Smoking and mortality in women diagnosed with breast cancer— a systematic review with meta-analysis based on 400,944 breast cancer cases

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Background: It is evident that smoking is causing disease and increased mortality in general. Recently published data are now suggesting that smoking might increase both the overall mortality in women diagnosed with breast cancer but also increase their risk of dying from their breast cancer.

Methods: A systematic review and meta-analysis on smoking status in women diagnosed with breast cancer, their mortality rate and cause of death. Based on all cohort studies published within the last ten years.

Results: Twelve studies met our inclusion criteria, and 400,944 women diagnosed with primary invasive breast cancer was included. Hazard ratio (HR) for breast cancer associated death in former smokers was 1.02 (0.93, 1.12) and for current smokers 1.28 (1.17, 1.41) when compared to never smokers. For all-cause death, the HR for former smokers was 1.12 (1.04, 1.19), and for current smokers 1.52 (1.32, 1.76) when compared to never smokers.

Conclusions: This large systematic review and meta-analysis found a 28% increase in breast cancer-associated mortality in those who were current smokers compared to never smokers. The mortality in former smokers was equal to the one found in never smokers. This indicates that breast cancer patients ceasing to smoke can lower their risk of dying from their breast cancer disease dramatically, and possibly regain the risk of a never smoker.

Keywords: Breast cancer; smoking cessation; mortality; disease-specific mortality

Introduction

Although improved prognosis, breast cancer is responsible for 540,000 deaths worldwide each year (1). Essential in reducing and fighting these deaths is the identification of the modifiable factors influencing incidence and mortality of breast cancer. Identifying these, could permit intervention, and help reduce breast cancer-related deaths. One possible modifiable factor is smoking.

The mortality among current smokers is 2 to 3 times as high as that among persons that have never smoked.

In the US alone, smoking is responsible for more than 480,000 deaths each year (2,3). As 18% of American adults are estimated to be current smokers it is safe to assume that there is a substantial portion of women diagnosed with breast cancer that are current smokers or that have previously smoked (2).

When advising our patient with newly diagnosed breast cancer on their smoking habits we advise against it on the basis of the increase in surgery related complications and mortality seen in the general population. Recent studies

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of breast cancer survivors find that a surprisingly low number of breast cancer patients quit or reduce smoking after diagnosis. Between zero to thirty percent change their smoking habits after diagnosis (4-6). This is low compared to other diseases. Lung cancer is highly associated with smoking and smoking cessation after diagnosis has been reported in around 40–87% of patients (7,8).

Little is known about the specific biological effect of smoking on breast cancer. Tobacco contains over 4,000 potentially harmful substances, with the most studied being nicotine. An increasing amount of published research is now indicating that tobacco smoke can facilitate tumor growth, angiogenesis, chemoresistance, and survival by regulating diverse signaling pathways (9,10). Biopsies made on lung cancer patients have shown that the smoke-specific chemical compounds, promotes progression of lung cancer via DNA alterations and modification of various protein expressions (11). A meta-analysis published in the British Medical Journal found a tendency of smoking after lung cancer diagnosis decreasing prognosis of death from all causes (12). Regarding breast cancer, there are some studies indicating that smoking among breast cancer patients is associated with several negative prognostic factors such as increased number of, and larger lymph node metastasis at diagnosis, and increased risk of metastases to lungs after diagnosis (13,14)

Vital, in order to motivate smoking cessation, is the investigation on the possible correlation between smoking and its effect on the nature and mortality of the disease. If present, this would be a powerful additional argument for smoking cessation.

This systematic review and meta-analysis aggregates previously published data from cohort studies in order to identify if there exists an excess mortality from breast cancer due to persistent smoking among breast cancer patients.

Methods

This systematic review and meta-analysis was conducted using the well-recognized methodology and reported in accordance with the PRISMA statement (15).

Eligibility criteria

Only cohort studies reporting on mortality among breast cancer patients with information on smoking as an exposure were included in the analysis.

Study selection and collection process

A computerized search was performed using MEDLINE, EMBASE, Cochrane Library and Cinahl. The last search was performed on the 27.07.2016. Reference lists of identified studies and previously published reviews were also explored. The search was limited to publication during the last 10 years and publications in the English language. The author MS searched the databases assisted by a research librarian. The search was performed using the terms; smoking, breast cancer/breast neoplasm, mortality/survival and cohorts studies. Variation of these terms was used depending on what database was being searched. All searches included MESH terms as well as a free words search. Search strategies for each individual database can be found in Supplementary file, appendix. Both authors reviewed the 146 identified articles by title and summary and the appropriate 49 were read in full to determine inclusion. Any disagreements between the reviewers were resolved by consensus and 12 articles were found to fulfill the inclusion criteria.

Risk of bias in individual studies

To determine the risk of bias in the individual studies both authors evaluated the included articles on the risk of selection bias, recall bias, information bias, misclassification bias, as well their assessment of exposure, outcome, follow-up time and the adjustments made. Each outcome was deemed "low risk of bias", "intermediate risk of bias" or "high risk of bias". "Low risk of bias" was given to those articles who were thoroughly discussing their article in relation to the specific bias. "Intermediate risk of bias" was given to those who were not specifically stating how the bias affected their results, but where we as readers had to evaluate this. "High risk of bias" was given to the articles where we did not feel an evaluation of the bias could be made sufficiently (*Figure S1*).

Synthesis of results

We categorized deaths into "all-cause death" and "breast cancer-related death". Patients were subcategorized depending on their current smoking status; never smoker, former smoker or current smoker. In all articles, never smokers were used as the baseline and the unit of outcome was hazard ratio (HR). Not all included articles had information on both all-cause and breast cancer-related death. Therefore, analysis on the different subcategories
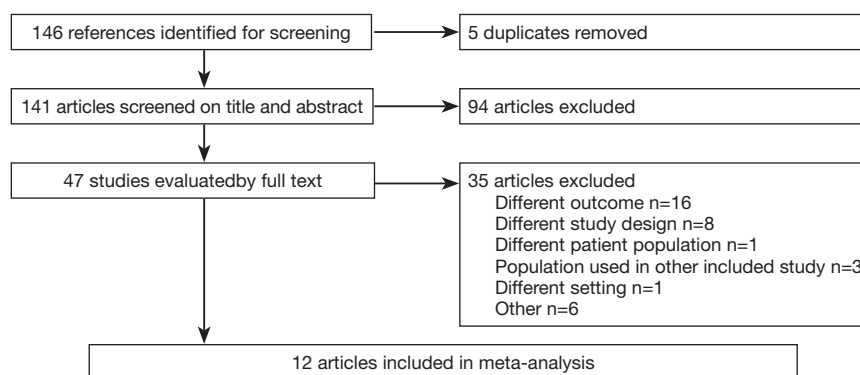
Figure 1 PRISMA—flowchart illustrating the selection of articles.

were based on between eight and eleven studies, even though the systematic review included twelve articles (*Table S1*). Regarding the article by Pierce *et al.*, former smoking was stratified into three groups depending on the number of pack years (py) smoked. No data on former smoking was therefore included in the meta-analysis.

HRs and confidence intervals (CIs) for all studies were collected and used to calculate the log(HR) and standard error (SE). The meta-analysis applied the random-effects model as we assumed that there had been some clinical heterogeneity. This resulted in studies being treated as random samples, with the assumption that the true effect varied between studies. Statistical heterogeneity was examined as between-study variation and quantified with the I^2 value calculated by RevMan. The I^2 measures the proportion of variation in the included studies. A value of 0% indicates no inconsistency between the results and a value of 100% indicates maximal inconsistency. A Tau^2 value was also calculated. The Tau^2 estimates the between-study variance and in general, a value >1 suggests a substantial statistical heterogeneity. The estimated Chi^2 is also an indicator for possible heterogeneity, where a Chi^2 larger than the degrees of freedom indicates heterogeneity. The associated p-value has a point of significance of 0.1.

The systematic review was performed using the Covidence software. The meta-analysis was performed using the Review Manager program (RevMan). Both developed and supported by the Nordic Cochrane Centre (16,17)

Results

Study selection

The database search provided 146 citations. After removal

of duplicates 141 were screened on title and abstract. Forty-seven articles were retrieved and read in full. Twelve articles were included in the final analysis (*Figure 1*).

Study characteristics

Characteristics of the included studies can be found in *Table S1*. Four of the included studies originated from the USA, two from Denmark and the remaining six from; Norway, Japan, Germany, Canada, United Kingdom and a European/American-cohort. Data originated from a large period of time 1974–2008 and included a total of 400,944 women diagnosed with breast cancer.

The median or mean age of the women included in the studies ranged from 44 to 67 years. Assessment of smoking status was, in 10 studies, based on questionnaires, filled out by the patients themselves. Bérubé *et al.* performed interviews and Seibold *et al.* combined these to determine correct status (18,19). Assessment of smoking status was, in six studies, performed at the time of breast cancer diagnosis and up to 24 months later (18,20-24). Four studies ascertained the information at the time of enrolment in the cohort, before breast cancer diagnosis (25-28) and the remaining two studies gathered data on smoking retrospectively, after the time of diagnosis (19,29). Smoking status was defined by information given by the patients in the questionnaires. Only Seibold *et al.* and Passarelli *et al.* had a minimum number of cigarettes that had to have been smoked in order to classify a patient as a smoker. In these articles >100 cigarettes smoked was the cut-off point of whether someone would classify as a smoker (19,24). The term former smoker was in all articles given to patients stating to have smoked in the past, but that was currently not smoking. The number of breast cancer patients
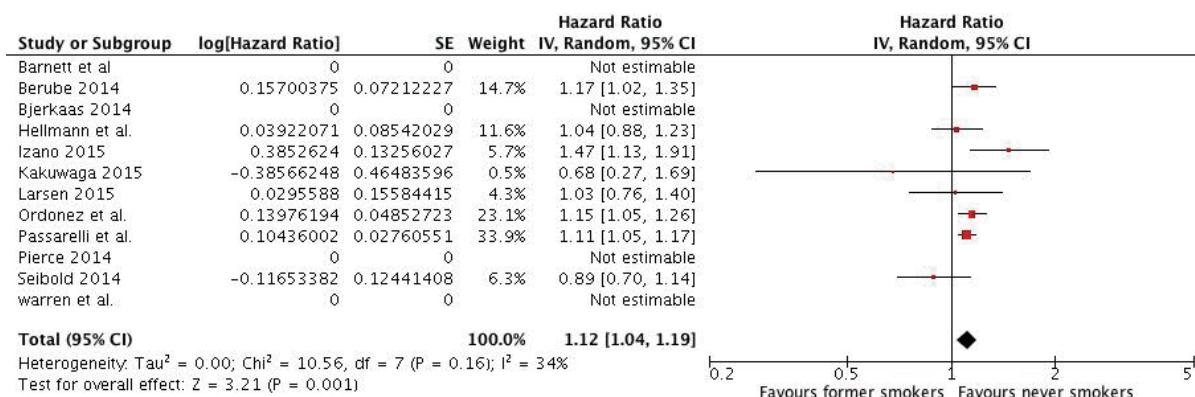
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Figure 2 Results and forest plot of the individual studies depicting all-cause mortality in former smokers compared to never smokers.

included in the cohorts ranged from a total of 528 in the smaller Danish study by Hellmann *et al.* to 350 918 breast cancer patients in the large European/American-cohort by Ordóñez-Mena *et al.* (25,26). The median in follow-up ranged from 6.0 years to 14.0 years.

Risk of bias within studies

Assessment of risk of bias within studies is shown in *Table S2* and *Figure S1*, appendix. In general, the studies did well when reporting on these issues.

Results of the individual studies

Characteristics and results of the individual studies can be seen in *Table S1*.

All-cause death
Ten articles reported HRs for all-cause deaths in former smokers (18-25,27,29). Four found a statistically significant increase in mortality with HRs ranging from 1.11–1.47 (18,21,23,24).

   Ten articles reported HRs for all-cause deaths in current smokers (18-25,27,29). Eight found a significant increase in mortality with HRs ranging from 1.16–2.45 (18,19,21-25,27).

Breast cancer-associated death
Nine articles reported HRs for breast cancer associated deaths in former smokers (18-22,24-26,28). Ordóñez-Mena *et al.* was the only one finding a statistically significant increase in mortality, HR 1.15 (1.50, 1.27) (26).

Pierce *et al.*, who stratified their group of former smokers into subgroups depending on pack-years (py) smoked found a statistically significant increase among those who had smoked >35 py (22).

   Ten articles reported HRs for breast cancer associated deaths in current smokers (18-26,28). Five detected a statistically significant increase in mortality with HRs ranging from 1.15–1.73 (22-24,26,28).

Synthesis of results

All-cause death
Our meta-analysis found HRs of all-cause death of 1.12 (1.04, 1.19) and 1.52 (1.32, 1.76) among former and current smokers, respectively, when compared to never smokers. (*Figures 2,3*)

Breast cancer-associated death
The corresponding results for the meta-analysis of breast cancer associated deaths were HRs of 1.02 (0.93, 1.12) and 1.28 (1.17, 1.42), when former smokers and current smokers, respectively, were compared to never smokers (*Figures 4,5*).

Discussion

This systematic review and meta-analysis found a significant increase in both all-cause and breast associated mortality in women diagnosed with breast cancer who were current smokers when they were compared to never smokers. Where former smokers were found to have an increase in all-cause mortality, no increase was found in breast-cancer associated death.
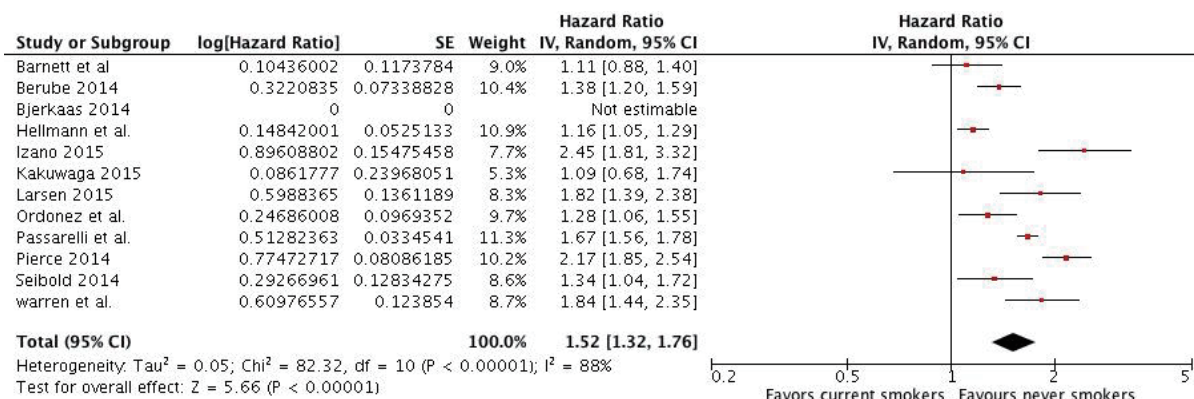
Figure 3 Results and forest plot of the individual studies depicting all-cause mortality in current smokers compared to never smokers.
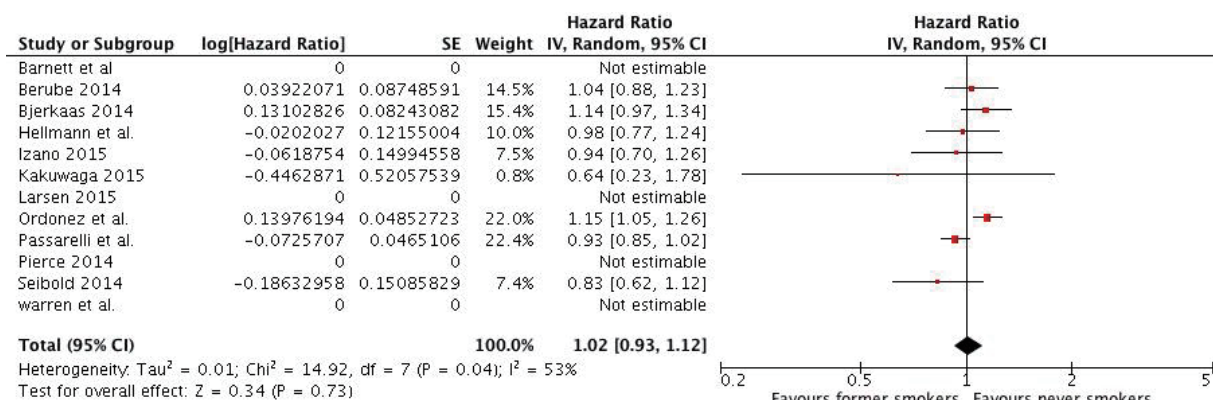

Figure 4 Results and forest plot of the individual studies depicting breast cancer-associated mortality in former smokers compared to never smokers.

Adjustment for confounders

The populations in our included articles all consist of women diagnosed with invasive breast cancer. When comparing these articles, it is vital that they have made adjustments for risk factors known to modify breast cancer risk, in order to reduce possible confounders. An article in the database UpToDate summarizes these factors. Among the most important are age, race/ethnicity, weight, increased estrogen exposure/age at menarche and menopause (30). Most articles have also adjusted for tumor size, lymph node status, histological grade and other variables important for cancer staging, all influencing survival of breast cancer. All articles presented comprehensive lists of their adjustments and 11 articles adjusted for all of the above-mentioned covariates. All adjustments made can be seen in *Table S1*. Regarding weight/BMI, the article by Larsen *et al.* chose

to look at BMI as an independent exposure (27). Larsen *et al.* had a broad focus, focusing on metabolic indicators, smoking, alcohol and socioeconomic position, rather than smoking alone. Bjerkaas *et al.* did not perform an adjustment on staging, but as our focus is breast cancer as a whole, this should not affect our results (28). Barnett *et al.* did not perform any adjustments to their statistics. They were simply investigating the impact of each individual lifestyle factor (29). Still, we regard all the articles as fulfilling our inclusion criteria. The different adjustments made in the individual articles is a source of uncertainty and this has been taken into consideration when concluding on our results. A great limitation of our study is the lack of follow-up information on our patients. There are many factors influencing breast cancer survival among these; therapies received after diagnosis, concurrent alcohol use and dietary factors to name a few. Information on these factors would
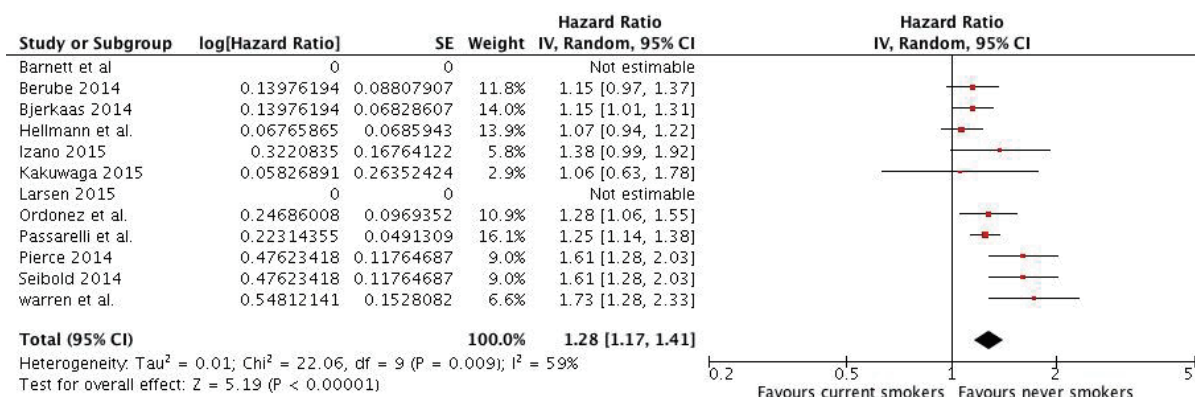
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Figure 5 Results and forest plot of the individual studies depicting breast cancer-associated mortality in current smokers compared to never smokers.

without a doubt, have strengthened our results and would have allowed us to conclude beyond smoking status at time of diagnosis.

Assessment of smoking status

Underreporting of smoking

The questionnaires used in the different studies have not been published and therefore we cannot conclude on how uniform they were in content. Bjerkaas *et al.* included data from three different cohorts resulting in three different questionnaires (28). This is also the case in the large cohort study by Ordóñez-Mena *et al.* (26). When investigating smoking habits by questionnaire there is a substantial risk of underreporting. A large review by Gorber *et al.* investigated 54 published studies on the accuracy of self-reported smoking and found that in most cases patients underestimated their smoking. In 41 out of 54 studies underreporting was observed ranging from a few per cent to forty-six per cent (31). In most of the studies included in our analysis, the questionnaire was filled out by the patient's themselves. The effect of possible underreporting should, however, be equally present in most of the included articles. Seibold *et al.* conducted interviews to fill out these forms and their patient's answers might be more uniform, and possibly more accurate, than the self-reported ones (19).

Classification of exposure variable: time of assessment of smoking status

Six of the included studies ascertained smoking status within a period of two years after breast cancer diagnosis (18,20-24). Four studies gathered status before breast

cancer diagnosis (25-28), while the remaining two studies gathered data on smoking after the time of diagnosis (19,29). A risk of misclassification is present in all studies as patients might change smoking habits after breast cancer diagnosis. None of the included studies have adjusted for this in their analysis. Seibold *et al.* did, however, investigate potential changes in smoking habits by making a follow-up phone call a few years after diagnosis (19). This showed that about one-third did not change their smoking habits, nearly 40% stopped and one-quarter smoked less than before breast cancer diagnosis. Only 1% smoked more. Sprague *et al.* observed the same tendency in their study, where women were 35% less likely to be smokers in the years after breast cancer diagnosis compared to 1 year prior to being diagnosed (32). This indicates that there is a real possibility that the group called current smokers in our studies, might be a very diverse group consisting of a large portion of patients that may have seized or at least reduced their smoking substantially. This would imply that the true HR is larger than the estimated HR for current smokers.

Classification of exposure variable: definition of smoking status

The three categories of smoking status in the included population were determined by self-reported patient data. Having the patients themselves report smoking status is an uncertainty in our analysis, as there is a possibility of patients falsely categorizing themselves as one or the other. Most of the included articles did not specify exactly what defines "a smoker". Only two of the articles specifies this, with a cut-off point between "a smoker" and "non-smoker" of a total of >100 cigarettes smoked (19,24). In

the other studies, there is therefore potentially a group of smokers having smoked a small amount of cigarettes but still defining themselves as smokers. One hundred cigarettes is, however, a relatively small amount, and the group of people having smoked below this number and categorized themselves as smokers should not significantly affect our results. Regarding the issue of self-reporting and the accuracy of these reports the main limitation today is that there is no clinical test to accurately quantify the amount of cigarettes previously smoked. To accurately determine whether a former smoker and a no smoker, is not using tobacco, the use of blood samples for serum-nicotine is an option. The pragmatic approach of patients self-reporting is arguably better as this is the situation we meet in daily clinical life.

Passive smoking as a confounder

In daily life, passive smoking is a big contributor to the total smoking exposure, especially when living with a smoking spouse. We have not been able to identify any studies on passive smoking and mortality from breast cancer. Only one of the included articles in our review, by Kakugawa *et al.*, investigated passive smoking in their population and adjusted for this in their analysis (20). Passive smoking could have affected our results as both an underestimation or overestimation of a patient's exposure to tobacco smoke could have taken place.

Classification of the outcome: mortality

All articles, except two, split mortality into the two groups; all-cause mortality and breast cancer-associated mortality. All of the included articles used the International Classification of Diseases (ICD-9/10) published by the World Health Organization. Uniformity across the included studies regarding this outcome classification resulted in very comparable results. However, different quality of outcome assessments was used. The majority relied solely on death certificates. Seibold *et al.* validated the death certificates by revising medical records to further secure correct cause of death (19). Bérubé *et al.* primarily used death certificates, but relied on family and relatives to fill out missing records, a possible source of error (18). Johansson *et al.* investigated the validity of death certificates and found that, regarding malignant neoplasms, there was generally an agreement between death certificates, hospital records, and cause of death (33). They also concluded that caution had to be taken with increasing periods of time since last discharge from the hospital. This due to the fact that deaths outside

of hospital wards were often registered by a physician other than the ones that had taken part in their primary care. This could also affect the accuracy of cause of deaths in our included studies.

Duplicate cases

Two studies consisted of data from different cohorts within the same geographical area, and with an overlap in time. Duplicates could, therefore, be present (22,28). Bjerkaas *et al.* screened for this and stated that when a patient was included in more than one cohort, only the first entry was used in their statistics (28). Pierce *et al.* did not specify whether or not duplicates were actively screened for, but as they obtained written consent from all included patients prior to sending them their questionnaires, this should not have been a problem (22). Even though a few duplicate cases exist, it would probably not be associated with neither the exposure nor the outcome variable and a possible bias due to duplicates is unlikely.

Statistical heterogeneity

When looking at heterogeneity between our studies the I^2 value calculated when doing the meta-analysis, ranged between 34–88%. The highest I^2 of 88% might indicate substantial inconsistency, between the groups included in our study. The calculated Tau^2 ranged from 0.00–0.05, not suggesting a substantial variation. The Chi^2 for all meta-analysis are also indicating heterogeneity. As there is evidence of possible heterogeneity across studies, extra care should be taken when concluding on our results.

Risk of bias between studies

Looking at *Table S2* and *Figure S1*, illustrating bias between our studies, there is a strong trend of low bias in all articles. This is, in our opinion, one of the strongest aspects of our article. Together with the, over 400,000 breast cancer cases included, this is the biggest and most comprehensive meta-analysis performed on this subject.

The importance of smoking cessation

From a clinical perspective, it is important to know what information to pass on to our patient. Previous smoking is not a factor possible to alteration, but future smoking is. Will cessation of smoking at the time of diagnosis improve chances of survival? As our article only investigates current, former and never smoking, this is not an easy question to answer. When looking at our included studies it is evident that current smoking increases mortality drastically.

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The trend regarding former smoking is that it increases mortality, but not to the same extent as current smoking. When looking at all-cause mortality, former smokers are still statistically significant at a higher risk of dying compared to never smokers. This increase in mortality was not observed when looking at former smoking and breast cancer associated death. There is, however, a probability that the effect seen is not limited to a patient's own smoking, but that other sources of smoke, such as passive smoking, could affect mortality. A recommendation of total smoke-abstinence may, therefore, be the best way of eliminating the effects of smoking on mortality.

Conclusions

The present systematic review and meta-analysis found that current smoking is associated with an increase in breast cancer-related mortality of 28%. No increase was observed in those who were former smokers. Smoking was associated with an increase in all-cause mortality for all patients. This study, therefore, supports previously published evidence of smoking increasing cancer-related mortality, and that seizing to smoke could reduce the risk of dying from breast cancer. Our findings provide good arguments for clinicians when advising on smoking cessation.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Search 1—Search strategies

Search date 27.07.16

Search strategy, MEDLINE, 28.07.16

((((("smoking"[MeSH Terms] OR "smoking"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]) AND "cohort studies"[MeSH Terms]) AND "last 10 years"[PDat]) AND ("last 10 years"[PDat])

Results 104 hits

Search strategy, EMBASE, 28.07.16

1. Exp cohort analysis/
2. Limit 1 to (English language and last 10 years)
3. *Smoking habit/ or *adolescent smoking/ or *smoking/ or *smoking cessation/
4. Exp breast cancer/ or exp breast tumor/ or exp breast dysplasia/ or exp breast carcinoma/
5. 1 and 2 and 3 and 4

Results 44

Search strategy, CINAHL

(MH "Prospective Studies+") AND (MH "Breast Neoplasms+") AND "breast cancer AND smoking AND mortality AND cohort studies" AND (MH "Mortality+") AND (MH "Smoking+")

Results 0

Search strategy, COCHRANE LIBRARY

ID SearchHits
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#2 Smoking 19,027
#3 MeSH descriptor: [Cohort Studies] explode all trees 126,470
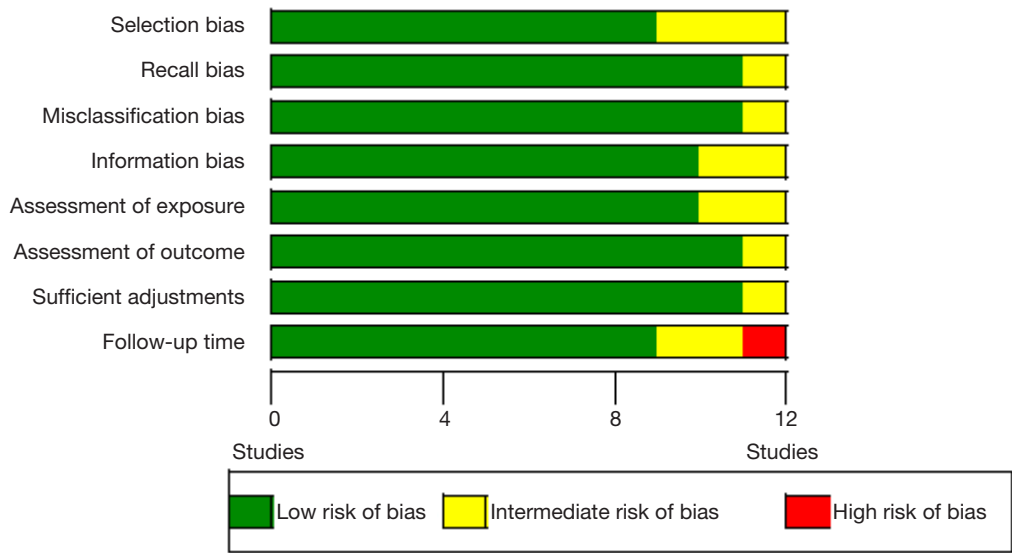#4 MeSH descriptor: [Mortality] explode all trees 12,384

Results 0

Figure S1 Figure illustrating the total evaluation of risk of bias in our included articles. Risk of bias was categorized as either; low risk of bias, intermediate risk of bias or high risk of bias.

Table S1 Characteristics and results of the included articles

Year	First author	Country	Population	Years	Assessment of smoking	Median follow-up time, years	No. Of breast cancer cases	Smoking and death due to breast cancer HR (95% CI)	Smoking and all-cause death HR (95% CI)	Adjustment	Age (mean/ median)
2015	Izano et al.	USA	1,011 women ages 40–84 from the Health and Functioning in Women study with newly diagnosed primary invasive breast cancer. Median age at study initiation was 63,494 women were never smokers, 286 were former smokers and 195 were current smokers	1984–1988	Questionnaire	11.0	975	Never: 1, Former: 0.94 (0.7–1.26), Current: 1.38 (0.99–1.91)	Never: 1, Former: 1.47 (1.13–1.90)*, Current: 2.45 (1.81–3.32)*	Breast cancer treatment, race/ethnicity, BMI, financial adequacy, education, positive lymph node involvement, tumor size at diagnosis, comorbidity, period of study entry, pack-years, age	63
2014	Bjerkaas et al.	NO	302,865 women from The Norwegian Counties Study, Cohort of Norway, the 40 Years Study with newly diagnosed primary invasive breast cancer. Median age at study initiation was 44,459 women were never smokers, 216 were former smokers and 431 were current smokers	1974–2003	Questionnaire	14.0	1,106‡	Never: 1, Former: 1.14 (0.97–1.34), Current: 1.15 (1.01–1.32)*		Age, education level, number of children, age at first childbirth, BMI, Age at enrollment, physical activity	44
2015	Larsen et al.	DK	29,875 women ages 50–64 participating in the cohort study; Diet, Cancer and Health. Of these 1,229 developed breast cancer. 452 women were never smokers, 346 were former smokers and 278 were current smokers. 151 were unspecified	1993–1997	Questionnaire	9.6	1,229		Never: 1, Former: 1.03 (0.76–1.40) ,Current: 1.82 (1.39–2.37)*	Age, Tumor size, lymph node status, no, of positive lymph nodes, malignancy grade, estrogen receptor status, Charlson Comorbidity Index	64.3
2015	Kakuwaga et al.	JP	848 women with newly diagnosed breast cancer at the Miyagi Cancer Center. Median age at study initiation was 57,690 women were never smokers, 40 were former smokers and 118 was current smokers	1997–2007	Questionnaire	6.7	848	Never: 1, Former: 0.64 (0.23–1.77), Current: 1.06 (0.63–1.77)	Never: 1, Former: 0.68 (0.27–1.67), Current: 1.09 (0.68–1.74)	Age, BMI, stage, hormone receptor status, radiation therapy, chemotherapy, endocrine therapy, family history, physical activity, comorbidities, menopausal status, passive smoking for spouse	56.9
2014	Seibold et al.	DE	12,857 women ages 50–74 from a German two-centre case control study "MARIE". Of these 3,340 developed breast cancer. 1,756 women were never smokers, 920 were former smokers and 664 was current smokers	2001–2005	Interview and questionnaire	6.0	3,340	Never: 1, Former: 0.83 (0.62–1.12), Current: 1.16 (0.86–1.56)	Never: 1, Former: 0.89 (0.70–1.14), Current: 1.34 (1.04–1.72)*	Age at diagnosis, study region, tumor size, nodal status, metastasis status, histological grading, joint estrogen/ progesterone status, mode of detection, radiotherapy, adult BMI, hormone replacement use at diagnosis, alcohol consumption, CVD, diabetes	50.9-63.5
2014	Bérubé et al.	CA	5,892 women diagnosed with primary breast cancer and treated at Centre des maladies du seine Deschenes-Fabia. Mean age at study initiation was 57. 3,510 women were never smokers, 1,303 were former smokers and 1,079 was current smokers	1987–2008	Interview	7.0	5,892	Never: 1, Former: 1.04 (0.88–1.24), Current: 1.15 (0.97–1.37)	Never: 1, Former: 1.17 (1.01–1.34)*, Current: 1.38 (1.20–1.60)*	Age at diagnosis, year of diagnosis, age at menarche, menopausal status, current hormone replacement therapy use, first degree family history of breast cancer, estrogen and progesterone receptor status, histological grade, size og tumor, regional or distant involvement, locoregional treatment, neoadjuvant therapy, adjuvant endocrine therapy, adjuvant chemotherapy	57.4
2014	Pierce et al.	USA	9,975 women from three US Cohorts; Womens Healthy Eating and Living, Life After Cancer Epidemiology and the Nurses' Health Study. 4,812 women were never smokers, 4,439 were former smokers and 710 were current smokers. 14 were unspecified	1976–2006	Questionnaire	11.1	9,975	Never: 1, Former: <20 py: 0.99 (0.85–1.15), 20–34 py 1.14 (0.91–1.43), >35 py 1.54 (1.28–2.03)*, Current: 1.61 (1.28–2.03)*	Never: 1, Former: <20 py: 0.97 (0.86–1.09), 20–34 py 1.26 (1.07–1.48)*, >35 py 1.68 (1.44–1.96), *Current: 2.17 (1.85–2.54)*	Age at diagnosis, cancer stage, tumor grade, race/ethnicity, education, obesity	59.2
2010	Hellmann et al.	DK	528 women from the Copenhagen City Heart Study. 146 were never smokers, 121 were former smokers and 261 were current smokers	1976–2003	Questionnaire	7.8	528	Never: 1, Former: 0.98 (0.77–1.24), Current: 1.07 (0.94–1.23)	Never: 1, Former: 1.04 (0.88–1.23), Current: 1.16 (1.05–1.29)*	Alcohol, smoking, physical activity, HRT, age, disease stage, menopausal status, parity, education, adjuvant treatment	66.9
2008	Barnett et al.	UK	4,560 women diagnosed with invasive breast cancer from the population-based SEARCH-study (Studies of Epidemiology and Risk Factors in Cancer Heredity. 2,318 were never smokers, 1,206 were former smokers and 902 were current smokers	1991–2005	Questionnaire	6.8	4,560		Never: 1, Former: 1.01 (0.83–1.23), Current: 1.11 (0.89–1.41)	No adjustments	51.4
2013	Warren et al.	USA	882 women diagnosed with breast cancer in the Roswell Park Cancer Institute Cohort. 480 were never smokers, 220 were former smokers and 143 were current smokers	1982–1998	Questionnaire	12.0†	882	Never: 1, Current: 1.73 (1.28–2.33)*	Never: 1, Current: 1.84 (1.44–2.34)*	Disease site, sex, age, race, date of diagnosis, BMI and pack-years	55.7
2016	Passarelli et al.	USA	20,619 women from the Collaborative Breast Cancer and Womens Longevity Study, diagnosed with breast cancer. 10,399 were never smokers, 6,233 were former smokers and 4,059 were classified as recent smokers	1988–2008	Questionnaire	12.0	20,691	Never: 1, Former: 0.93 (0.85–1.02), Recent: 1.25 (1.13–1.37)*	Never: 1, Former: 1.11 (1.05–1.17)*, Recent: 1.67 (1.57–1.79)*	Age, study phase, state of residence, education, BMI, parous status, age at first birth, menopausal status, HRT, mammography history, alcohol, family history	58
2016	Ordonez et al.	EUR/US	CHANCES consortium; COSM (Cohort of Swedish Men), EPIC-elderly (European Prospective Investigation into Cancer and Nutrition), ESTHER (Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankunden in der älteren Bevölkerung), HAPIEE (Health, Alcohol and Psychosocial factors in Eastern Europe) MORGAM (Monica Risk, Genetics, Archiving and Monograph) NIH-AARP (National Institute og Health - American Association og Retires Persons) RS (Rotterdam Study) SENECA (Survey in Europe on Nutrition and the Elderly, a Concerned Action, SMC (Swedish Mammography Cohort), TROMSØ, VIP (Västerbotten Intervention Programme)	1982–2008	Questionnaire	12.0	350,918	Never: 1, Former: 1.15 (1.05–1.27)*, Current: 1.28 (1.06–1.55)*		Sex, age, BMI, education, vigorous physical activity, history of diabetes, alcohol	60

*, statistically significant; †, minimum; ‡, number of breast cancer deaths. HR, hazard ratio; CI, confidence interval.

Table S2 Table illustrating the result of the evaluation of bias in our included articles. Risk of bias was categorized as either; low risk of bias, intermediate risk of bias or high risk of bias

First Author	Selection bias	Recall bias	Misclassification bias	Information bias	Assessment of exposure	Assessment of outcome	Sufficient adjustments	Follow-up time	Free from others bias
Izano *et al.*	+	+	+	+	+	+	+	+	+
Bjerkaas *et al.*	+	+	+	+	+	+	+	−	+
Larsen *et al.*	+	+	+	+	+	+	+	+	+
Kakuwaga *et al.*	+	+	O	+	+	O	+	+	+
Seibold *et al.*	O	+	+	+	+	+	+	O	+
Bérubé *et al.*	+	+	+	+	+	+	+	O	+
Pierce *et al.*	O	+	+	+	+	+	+	+	+
Hellmann *et al.*	+	+	+	+	+	+	+	+	+
Barnett *et al.*	+	+	+	O	O	+	O	+	+
Warren *et al.*	O	+	+	+	+	+	+	+	+
Passarelli *et al.*	+	+	+	O	+	+	+	+	+
Ordonez *et al.*	+	O	+	+	O	+	+	+	+

+, low risk; O, unclear risk of bias; −, high risk of bias.