–terminology consensus project process and outcome. Int J Behav Nutr Phys Act. 2017;14 (1):75
418 de Boer MC, Wörner EA, Verlaan D, et al. The mechanisms and effects of physical activity on breast cancer. Clin Breast Cancer. 2017;17 (4):272-278
419 McTiernan A, Tworoger SS, Rajan KB, et al. Effect of exercise on serum androgens in postmenopausal women: a 12-month randomized clinical trial. Cancer Epidemiol Biomarkers Prev. 2004;13 (7):1099-1105
420 Mitsuzono R and Ube M. Effects of endurance training on blood lipid profiles in adolescent female distance runners. Kurume Med J. 2006;53 (1+2):29-35
421 Wu Y, Zhang D and Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat. 2013;137 (3):869-882
422 Neilson HK, Farris MS, Stone CR, et al. Moderate-vigorous recreational physical activity and breast cancer risk, stratified by menopause status: a systematic review and meta-analysis. Menopause. 2017;24 (3):322-344
423 Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ. 2016;354 i3857
424 Pizot C, Boniol M, Mullie P, et al. Physical activity, hormone replacement therapy and breast cancer risk: a meta-analysis of prospective studies. Eur J Cancer. 2016;52 138-154
425 Moore SC, Lee I-M, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med. 2016;176 (6):816-825
426 Johnsson A, Broberg P, Johnsson A, et al. Occupational sedentariness and breast cancer risk. Acta Oncol. 2017;56 (1):75-80
427 Harris HR, Bergkvist L and Wolk A. Adherence to the World Cancer Research Fund/American Institute for Cancer Research recommendations and breast cancer risk. Int J Cancer. 2016;138 (11):2657-2664
428 Hansen J. Night shift work and risk of breast cancer. Curr Environ Health Rep. 2017;4 (3):325-339
429 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Painting, firefighting, and shiftwork. Lyon, France, 2010
430 Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. Lancet Oncol. 2007;8 (12):1065-1066
431 Stevens RG, Blask DE, Brainard GC, et al. Meeting report: the role of environmental lighting and circadian disruption in cancer and other diseases. Environ Health Perspect. 2007;115 (9):1357
432 González-González A, Mediavilla MD and Sánchez-Barceló EJ. Melatonin: a molecule for reducing breast cancer risk. Molecules. 2018;23 (2):336
433 International Agency for Research on Cancer. Internal report 14/002. Report on the Advisory group to Recommend Priorities for IARC monographs during 2015-2019. Lyon, France, 2014
434 Travis RC, Balkwill A, Fensom GK, et al. Night shift work and breast cancer incidence: three prospective studies and meta-analysis of published studies. J Natl Cancer Inst. 2016;108 (12):djw169
435 Lin X, Chen W, Wei F, et al. Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. Sleep Med. 2015;16 (11):1381-1387
436 He C, Anand ST, Ebell MH, et al. Circadian disrupting exposures and breast cancer risk: a meta-analysis. Int Arch Occup Environ Health. 2015;88 (5):533-547
437 Jia Y, Lu Y, Wu K, et al. Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. Cancer Epidemiol. 2013;37 (3):197-206

438 Wang F, Yeung K, Chan W, et al. A meta-analysis on dose–response relationship between night shift work and the risk of breast cancer. Ann Oncol. 2013;24 (11):2724-2732
439 Kamdar BB, Tergas AI, Mateen FJ, et al. Night-shift work and risk of breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013;138 (1):291-301
440 Wegrzyn LR, Tamimi RM, Rosner BA, et al. Rotating night-Shift work and the risk of breast cancer in the nurses' health studies. Am J Epidemiol. 2017;186 (5):532-540
441 James P, Bertrand KA, Hart JE, et al. Outdoor light at night and breast cancer incidence in the Nurses' Health Study II. Environ Health Perspect. 2017;125 (8):087010
442 Coccheri S. Use and misuse of aspirin in primary cardiovascular prevention. Clin Med Insights Cardiol. 2017;11 1179546817702149
443 Thun MJ, Jacobs EJ and Patrono C. The role of aspirin in cancer prevention. Nat Rev Clin Oncol. 2012;9 (5):259-67
444 Bosetti C, Rosato V, Gallus S, et al. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol. 2012;23 (6):1403-1415
445 Harris RE, Casto BC and Harris ZM. Cyclooxygenase-2 and the inflammogenesis of breast cancer. World J Clin Oncol. 2014;5 (4):677
446 U.S. Preventive Services Task Force. Final update summary: aspirin use to prevent cardiovascular disease and colorectal cancer: preventive medication. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer. Accessed: May 2018
447 Cook NR, Lee I-M, Zhang SM, et al. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Ann Intern Med. 2013;159 (2):77-85
448 Luo T, Yan HM, He P, et al. Aspirin use and breast cancer risk: a meta-analysis. Breast Cancer Res Treat. 2012;131 (2):581-7
449 Algra AM and Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol. 2012;13 (5):518-527
450 de Pedro M, Baeza S, Escudero M-T, et al. Effect of COX-2 inhibitors and other non-steroidal inflammatory drugs on breast cancer risk: a meta-analysis. Breast Cancer Res Treat. 2015;149 (2):525-536
451 Zhong S, Chen L, Zhang X, et al. Aspirin use and risk of breast cancer: systematic review and meta-analysis of observational studies. Cancer Epidemiol Biomarkers Prev. 2015;24 (11):1645-55
452 Zhao Y-s, Zhu S, Li X-w, et al. Association between NSAIDs use and breast cancer risk: a systematic review and meta-analysis. Breast Cancer Res Treat. 2009;117 (1):141-150
453 Takkouche B, Regueira-Méndez C and Etminan M. Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis. J Natl Cancer Inst. 2008;100 (20):1439-1447
454 Lu L, Shi L, Zeng J, et al. Aspirin as a potential modality for the chemoprevention of breast cancer: a dose-response meta-analysis of cohort studies from 857,831 participants. Oncotarget. 2017;8 (25):40389
455 Clarke CA, Canchola AJ, Moy LM, et al. Regular and low-dose aspirin, other non-steroidal anti-inflammatory medications and prospective risk of HER2-defined breast cancer: the California Teachers Study. Breast Cancer Res. 2017;19 (1):52
456 Bardia A, Keenan TE, Ebbert JO, et al. Personalizing aspirin use for targeted breast cancer chemoprevention in postmenopausal women. Mayo Clin Proc. 2016;91 (1):71-80
457 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Some drugs and herbal products. Lyon, France, 2016
458 Karasneh RA, Murray LJ and Cardwell CR. Cardiac glycosides and breast cancer risk: a systematic review and meta-analysis of observational studies. Int J Cancer. 2017;140 (5):1035-1041

459 Osman MH, Farrag E, Selim M, et al. Cardiac glycosides use and the risk and mortality of cancer; systematic review and meta-analysis of observational studies. PLoS One. 2017;12 (6):e0178611
460 Zhang C, Xie S-H, Xu B, et al. Digitalis use and the risk of breast cancer: a systematic review and meta-analysis. Drug Saf. 2017;40 (4):285-292
461 Chung M-H, Wang Y-W, Chang Y-L, et al. Risk of cancer in patients with heart failure who use digoxin: a 10-year follow-up study and cell-based verification. Oncotarget. 2017;8 (27):44203
462 Ahern TP, Tamimi RM, Rosner BA, et al. Digoxin use and risk of invasive breast cancer: evidence from the Nurses' Health Study and meta-analysis. Breast Cancer Res Treat. 2014;144 (2):427-435
463 Biggar RJ, Wohlfahrt J, Oudin A, et al. Digoxin use and the risk of breast cancer in women. J Clin Oncol. 2011;29 (16):2165-2170
464 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Human papillomaviruses. Lyon, France, 2007
465 Lawson JS, Glenn WK and Whitaker NJ. Human papilloma viruses and breast cancer–assessment of causality. Front Oncol. 2016;6 207
466 Grulich AE and Vajdic CM. The epidemiology of cancers in human immunodeficiency virus infection and after organ transplantation. Semin Oncol. 2015;42 (2):247-257
467 Lawson JS, Glenn WK, Salyakina D, et al. Human papilloma viruses and breast cancer. Front Oncol. 2015;5 277
468 Bae JM and Kim EH. Human papillomavirus infection and risk of breast cancer: a meta-analysis of case-control studies. Infect Agent Cancer. 2016;11 (1):14
469 Zhou Y, Li J, Ji Y, et al. Inconclusive role of human papillomavirus infection in breast cancer. Infect Agent Cancer. 2015;10 (1):36
470 Simões PW, Medeiros LR, Pires PDS, et al. Prevalence of human papillomavirus in breast cancer: a systematic review. Int J Gynecol Cancer. 2011;22 (3):343-347
471 Li N, Bi X, Zhang Y, et al. Human papillomavirus infection and sporadic breast carcinoma risk: a meta-analysis. Breast Cancer Res Treat. 2011;126 (2):515-520
472 Gannon O, Antonsson A, Bennett I, et al. Viral infections and breast cancer–a current perspective. Cancer Lett. 2018;420 182-189
473 Salman NA, Davies G, Majidy F, et al. Association of high risk human papillomavirus and breast cancer: A UK based Study. Sci Rep. 2017;7 43591
474 Altman D, Yin L and Falconer H. Long term cancer risk after hysterectomy on benign indications: Population based cohort study. Int J Cancer. 2016;138 (11):2631-2638
475 Gaudet MM, Gapstur SM, Sun J, et al. Oophorectomy and hysterectomy and cancer incidence in the Cancer Prevention Study-II Nutrition Cohort. Obstet Gynecol. 2014;123 (6):1247-1255
476 Woolcott CG, Maskarinec G, Pike MC, et al. Breast cancer risk and hysterectomy status: the Multiethnic Cohort study. Cancer Causes Control. 2009;20 (5):539-547
477 Henderson KD, Sullivan-Halley J, Reynolds P, et al. Incomplete pregnancy is not associated with breast cancer risk: the California Teachers Study. Contraception. 2008;77 (6):391-396
478 Guo J, Huang Y, Yang L, et al. Association between abortion and breast cancer: an updated systematic review and meta-analysis based on prospective studies. Cancer Causes Control. 2015;26 (6):811-819
479 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83 000 women with breast cancer from 16 countries. Lancet. 2004;363 (9414):1007-16
480 Michels KB, Xue F, Colditz GA, et al. Induced and spontaneous abortion and incidence of breast cancer among young women: a prospective cohort study. Arch Intern Med. 2007;167 (8):814-820
481 Reeves GK, Kan SW, Key T, et al. Breast cancer risk in relation to abortion: Results from the EPIC study. Int J Cancer. 2006;119 (7):1741-5

482 Brewster DH, Stockton DL, Dobbie R, et al. Risk of breast cancer after miscarriage or induced abortion: a Scottish record linkage case-control study. J Epidemiol Community Health. 2005;59 (4):283-7
483 Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst. 2002;94 (3):182-192
484 Donin N, Filson C, Drakaki A, et al. Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008. Cancer. 2016;122 (19):3075-3086
485 Corkum M, Hayden JA, Kephart G, et al. Screening for new primary cancers in cancer survivors compared to non-cancer controls: a systematic review and meta-analysis. J Cancer Surviv. 2013;7 (3):455-463
486 Lee Y-T, Liu C-J, Hu Y-W, et al. Incidence of second primary malignancies following colorectal cancer: a distinct pattern of occurrence between colon and rectal cancers and association of co-morbidity with second primary malignancies in a population-based cohort of 98,876 patients in Taiwan. Medicine (Baltimore). 2015;94 (26):
487 Guan X, Jin Y, Chen Y, et al. The Incidence characteristics of second primary malignancy after diagnosis of primary colon and rectal cancer: a population based study. PLoS One. 2015;10 (11):e0143067
488 Tabuchi T, Ito Y, Ioka A, et al. Incidence of metachronous second primary cancers in Osaka, Japan: update of analyses using population-based cancer registry data. Cancer Sci. 2012;103 (6):1111-1120
489 Chen S-C, Liu C-J, Hu Y-W, et al. Second primary malignancy risk among patients with gastric cancer: a nationwide population-based study in Taiwan. Gastric Cancer. 2016;19 (2):490-497
490 Morais S, Antunes L, Bento MJ, et al. Risk of second primary cancers among patients with a first primary gastric cancer: a population-based study in North Portugal. Cancer Epidemiol. 2017;50 85-91
491 Ibrahim EM, Abouelkhair KM, Kazkaz GA, et al. Risk of second breast cancer in female Hodgkin's lymphoma survivors: a meta-analysis. BMC Cancer. 2012;12 (1):197
492 Schaapveld M, Aleman BM, van Eggermond AM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med. 2015;373 (26):2499-2511
493 Veit-Rubin N, Rapiti E, Usel M, et al. Risk, characteristics, and prognosis of breast cancer after Hodgkin's lymphoma. Oncologist. 2012;17 (6):783-91
494 Baras N, Dahm S, Haberland J, et al. Subsequent malignancies among long-term survivors of Hodgkin lymphoma and non-Hodgkin lymphoma: a pooled analysis of German cancer registry data (1990–2012). Br J Haematol. 2017;177 (2):226-242
495 Dörffel W, Riepenhausen M, Lüders H, et al. Secondary malignancies following treatment for hodgkin's lymphoma in childhood and adolescence: a cohort study with more than 30 years' follow-up. Dtsch Arztebl Int. 2015;112 (18):320
496 Royle JS, Baade P, Joske D, et al. Risk of second cancer after lymphohematopoietic neoplasm. Int J Cancer. 2011;129 (4):910-919
497 Pirani M, Marcheselli R, Marcheselli L, et al. Risk for second malignancies in non-Hodgkin's lymphoma survivors: a meta-analysis. Ann Oncol. 2011;22 (8):1845-1858
498 Chen S-C, Teng C-J, Hu Y-W, et al. Secondary primary malignancy risk among patients with esophageal cancer in Taiwan: a nationwide population-based study. PLoS One. 2015;10 (1):e0116384
499 Chuang S-C, Hashibe M, Scelo G, et al. Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries. Cancer Epidemiol Biomarkers Prev. 2008;17 (6):1543-1549
500 Levi F, Randimbison L, Blanc-Moya R, et al. Second neoplasms after invasive and borderline ovarian cancer. Eur J Cancer Prev. 2009;18 (3):216-219
501 Spanogle JP, Clarke CA, Aroner S, et al. Risk of second primary malignancies following cutaneous melanoma diagnosis: a population-based study. J Am Acad Dermatol. 2010;62 (5):757-767

502 Levi F, Randimbison L, Te VC, et al. Risk of prostate, breast and colorectal cancer after skin cancer diagnosis. Int J Cancer. 2008;123 (12):2899-2901
503 Lin C-Y, Lin C-L, Huang W-S, et al. Risk of breast cancer in patients with thyroid cancer receiving or not receiving 131I treatment: a nationwide population-based cohort study. J Nucl Med. 2016;57 685-690
504 Cho YY, Lim J, Oh CM, et al. Elevated risks of subsequent primary malignancies in patients with thyroid cancer: A nationwide, population-based study in Korea. Cancer. 2015;121 (2):259-268
505 Kim C, Bi X, Pan D, et al. The risk of second cancers after diagnosis of primary thyroid cancer is elevated in thyroid microcarcinomas. Thyroid. 2013;23 (5):575-582
506 Lu C-H, Lee K-D, Chen P-T, et al. Second primary malignancies following thyroid cancer: a population-based study in Taiwan. Eur J Endocrinol. 2013;EJE-13-0309
507 Balk EM, Earley A, Avendano EA, et al. Long-term health outcomes in women with silicone gel breast implants: a systematic review. Ann Intern Med. 2016;164 (3):164-175
508 Noels EC, Lapid O, Lindeman JH, et al. Breast implants and the risk of breast cancer: a meta-analysis of cohort studies. Aesthet Surg J. 2015;35 (1):55-62
509 Hopper I, Ahern S, McNeil JJ, et al. Improving the safety of breast implants: implant-associated lymphoma. Med J Aust. 2017;207 (5):185-186
510 Therapeutic Goods Administration (TGA). Breast implants and anaplastic large cell lymphoma. https://www.tga.gov.au/node/733565. Accessed: July 2018
511 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Surgical implants and other foreign bodies. Lyon, France, 1999
512 Doren EL, Miranda RN, Selber JC, et al. US epidemiology of breast implant–associated anaplastic large cell lymphoma. Plast Reconstr Surg. 2017;139 (5):1042-1050
513 Leberfinger AN, Behar BJ, Williams NC, et al. Breast implant–associated anaplastic large cell lymphoma: a systematic review. JAMA Surg. 2017;152 (12):1161-1168
514 de Boer M, van Leeuwen FE, Hauptmann M, et al. Breast implants and the risk of anaplastic large-cell lymphoma in the breast. JAMA Oncol. 2018;4 (3):335-341
515 Schliep KC, Mumford SL, Vladutiu CJ, et al. Perceived stress, reproductive hormones, and ovulatory function: a prospective cohort study. Epidemiology. 2015;26 (2):177
516 Dhabhar FS, Saul AN, Daugherty C, et al. Short-term stress enhances cellular immunity and increases early resistance to squamous cell carcinoma. Brain Behav Immun. 2010;24 (1):127-137
517 Lin Y, Wang C, Zhong Y, et al. Striking life events associated with primary breast cancer susceptibility in women: a meta-analysis study. J Exp Clin Cancer Res. 2013;32 (1):53
518 Santos MCL, Horta BL, Amaral JJFd, et al. Association between stress and breast cancer in women: a meta-analysis. Cad Saude Publica. 2009;25 S453-S463
519 Duijts SF, Zeegers MP and Borne BV. The association between stressful life events and breast cancer risk: a meta-analysis. Int J Cancer. 2003;107 (6):1023-1029
520 Schoemaker MJ, Jones ME, Wright LB, et al. Psychological stress, adverse life events and breast cancer incidence: a cohort investigation in 106,000 women in the United Kingdom. Breast Cancer Res. 2016;18 (1):72
521 Sawada T, Nishiyama T, Kikuchi N, et al. The influence of personality and perceived stress on the development of breast cancer: 20-year follow-up of 29,098 Japanese women. Sci Rep. 2016;6 32559
522 Surtees PG, Wainwright NW, Luben RN, et al. No evidence that social stress is associated with breast cancer incidence. Breast Cancer Res Treat. 2010;120 (1):169-174
523 Heikkilä K, Nyberg ST, Theorell T, et al. Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116 000 European men and women. BMJ. 2013;346 f165

524 Van Netten J, Mogentale T, Smith MA, et al. Physical trauma and breast cancer. Lancet. 1994;343 (8903):978-979
525 Kopans D, Van Netten J, Mogentale T, et al. Physical trauma and breast cancer. Lancet. 1994;343 (8909):1364-1365
526 Song CT, Teo I and Song C. Systematic review of seat-belt trauma to the female breast: a new diagnosis and management classification. J Plast Reconstr Aesthet Surg. 2015;68 (3):382-389
527 Rigby J, Morris J, Lavelle J, et al. Can physical trauma cause breast cancer? Eur J Cancer Prev. 2002;11 (3):307-311
528 Gatta G, Di Grezia G, Lieto R, et al. No evidence for an association between trauma and breast carcinoma: A retrospective cohort study. GARJMMS. 2012;1
529 World Health Organization (WHO). Diabetes. Fact Sheet No. 312. http://www.who.int/en/news-room/fact-sheets/detail/diabetes. Accessed: March 2018
530 Boyle P, Boniol M, Koechlin A, et al. Diabetes and breast cancer risk: a meta-analysis. Br J Cancer. 2012;107 (9):1608
531 Ferroni P, Riondino S, Buonomo O, et al. Type 2 diabetes and breast cancer: the interplay between impaired glucose metabolism and oxidant stress. Oxid Med Cell Longev. 2015;2015
532 Xue F and Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am J Clin Nutr. 2007;86 (3):823S-835S
533 La Vecchia C, Giordano SH, Hortobagyi GN, et al. Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle. Oncologist. 2011;16 (6):726-729
534 De Bruijn K, Arends L, Hansen B, et al. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. Br J Surg. 2013;100 (11):1421-1429
535 Hardefeldt PJ, Edirimanne S and Eslick GD. Diabetes increases the risk of breast cancer: a meta-analysis. Endocr Relat Cancer. 2012;ERC-12-0242
536 Liao S, Li J, Wei W, et al. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. Asian Pac J Cancer Prev. 2011;12 (4):1061-5
537 Bowker SL, Richardson K, Marra CA, et al. Risk of breast cancer after onset of type 2 diabetes: evidence of detection bias in postmenopausal women. Diabetes Care. 2011;34 (12):2542-4
538 Gini A, Bidoli E, Zanier L, et al. Cancer among patients with type 2 diabetes mellitus: a population-based cohort study in northeastern Italy. Cancer Epidemiol. 2016;41 80-87
539 Xu H-L, Fang H, Xu W-H, et al. Cancer incidence in patients with type 2 diabetes mellitus: a population-based cohort study in Shanghai. BMC Cancer. 2015;15 (1):852
540 World Health Organization (WHO) & Food and Agriculture Organization of the United Nations (FAO). BISPHENOL A (BPA) - Current state of knowledge and future actions by WHO and FAO. http://www.who.int/foodsafety/publications/fs_management/No_05_Bisphenol_A_Nov09_en.pdf. Accessed: April 2018
541 Del Pup L, Mantovani A, Cavaliere C, et al. Carcinogenetic mechanisms of endocrine disruptors in female cancers (Review). Oncol Rep. 2016;36 (2):603-12
542 Rodgers KM, Udesky JO, Rudel RA, et al. Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. Environ Res. 2018;160 152-182
543 Trabert B, Falk RT, Figueroa JD, et al. Urinary bisphenol A-glucuronide and postmenopausal breast cancer in Poland. Cancer Causes Control. 2014;25 (12):1587-1593
544 Yang M, Ryu J-H, Jeon R, et al. Effects of bisphenol A on breast cancer and its risk factors. Arch Toxicol. 2009;83 (3):281-285

545 Brophy JT, Keith MM, Watterson A, et al. Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: a Canadian case–control study. Environ Health. 2012;11 (1):87
546 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Occupational exposures in insecticide application, and some pesticides. Lyon, France, 1991
547 World Health Organization (WHO). The use of DDT in malaria vector control. http://apps.who.int/iris/handle/10665/69945. Accessed: April 2018
548 International Agency for Research on Cancer (IARC) and World Health Organization (WHO). DDT, lindane and 2,4-D. Volume 113. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC, Lyon, France, 2018
549 Park J-H, Cha ES, Ko Y, et al. Exposure to dichlorodiphenyltrichloroethane and the risk of breast cancer: a systematic review and meta-analysis. Osong Public Health Res Perspect. 2014;5 (2):77-84
550 Loomis D, Guyton K, Grosse Y, et al. Carcinogenicity of lindane, DDT, and 2, 4-dichlorophenoxyacetic acid. Lancet Oncol. 2015;16 (8):891
551 Ingber SZ, Buser MC, Pohl HR, et al. DDT/DDE and breast cancer: A meta-analysis. Regul Toxicol Pharmacol. 2013;67 (3):421-433
552 Adami HO, Lipworth L, Titus-Ernstoff L, et al. Organochlorine compounds and estrogen-related cancers in women. Cancer Causes Control. 1995;6 (6):551-66
553 López-Cervantes M, Torres-Sánchez L, Tobías A, et al. Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence. Environ Health Perspect. 2004;112 (2):207
554 Wilke K, Martin A, Terstegen L, et al. A short history of sweat gland biology. Int J Cosmet Sci. 2007;29 (3):169-179
555 Darbre PD. Recorded quadrant incidence of female breast cancer in Great Britain suggests a disproportionate increase in the upper outer quadrant of the breast. Anticancer Res. 2005;25 (3C):2543-2550
556 Giulivo M, de Alda ML, Capri E, et al. Human exposure to endocrine disrupting compounds: their role in reproductive systems, metabolic syndrome and breast cancer. a review. Environ Res. 2016;151 251-264
557 Golden R, Gandy J and Vollmer G. A review of the endocrine activity of parabens and implications for potential risks to human health. Crit Rev Toxicol. 2005;35 (5):435-458
558 Namer M, Luporsi E, Gligorov J, et al. The use of deodorants/antiperspirants does not constitute a risk factor for breast cancer. Bull Cancer (Paris). 2008;95 (9):871-80
559 Willhite CC, Karyakina NA, Yokel RA, et al. Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts. Crit Rev Toxicol. 2014;44 (sup4):1-80
560 Harvey PW and Darbre P. Endocrine disrupters and human health: could oestrogenic chemicals in body care cosmetics adversely affect breast cancer incidence in women? A review of evidence and call for further research. J Appl Toxicol. 2004;24 (3):167-176
561 Harvey PW. Parabens, oestrogenicity, underarm cosmetics and breast cancer: a perspective on a hypothesis. J Appl Toxicol. 2003;23 (5):285-288
562 Fakri S, Al Azzawi A and Al Tawil N. Antiperspirant use as a risk factor for breast cancer in Iraq. East Mediterr Health J. 2006;12 (3-4):478-82
563 Mirick DK, Davis S and Thomas DB. Antiperspirant use and the risk of breast cancer. J Natl Cancer Inst. 2002;94 (20):1578-1580
564 Hardefeldt PJ, Edirimanne S and Eslick GD. Deodorant use and breast cancer risk. Epidemiology. 2013;24 (1):172
565 Allam MF. Breast cancer and deodorants/antiperspirants: a systematic review. Cent Eur J Public Health. 2016;24 (3):245

566 Linhart C, Talasz H, Morandi EM, et al. Use of underarm cosmetic products in relation to risk of breast cancer: a case-control study. EBioMedicine. 2017;21 79-85
567 Birnbaum LS. The mechanism of dioxin toxicity: relationship to risk assessment. Environ Health Perspect. 1994;102 (Suppl 9):157
568 Kulkarni PS, Crespo JG and Afonso CA. Dioxins sources and current remediation technologies--a review. Environ Int. 2008;34 (1):139-53
569 Fries GF. A review of the significance of animal food products as potential pathways of human exposures to dioxins. J Anim Sci. 1995;73 (6):1639-1650
570 US Environmental Protection Agency (EPA). Exposure and human health reassessment of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. US Environmental Protection Agency, Washington DC, 2000
571 World Health Organization. Dioxins and their effects on human health. http://www.who.int/news-room/fact-sheets/detail/dioxins-and-their-effects-on-human-health. Accessed: July 2018
572 Matthews J and Gustafsson J-Å. Estrogen receptor and aryl hydrocarbon receptor signaling pathways. Nucl Recept Signal. 2006;4
573 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofuran. Lyon, France, 1997
574 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Chemical agents and related occupations. Lyon, France, 2012
575 Bekki K, Vogel H, Li W, et al. The aryl hydrocarbon receptor (AhR) mediates resistance to apoptosis induced in breast cancer cells. Pestic Biochem Physiol. 2015;120 5-13
576 Xu J, Ye Y, Huang F, et al. Association between dioxin and cancer incidence and mortality: a meta-analysis. Sci Rep. 2016;6 38012
577 Warner M, Eskenazi B, Mocarelli P, et al. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. Environ Health Perspect. 2002;110 (7):625-8
578 Reynolds P, Hurley SE, Petreas M, et al. Adipose levels of dioxins and risk of breast cancer. Cancer Causes Control. 2005;16 (5):525-35
579 Viel JF, Clement MC, Hagi M, et al. Dioxin emissions from a municipal solid waste incinerator and risk of invasive breast cancer: a population-based case-control study with GIS-derived exposure. Int J Health Geogr. 2008;7 4
580 Dai D and Oyana TJ. Spatial variations in the incidence of breast cancer and potential risks associated with soil dioxin contamination in Midland, Saginaw, and Bay Counties, Michigan, USA. Environ Health. 2008;7 (1):49
581 Danjou AM, Fervers B, Boutron-Ruault M-C, et al. Estimated dietary dioxin exposure and breast cancer risk among women from the French E3N prospective cohort. Breast Cancer Res. 2015;17 (1):39
582 Grosse Y, Baan R, Straif K, et al. Carcinogenicity of 1, 3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide. Lancet Oncol. 2007;8 (8):679-680
583 Tates A, Grummt T, Törnqvist M, et al. Biological and chemical monitoring of occupational exposure to ethylene oxide. Mutat Res. 1991;250 (1):483-497
584 Boffetta P, van der Hel O, Norppa H, et al. Chromosomal aberrations and cancer risk: results of a cohort study from Central Europe. Am J Epidemiol. 2007;165 (1):36-43
585 Steenland K, Whelan E, Deddens J, et al. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control. 2003;14 (6):531-539
586 Hagmar L, Welinder H, Lindén K, et al. An epidemiological study of cancer risk among workers exposed to ethylene oxide using hemoglobin adducts to validate environmental exposure assessments. Int Arch Occup Environ Health. 1991;63 (4):271-277
587 Norman SA, Berlin JA, Soper KA, et al. Cancer incidence in a group of workers potentially exposed to ethylene oxide. Int J Epidemiol. 1995;24 (2):276-284

588 Mikoczy Z, Tinnerberg H, Björk J, et al. Cancer incidence and mortality in Swedish Sterilant workers exposed to ethylene oxide: updated cohort study findings 1972–2006. Int J Environ Res Public Health. 2011;8 (6):2009-2019
589 Benedetti M, Zona A, Beccaloni E, et al. Incidence of Breast, Prostate, Testicular, and Thyroid Cancer in Italian Contaminated Sites with Presence of Substances with Endocrine Disrupting Properties. Int J Environ Res Public Health. 2017;14 (4):355
590 Pirastu R, Comba P, Iavarone I, et al. Environment and health in contaminated sites: the case of Taranto, Italy. J Environ Public Health. 2013;2013
591 Guajardo OA and Oyana TJ. A critical assessment of geographic clusters of breast and lung cancer incidences among residents living near the Tittabawassee and Saginaw Rivers, Michigan, USA. J Environ Public Health. 2009;2009
592 Pesatori AC, Consonni D, Rubagotti M, et al. Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up. Environ Health. 2009;8 (1):39
593 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Outdoor air pollution. Lyon, France, 2015
594 Goldberg MS, Labrèche F, Weichenthal S, et al. The association between the incidence of postmenopausal breast cancer and concentrations at street-level of nitrogen dioxide and ultrafine particles. Environ Res. 2017;158 7-15
595 Hart JE, Bertrand KA, DuPre N, et al. Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. Environ Health. 2018;17 (1):28
596 Keramatinia A, Hassanipour S, Nazarzadeh M, et al. Correlation between nitrogen dioxide as an air pollution indicator and breast cancer: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2016;17 (1):419-24
597 Andersen ZJ, Ravnskjœr L, Andersen KK, et al. Long-term exposure to fine particulate matter and breast cancer incidence in the Danish Nurse Cohort Study. Cancer Epidemiol Biomarkers Prev. 2016;26 (3):428-430
598 Shmuel S, White AJ and Sandler DP. Residential exposure to vehicular traffic-related air pollution during childhood and breast cancer risk. Environ Res. 2017;159 257-263
599 Reding KW, Young MT, Szpiro AA, et al. Breast cancer risk in relation to ambient air pollution exposure at residences in the Sister Study Cohort. Cancer Epidemiol Biomarkers Prev. 2015;24 (12):1907-9
600 Hart JE, Bertrand KA, DuPre N, et al. Long-term particulate matter exposures during adulthood and risk of breast cancer incidence in the Nurses' Health Study II Prospective Cohort. Cancer Epidemiol Biomarkers Prev. 2016;cebp. 0246.2016
601 Garcia E, Hurley S, Nelson DO, et al. Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. Environ Health. 2015;14 (1):14
602 Xue X, Xue J, Liu W, et al. Trophic magnification of parabens and their metabolites in a subtropical marine food web. Environ Sci Technol. 2017;51 (2):780-789
603 Towers CV, Terry PD, Lewis D, et al. Transplacental passage of antimicrobial paraben preservatives. J Expo Sci Environ Epidemiol. 2015;25 (6):604
604 Barr L, Metaxas G, Harbach C, et al. Measurement of paraben concentrations in human breast tissue at serial locations across the breast from axilla to sternum. J Appl Toxicol. 2012;32 (3):219-232
605 Darbre P, Aljarrah A, Miller W, et al. Concentrations of parabens in human breast tumours. J Appl Toxicol. 2004;24 (1):5-13
606 Pugazhendhi D, Pope G and Darbre P. Oestrogenic activity of p-hydroxybenzoic acid (common metabolite of paraben esters) and methylparaben in human breast cancer cell lines. J Appl Toxicol. 2005;25 (4):301-309
607 Darbre PD and Harvey PW. Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. J Appl Toxicol. 2008;28 (5):561-578
608 Reeves KW, Diaz SM, Hankinson SE, et al. Phthalate metabolites and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2018;27 (3):355

609 Lopez-Carrillo L, Hernandez-Ramirez RU, Calafat AM, et al. Exposure to phthalates and breast cancer risk in northern Mexico. Environ Health Perspect. 2010;118 (4):539-44
610 Holmes AK, Koller KR, Kieszak SM, et al. Case-control study of breast cancer and exposure to synthetic environmental chemicals among Alaska Native women. Int J Circumpolar Health. 2014;73 25760
611 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Polychlorinated biphenyls and Polybrominated biphenyls Lyon, France, 2016
612 Zhang J, Huang Y, Wang X, et al. Environmental polychlorinated biphenyl exposure and breast cancer risk: a meta-analysis of observational studies. PLoS One. 2015;10 (11):e0142513
613 World Cancer Research Fund and American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Breast Cancer. London, UK, 2017
614 Leng L, Li J, Luo X-m, et al. Polychlorinated biphenyls and breast cancer: A congener-specific meta-analysis. Environ Int. 2016;88 133-141
615 Donat-Vargas C, Åkesson A, Berglund M, et al. Dietary exposure to polychlorinated biphenyls and risk of breast, endometrial and ovarian cancer in a prospective cohort. Br J Cancer. 2016;115 (9):1113
616 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Some aromatic amines, organic dyes, and related exposures. Lyon, France, 2010
617 Johansson GM, Jönsson BAG, Axmon A, et al. Exposure of hairdressers to ortho- and meta-toluidine in hair dyes. Occup Environ Med. 2015;72 (1):57
618 Takkouche B, Regueira-Méndez C and Montes-Martínez A. Risk of cancer among hairdressers and related workers: a meta-analysis. Int J Epidemiol. 2009;38 (6):1512-1531
619 Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer–follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48 (5):646-790
620 Ekenga CC, Parks CG and Sandler DP. Chemical exposures in the workplace and breast cancer risk: a prospective cohort study. Int J Cancer. 2015;137 (7):1765-1774
621 Rosenberg L, Boggs DA, Adams-Campbell LL, et al. Hair relaxers not associated with breast cancer risk: evidence from the black women's health study. Cancer Epidemiol Biomarkers Prev. 2007;16 (5):1035-1037
622 Takkouche B, Etminan M and Montes-Martínez A. Personal use of hair dyes and risk of cancer: a meta-analysis. JAMA. 2005;293 (20):2516-2525
623 Gera R, Mokbel R, Igor I, et al. Does the use of hair dyes increase the risk of developing breast cancer? a meta-analysis and review of the literature. Anticancer Res. 2018;38 (2):707-716
624 Mendelsohn JB, Li Q-Z, Ji B-T, et al. Personal use of hair dye and cancer risk in a prospective cohort of Chinese women. Cancer Sci. 2009;100 (6):1088-1091
625 Brinton LA, Figueroa JD, Ansong D, et al. Skin lighteners and hair relaxers as risk factors for breast cancer: results from the Ghana breast health study. Carcinogenesis. 2018;39 (4):571-579
626 Llanos AAM, Rabkin A, Bandera EV, et al. Hair product use and breast cancer risk among African American and White women. Carcinogenesis. 2017;38 (9):883-892
627 Zamanian A and Hardiman C. Electromagnetic radiation and human health: A review of sources and effects. HFE. 2005;4 (3):16-26
628 McColl N, Auvinen A, Kesminiene A, et al. European Code against Cancer 4th Edition: ionising and non-ionising radiation and cancer. Cancer Epidemiol. 2015;39 S93-S100
629 Australian Radiation Protection and Nuclear Safety Agency (ARPANSA). Extremely low frequency electric and magnetic fields. www.arpansa.gov.au/understanding-radiation/what-is-radiation/non-ionising-radiation/low-frequency-electric-magnetic-fields. Accessed: October 2018

630 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Non-ionizing radiation: static and extremely low-frequency (ELF) electric and magnetic fields. World Health Organization, Lyon, France, 2002
631 Zhang Y, Lai J, Ruan G, et al. Meta-analysis of extremely low frequency electromagnetic fields and cancer risk: a pooled analysis of epidemiologic studies. Environ Int. 2016;88 36-43
632 Zhao G, Lin X, Zhou M, et al. Relationship between exposure to extremely low-frequency electromagnetic fields and breast cancer risk: a meta-analysis. Eur J Gynaecol Oncol. 2014;35 (3):264-269
633 Chen Q, Lang L, Wu W, et al. A meta-analysis on the relationship between exposure to ELF-EMFs and the risk of female breast cancer. PLoS One. 2013;8 (7):e69272
634 Chen C, Ma X, Zhong M, et al. Extremely low-frequency electromagnetic fields exposure and female breast cancer risk: a meta-analysis based on 24,338 cases and 60,628 controls. Breast Cancer Res Treat. 2010;123 (2):569-576
635 Koeman T, Van Den Brandt PA, Slottje P, et al. Occupational extremely low-frequency magnetic field exposure and selected cancer outcomes in a prospective Dutch cohort. Cancer Causes Control. 2014;25 (2):203-214
636 Li W, Ray RM, Thomas DB, et al. Occupational exposure to magnetic fields and breast cancer among women textile workers in Shanghai, China. Am J Epidemiol. 2013;178 (7):1038-1045
637 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Non-ionizing radiation, Part 2: Radiofrequency electromagnetic fields. Lyon, France, 2013
638 National Cancer Institute (NCI). Radiation. https://www.cancer.gov/about-cancer/causes-prevention/risk/radiation. Accessed: October 2018
639 Baan R, Grosse Y, Lauby-Secretan B, et al. Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol. 2011;12 (7):624-626
640 Schüz J, Jacobsen R, Olsen JH, et al. Cellular telephone use and cancer risk: update of a nationwide Danish cohort. J Natl Cancer Inst. 2006;98 (23):1707-1713
641 Benson VS, Pirie K, Schuz J, et al. Mobile phone use and risk of brain neoplasms and other cancers: prospective study. Int J Epidemiol. 2013;42 (3):792-802
642 Hallberg Ö. Cancer incidence vs. FM radio transmitter density. Electromagn Biol Med. 2016;35 (4):343-347
643 Davis S, Mirick DK and Stevens RG. Residential magnetic fields and the risk of breast cancer. Am J Epidemiol. 2002;155 (5):446-454
644 Grajewski B, Waters MA, Yong LC, et al. Airline pilot cosmic radiation and circadian disruption exposure assessment from logbooks and company records. Ann Occup Hyg. 2011;55 (5):465-475
645 Zeeb H, Hammer GP and Blettner M. Epidemiological investigations of aircrew: an occupational group with low-level cosmic radiation exposure. J Radiol Prot. 2012;32 (1):N15-9
646 Liu T, Zhang C and Liu C. The incidence of breast cancer among female flight attendants: an updated meta-analysis. J Travel Med. 2016;23 (6):taw055
647 Tokumaru O, Haruki K, Bacal K, et al. Incidence of cancer among female flight attendants: a meta-analysis. J Travel Med. 2006;13 (3):127-132
648 Buja A, Mastrangelo G, Perissinotto E, et al. Cancer incidence among female flight attendants: a meta-analysis of published data. J Womens Health. 2006;15 (1):98-105
649 Rafnsson V. The incidence of breast cancer among female flight attendants: an updated meta-analysis. J Travel Med. 2017;24 (5):
650 Pinkerton LE, Hein MJ, Anderson JL, et al. Breast cancer incidence among female flight attendants: exposure–response analyses. Scand J Work Environ Health. 2016;42 (6):538-546
651 Schubauer-Berigan MK, Anderson JL, Hein MJ, et al. Breast cancer incidence in a cohort of US flight attendants. Am J Ind Med. 2015;58 (3):252-266

652 Pukkala E, Helminen M, Haldorsen T, et al. Cancer incidence among Nordic airline cabin crew. Int J Cancer. 2012;131 (12):2886-2897
653 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization and International Agency for Research on Cancer. Radiation. Lyon, France, 2012
654 Holick MF. Vitamin D and sunlight: strategies for cancer prevention and other health benefits. Clin J Am Soc Nephrol. 2008;3 (5):1548-54
655 Van der Rhee H, de Vries E and Coebergh JW. Regular sun exposure benefits health. Med Hypotheses. 2016;97 34-37
656 Welsh J. Vitamin D and breast cancer: insights from animal models. Am J Clin Nutr. 2004;80 (6):1721S-1724S
657 Freedman DM, Dosemeci M and McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. Occup Environ Med. 2002;59 (4):257-62
658 John EM, Schwartz GG, Dreon DM, et al. Vitamin D and breast cancer risk: the NHANES I epidemiologic follow-up study, 1971–1975 to 1992. Cancer Epidemiol Biomarkers Prev. 1999;8 (5):399-406
659 Zamoiski RD, Freedman DM, Linet MS, et al. Prospective study of ultraviolet radiation exposure and risk of breast cancer in the United States. Environ Res. 2016;151 419-427
660 Lin SW, Wheeler DC, Park Y, et al. Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. Int J Cancer. 2012;131 (6):E1015-E1023
661 Yang L, Veierød MB, Löf M, et al. Prospective study of UV exposure and cancer incidence among Swedish women. Cancer Epidemiol Biomarkers Prev. 2011;
662 Estébanez N, Gómez-Acebo I, Palazuelos C, et al. Vitamin D exposure and Risk of Breast Cancer: a meta-analysis. Sci Rep. 2018;8 (1):9039
663 Gandini S, Boniol M, Haukka J, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer. 2011;128 (6):1414-1424
664 Friis S, Kesminiene A, Espina C, et al. European Code against Cancer 4th Edition: medical exposures, including hormone therapy, and cancer. Cancer Epidemiol. 2015;39 S107-S119
665 Ronckers CM, Doody MM, Lonstein JE, et al. Multiple diagnostic X-rays for spine deformities and risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 2008;17 (3):605-613
666 Australian Radiation Protection and Nuclear Safety Agency (ARPANSA). Fact Sheet - Ionising Radiation and Health. Australian Government. https://www.arpansa.gov.au/sites/g/files/net3086/f/legacy/pubs/factsheets/IonisingRadiationandHealth.pdf. Accessed: November 2018
667 Abdullah KA, McEntee MF, Reed W, et al. Radiation dose and diagnostic image quality associated with iterative reconstruction in coronary CT angiography: A systematic review. J Med Imaging Radiat Oncol. 2016;60 (4):459-68
668 den Harder AM, Willemink MJ, de Ruiter QM, et al. Achievable dose reduction using iterative reconstruction for chest computed tomography: A systematic review. Eur J Radiol. 2015;84 (11):2307-13
669 Brenner AV, Preston DL, Sakata R, et al. Incidence of Breast Cancer in the Life Span Study of Atomic Bomb Survivors: 1958-2009. Radiat Res. 2018;190 (4):433-444
670 Obdeijn IM, Heijnsdijk EA, Hunink MG, et al. Mammographic screening in BRCA1 mutation carriers postponed until age 40: Evaluation of benefits, costs and radiation risks using models. Eur J Cancer. 2016;63 135-42
671 Berrington de Gonzalez A, Gilbert E, Curtis R, et al. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. Int J Radiat Oncol Biol Phys. 2013;86 (2):224-33
672 Phillips WT and Blumhardt R. Radiation-Induced Breast Cancer. Ann Intern Med. 2016;165 (6):451-452

673 Mathews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013;346 f2360
674 Preston DL, Cullings H, Suyama A, et al. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. J Natl Cancer Inst. 2008;100 (6):428-36
675 Miglioretti DL, Lange J, van den Broek JJ, et al. Radiation-Induced Breast Cancer Incidence and Mortality From Digital Mammography Screening: A Modeling Study. Ann Intern Med. 2016;164 (4):205-14
676 Berrington de Gonzalez A, Curtis RE, Kry SF, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol. 2011;12 (4):353-60
677 Nelson HD, Fu R, Cantor A, et al. Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med. 2016;164 (4):244-55
678 Morrell S, Taylor R, Roder D, et al. Mammography screening and breast cancer mortality in Australia: an aggregate cohort study. J Med Screen. 2012;19 (1):26-34
679 Morrell S, Taylor R, Roder D, et al. Mammography service screening and breast cancer mortality in New Zealand: a National Cohort Study 1999-2011. Br J Cancer. 2017;116 (6):828-839
680 Pijpe A, Andrieu N, Easton DF, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). BMJ. 2012;6 (345):
681 Colin C, Foray N, Di Leo G, et al. Radiation induced breast cancer risk in BRCA mutation carriers from low-dose radiological exposures: a systematic review. Radioprotection. 2017;52 (4):231-240
682 Pauwels EK, Foray N and Bourguignon MH. Breast Cancer Induced by X-Ray Mammography Screening? A Review Based on Recent Understanding of Low-Dose Radiobiology. Med Princ Pract. 2016;25 (2):101-9
683 Doi K, Mieno MN, Shimada Y, et al. Methodological extensions of meta-analysis with excess relative risk estimates: application to risk of second malignant neoplasms among childhood cancer survivors treated with radiotherapy. J Radiat Res (Tokyo). 2014;55 (5):885-901
684 Wakeford R. The cancer epidemiology of radiation. Oncogene. 2004;23 (38):6404
685 De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. J Clin Oncol. 2009;27 (26):4239-46
686 Elkin EB, Klem ML, Gonzales AM, et al. Characteristics and outcomes of breast cancer in women with and without a history of radiation for Hodgkin's lymphoma: a multi-institutional, matched cohort study. J Clin Oncol. 2011;29 (18):2466-2473
687 Moskowitz CS, Chou JF, Wolden SL, et al. Breast cancer after chest radiation therapy for childhood cancer. J Clin Oncol. 2014;32 (21):2217
688 Cancer Australia. Position Statement – Lifestyle risk factors and the primary prevention of cancer. https://canceraustralia.gov.au/publications-and-resources/position-statements/lifestyle-risk-factors-and-primary-prevention-cancer. Accessed: August 2018
689 Morton LM, Sampson JN, Armstrong GT, et al. Genome-Wide Association Study to Identify Susceptibility Loci That Modify Radiation-Related Risk for Breast Cancer After Childhood Cancer. J Natl Cancer Inst. 2017;109 (11):
690 Sud A, Thomsen H, Sundquist K, et al. Risk of second cancer in Hodgkin lymphoma survivors and influence of family history. J Clin Oncol. 2017;35 (14):1584-1590
691 Cooke R, Jones M, Cunningham D, et al. Breast cancer risk following Hodgkin lymphoma radiotherapy in relation to menstrual and reproductive factors. Br J Cancer. 2013;108 (11):2399

692 Teepen JC, van Leeuwen FE, Tissing WJ, et al. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER Study cohort: role of chemotherapy. J Clin Oncol. 2017;35 (20):2288-2298
693 Adams MJ, Dozier A, Shore RE, et al. Breast cancer risk 55+ years after irradiation for an enlarged thymus and its implications for early childhood medical irradiation today. Cancer Epidemiol Biomarkers Prev. 2010;19 (1):48-58
694 Moskowitz CS, Chou JF, Sklar CA, et al. Radiation-associated breast cancer and gonadal hormone exposure: a report from the Childhood Cancer Survivor Study. Br J Cancer. 2017;117 (2):290
695 Moskowitz CS, Malhotra J, Chou JF, et al. Breast cancer following spinal irradiation for a childhood cancer: A report from the Childhood Cancer Survivor Study. Radiother Oncol. 2015;117 (2):213-216
696 Inskip PD, Robison LL, Stovall M, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol. 2009;27 (24):3901-7
697 Ahn HY, Min HS, Yeo Y, et al. Radioactive iodine therapy did not significantly increase the incidence and recurrence of subsequent breast cancer. J Clin Endocrinol Metab. 2015;100 (9):3486-3493
698 Sawka AM, Thabane L, Parlea L, et al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid. 2009;19 (5):451-457
699 Zhang Y, Liang J, Li H, et al. Risk of second primary breast cancer after radioactive iodine treatment in thyroid cancer: a systematic review and meta-analysis. Nucl Med Commun. 2016;37 (2):110-115
700 International Agency for Research on Cancer/World Health Organisation. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Preamble. Lyon, France, 2015
701 Cairns B, Reeves G, Yang T, et al. OP25 Having been breastfed as an infant and risk of cancer in adult women: cohort study. J Epidemiol Community Health. 2014;68 (Suppl 1):A15-A15
702 Elshof LE, Schaapveld M, Rutgers EJ, et al. The method of detection of ductal carcinoma in situ has no therapeutic implications: results of a population-based cohort study. Breast Cancer Res. 2017;19 (1):26
703 Rakovitch E, Nofech-Mozes S, Hanna W, et al. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. Breast Cancer Res Treat. 2015;152 (2):389-398
704 Rakovitch E, Nofech-Mozes S, Narod SA, et al. Can we select individuals with low risk ductal carcinoma in situ (DCIS)? A population-based outcomes analysis. Breast Cancer Res Treat. 2013;138 (2):581-590
705 Chen Z, Shao J, Gao X, et al. Effect of passive smoking on female breast cancer in China: a meta-analysis. Asia Pac J Public Health. 2015;27 (2):NP58-NP64
706 Gaudet MM, Gapstur SM, Sun J, et al. Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst. 2013;105 (8):515-25
707 Cook NR, Lee I, Gaziano J, et al. Low-dose aspirin in the primary prevention of cancer: The women's health study: a randomized controlled trial. JAMA. 2005;294 (1):47-55
708 Warner M, Mocarelli P, Samuels S, et al. Dioxin exposure and cancer risk in the Seveso Women's Health Study. Environ Health Perspect. 2011;119 (12):1700
709 Bruin MLD, Sparidans J, Veer MBvt, et al. Breast Cancer Risk in Female Survivors of Hodgkin's Lymphoma: Lower Risk After Smaller Radiation Volumes. J Clin Oncol. 2009;27 (26):4239-4246