

MANAGEMENT OF WOMEN AT HIGH FAMILIAL RISK FOR BREAST AND OVARIAN CANCER

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Abstract

Women with a strong family history of breast and/or ovarian cancer have a greatly increased risk for the development of these diseases. The key question for these women is what they can do to ameliorate their cancer risk. Fortunately, there are now several interventions which clearly reduce breast and ovarian cancer risk in high-risk women. These include risk-reducing bilateral mastectomy and salpingo oophorectomy and chemoprevention with tamoxifen or raloxifene. For those women who do not undergo risk-reducing bilateral mastectomy, screening is generally recommended in order to try and detect breast cancers at an early stage. Breast magnetic resonance imaging has an emerging role in such screening programs. Cancer screening does not reduce cancer risk and its impact on reduction of mortality in this group is uncertain. Women at high risk should be fully informed of their surgical, chemopreventive and screening options. A risk management plan should be tailored to each woman, particularly taking into account the level of her short-term (rather than life-time) risk, her lifestyle plans (such as child-bearing), competing risks (particularly in women with a prior cancer) and her personal preferences. The risk management plan should be reviewed regularly and altered as the individual's short-term risk level and circumstances change, and as the evidence base for various interventions builds. Participation in appropriate clinical trials should be offered.

Who is at high risk for breast/ovarian cancer?

Breast cancer and ovarian cancer are diagnosed in about 12,000 and 1100 Australian women per year respectively.¹ Between 1% and 5% of all breast cancer cases and around 10% of invasive epithelial ovarian cancer cases are due to the inheritance of mutations in known cancer predisposition genes.^{2,3}

In less than 1% of the population, the number of blood relatives affected with cancer, their ages at diagnosis and the types of cancers suggest a high likelihood of a dominantly-inherited mutation in a breast cancer and/or ovarian cancer-predisposition gene (see Table 1).

Referral of such women to a family cancer centre for formal risk assessment, consideration of genetic testing and discussion of management options is considered by many to be a standard of care.

BRCA1 and BRCA2 are the genes most commonly associated with breast and ovarian cancer predisposition. Carriers of mutations in these genes have a significantly elevated lifetime risk of breast cancer or ovarian cancer.^{4,5} Several other genes are also associated with an increased risk of breast and/or ovarian malignancy (see Table 2).

Families meeting high risk criteria (see Table 1), but in whom a mutation cannot be found, are still considered at high risk because genetic testing is not 100% sensitive, and because there may be a mutation in an as yet unidentified cancer predisposition gene.

What are the risk management options for high-risk women?

Management of women with a strong family history and/or a documented gene mutation is complex and

dynamic. Optimal risk management is likely to be in the context of a multidisciplinary team. Multidisciplinary risk management clinics have been set up at several family cancer centres within Australia.⁶ Figures 1 and 2 outline the options with respect to risk management strategies currently available.

Risk-reducing surgery

An individual's level of risk should be fully clarified prior to undertaking risk-reducing surgery. If possible, genetic testing of a family member with cancer should occur. If a mutation is found, the woman contemplating surgery should be tested for that mutation. In that way, unnecessary surgery in women who have not inherited the cancer causing family mutation can be avoided.

Bilateral risk-reducing mastectomy

Bilateral risk-reducing mastectomy (BRRM) is the most effective method of breast cancer prevention, reducing risk by about 90%.⁷⁻¹⁰ It is usually done in conjunction with immediate reconstruction. Total mastectomy is likely to reduce risk more than subcutaneous mastectomy, however the latter is a reasonable option for women wishing to retain the native nipple and areola complex,¹¹ provided they are informed that the benefits may be slightly less. BRRM carries the risk of surgical complications;¹² additionally cosmetic complications following reconstruction may occur.¹³

In descriptive studies women who have undergone BRRM report lessened concern about cancer and decreased perceived cancer risk,¹⁴⁻¹⁶ but also dissatisfaction with reconstruction,¹⁷ feelings of femininity and sexual relationships.^{14,18} Because BRRM can have adverse psychological and body image consequences, it should not be performed without prior counselling.

Table 1: Risk of breast or ovarian cancer based on family history alone^{113,114}

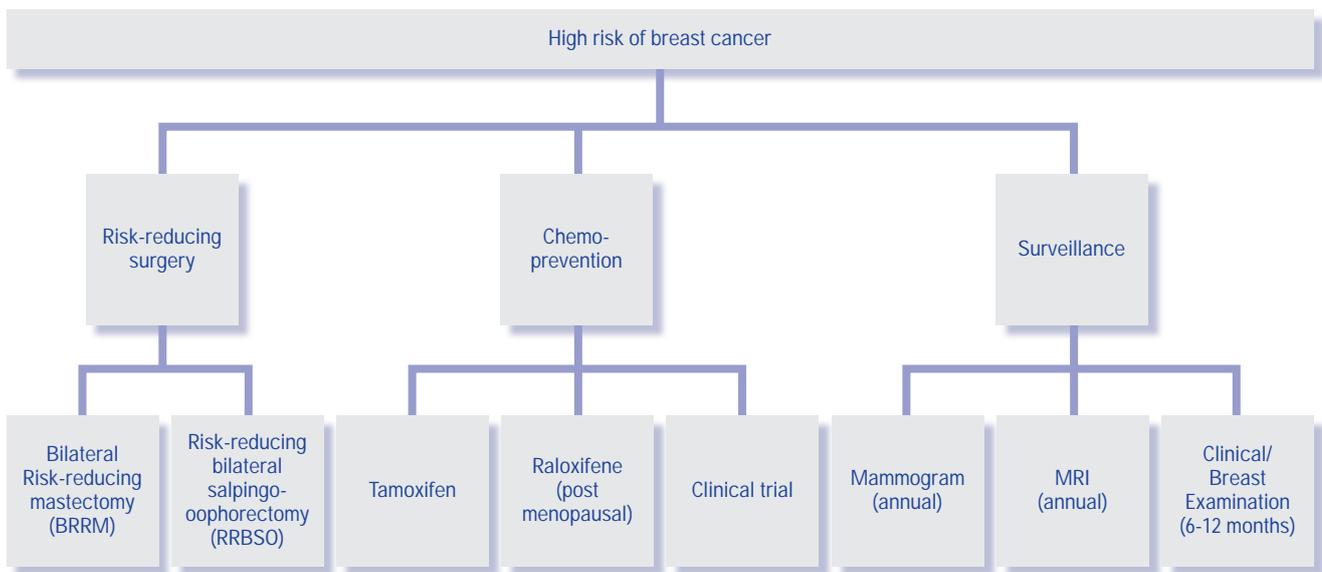
Cancer type	Features	Lifetime risk	% of population
Breast cancer	<p>Two 1st or 2nd degree relatives (same side of family) with breast or ovarian cancer.</p> <p>plus one or more of:</p> <ul style="list-style-type: none"> ■ additional relative(s) with breast or ovarian cancer ■ onset of breast cancer before the age of 40 ■ bilateral breast cancer ■ breast and ovarian cancer in the same woman ■ Ashkenazi Jewish ancestry ■ breast cancer in a male relative <p>or</p> <p>One 1st or 2nd degree relative diagnosed with breast cancer ≤45yo, plus another 1st or 2nd degree relative (same side of family) with sarcoma (bone or soft tissue) ≤45yo</p>	25-50**%	<1%
Ovarian cancer	<p>One 1st degree relative diagnosed with epithelial ovarian cancer in a family of Ashkenazi Jewish ancestry.</p> <p>Two 1st or 2nd degree relatives (same side of the family) diagnosed with ovarian cancer, especially if ≥1 of the following:</p> <ul style="list-style-type: none"> ■ additional relative(s) with breast or ovarian cancer ■ onset of breast cancer before the age of 40 ■ bilateral breast cancer ■ breast and ovarian cancer in the same woman ■ breast cancer in a male relative <p>Three or more 1st or 2nd degree relatives on the same side of the family diagnosed with any cancers associated with HNPCC*:</p> <ul style="list-style-type: none"> ■ colorectal cancer (especially if <50y) ■ endometrial cancer ■ ovarian cancer ■ gastric cancer ■ cancers involving the renal tract 	3-30**	<1%

*HNPCC = hereditary non-polyposis colorectal cancer
 ** higher if woman documented to carry a mutation in a breast and ovarian cancer predisposition gene.

Table 2: High risk genes, frequency and increased risks of breast and ovarian cancer^{115,116}

Gene	Syndrome	Breast cancer risk by age 70yo	Ovarian cancer risk by age 70yo	Associated cancers
BRCA1	Hereditary breast/ovarian cancer	39-87%	20-40%	Pancreas
BRCA2	Hereditary breast/ovarian cancer	26-91%	10-20%	Prostate Pancreas
p53	Li-Fraumeni Syndrome	>90%	n/a	Soft tissue sarcoma Osteosarcoma Brain tumours Adrenocortical carcinoma Leukaemia Colon
PTEN	Cowden Syndrome	25-50%	~1%	Thyroid Endometrial Genitourinary
STK11/LKB1	Peutz-Jeghers Syndrome	45-54%	(usually sex cord tumors rather than epithelial ovarian cancer)	Small intestine Colorectal Uterine Testicular
CDH1	Hereditary diffuse gastric carcinoma	39% (lobular)	n/a	Diffuse gastric cancer
MLH1, MSH2, MSH6, PMS1, PMS2 (mismatch repair)	Hereditary non-polyposis colorectal cancer/ Lynch syndrome	n/a	10%	Small intestine Colorectal Stomach Uterus Ureter/renal pelvis

Figure 1. Breast cancer: risk reduction and surveillance strategies



In Australia, uptake rates for BRRM have been relatively low by international standards.¹⁹ In high-risk women attending family cancer clinics, (90% of whom were not known mutation carriers), the uptake rate over a three-year follow-up period was 4.4%. Those who underwent the procedure were more likely to have more first degree relatives with breast cancer than those who did not.¹⁶ In another study of mutation carriers in the kConFab research cohort,²⁰ the uptake rate of BRRM was 11%, three years after learning their mutation result.²¹

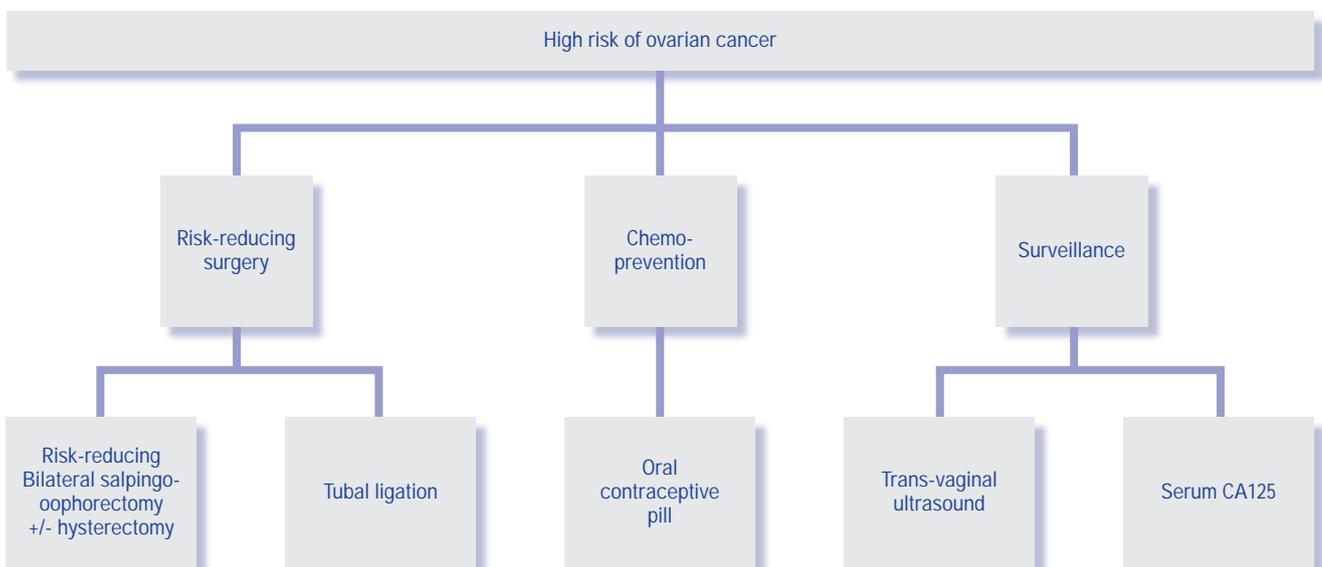
Risk-reducing bilateral salpingo-oophorectomy

Risk-reducing bilateral salpingo-oophorectomy (RRBSO) reduces ovarian and fallopian tube cancer risk by about 90% and, for premenopausal women, also reduces breast cancer risk by about 50% in BRCA1 and BRCA2 mutation carriers.²²⁻²⁷ RRBSO has recently been shown to reduce overall and cancer specific mortality.²² It is an

appropriate option for women who carry a BRCA1 or BRCA2 mutation, or who have a family history of breast and epithelial ovarian cancer (but is not generally recommended for women with a breast cancer-only family history). In Australia, uptake rates for RRBSO have been higher than for BRRM, with approximately 30% of mutation carriers undergoing RRBSO within three years of learning of their mutation result.²¹

RRBSO includes removal of the fallopian tube because of the increased risk of fallopian tube cancer in these women. Concurrent hysterectomy increases the complexity of the surgery, but is sometimes advocated to avoid the risk of endometrial cancer if progesterone-containing HRT or tamoxifen is planned for subsequent use. Primary peritoneal carcinoma may occur despite RRBSO,²⁸ with the rates of such malignancies varying from 2-11%.²⁹

Figure 2. Ovarian cancer: risk reduction and surveillance strategies



For pre-menopausal women, RRBSO causes abrupt menopause. Observational studies suggest that the use of hormone replacement therapy (HRT), after RRBSO in BRCA1/2 mutation carriers, does not offset the breast cancer risk reduction conferred by the procedure.³⁰ Results from the US based Women's Health Initiative Study suggest caution in advising prolonged post-menopausal HRT in women.^{31,32}

Optimal timing of RRBSO is controversial and needs to be individualised. Clearly it should not be undertaken until childbearing is completed. Ovarian cancer risk does not generally start to increase above that of the general population until about age 40 (BRCA1 carriers) or 50 (BRCA2 carriers). Thus, if ovarian cancer risk reduction is the major objective (eg. the patient is using other strategies to decrease breast cancer risk), surgery can be delayed until age 35-40 in BRCA1 carriers and age 45-50 in BRCA2 carriers. However, if reduction in breast cancer risk is also an objective, earlier RRBSO may be appropriate.

Tubal ligation

Tubal ligation has been associated with decreased risk for ovarian cancer in observational studies.³³⁻³⁵ One case control study showed that tubal ligation reduced ovarian cancer risk by about 60% in BRCA1 carriers. A protective effect was not seen in BRCA2 carriers, however was not excluded.³⁶ In BRCA1/2 mutation carriers who have completed childbearing, but who choose not to undergo premenopausal RRBSO, tubal ligation should be considered as an effective contraceptive means which may also decrease ovarian cancer risk.

Chemoprevention

Breast cancer chemoprevention

Chemoprevention, with the selective oestrogen receptor modulators (SERMs) tamoxifen or raloxifene, reduces breast cancer risk by about 40%.³⁷⁻⁴² Tamoxifen is the only evidence-based option for pre-menopausal women; for post-menopausal women raloxifene is also an option. These two agents have been compared in a randomised trial and are equally efficacious in preventing oestrogen receptor positive invasive breast cancers, with tamoxifen superior for prevention of non-invasive cancers.⁴³ Raloxifene is associated with fewer gynaecological side-effects, thromboembolic events and cataracts than tamoxifen. These agents probably should not be used in women with previous history of deep venous thrombosis, smokers, or those with other uncontrolled cardiovascular risk factors.

SERMs have not been shown to reduce risk for oestrogen receptor negative breast cancer and this has been used as an argument against using them in BRCA1 carriers, who usually develop ER negative tumours.^{44,45} Indeed, a sub-analysis of mutation carriers in the largest prevention trial suggested that the benefit of tamoxifen might be limited to BRCA2 carriers, however the study was under-powered and included fewer than 10 BRCA1 carriers.⁴⁶ Although BRCA1 associated breast cancers are usually oestrogen receptor negative, initiation of these tumours may well involve the oestrogen

pathway,^{47,48} which is consistent with the observation that interventions reducing oestrogen exposure in these women (eg. pre-menopausal oophorectomy), appear to reduce risk. For this reason, tamoxifen chemoprevention may be considered a reasonable option, although enrolment in trials of novel chemoprevention agents such as retinoids should be considered.⁴⁹

Aromatase inhibitors show promise as chemopreventive agents, based on their ability to reduce contralateral breast cancer risk in the adjuvant disease setting.⁵⁰ A clinical trial of anastrozole as chemoprevention (IBIS II) is underway. Participation should be discussed with high risk women, particularly those with a contraindication to SERMs.

Ovarian cancer chemoprevention

While there are no randomised trials, observational studies demonstrate a reduced risk of ovarian cancer in the general population and in high risk individuals who take the oral contraceptive pill.^{33,51-54} Most studies suggest up to a 50% reduction in the risk of ovarian cancer in BRCA1/2 carriers.^{53,55,56} Oral contraceptive pill use in this setting has been tempered by concern about the effect on breast cancer risk (discussed below in the 'lifestyle factors' section). However, as ovarian cancer carries a higher mortality rate than breast cancer, in pre-menopausal women who choose not to undergo RRSO, the oral contraceptive pill is a reasonable strategy to reduce risk, while being mindful of the uncertainty regarding impact on breast cancer risk. For women who have undergone BRRM, but wish to postpone RRSO until later, it is potentially a useful strategy as there is no concern about the possible impact on breast cancer risk.

Surveillance strategies

Surveillance strategies do not reduce cancer risk, however are aimed at detecting malignancy at an early stage when it may be amenable to curative treatment. Evidence on the efficacy of intensive surveillance in high risk women is limited.

Breast cancer screening/surveillance

Mammography

In the general population, mammographic screening has been demonstrated to reduce breast cancer mortality in women older than 50 years by 20-25%.^{57,58} The efficacy of mammographic screening in younger, high risk women remains controversial.⁵⁹ Anecdotal reports document both success and failure of mammography to detect breast cancer in carriers of BRCA1 mutations,⁶⁰ and the sensitivity of mammographic screening in high-risk women over a variety of studies ranges from 50-91%.⁶¹

Some have suggested that annual mammography may not be frequent enough in BRCA1 mutation carriers because these cancers are usually high grade and may develop between screens.^{9,62-64} However, enthusiasm for more frequent mammographic screening is limited, partly by the question of whether ionising radiation may induce cancers in mutation carriers, because these individuals may have difficulty repairing DNA damage

caused by radiation.⁶⁵ Studies have had conflicting results. Two studies of BRCA1/2 carriers found no increased risk of breast cancer associated with mammography.^{66,67} However, a recent retrospective cohort study of 1601 BRCA1/2 carriers demonstrated an increased risk of breast cancer (HR1.54, $p=0.007$) with any reported exposure to chest x-rays, especially in younger women.⁶⁸

Currently, women at high risk are recommended to undergo annual mammography, either from the age of 40 or five years earlier than the age at diagnosis of the youngest breast cancer case in the family, whichever is earlier. For women with proven gene mutations mammographic screening is often considered in the 30s.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an emerging screening modality for high risk women because of its high sensitivity.^{69,75,76} The American Cancer Society supports annual MRI screening for individuals with a known BRCA mutation, individuals untested but with a first-degree relative with a BRCA mutation and individuals with an estimated lifetime breast cancer risk >20-25%.⁷⁶ The European National Institute for Health and Clinical Excellence (NICE) guidelines recommend annual MRI in similar circumstances and in those with TP53 mutations a 10-year risk of >8% (30-39yo), or a 10-year risk >12% with dense breasts on mammography (40-49yo).⁷⁷

The high sensitivity of MRI screening is offset to some extent by its low specificity. This results in high false-positive rates, which may result in anxiety and unnecessary biopsy. There is no data on mortality benefits and lead-time bias may be a factor. While further research is needed, many Australian clinicians have begun to adopt the practice of MRI surveillance in high-risk women.

Breast clinical and self-examination

Clinical breast examination (CBE) may be an important adjunct in breast cancer screening in young, high risk women, as it may detect mammographically silent cancers, or may detect interval cancers between mammographic screenings. In addition, CBE is a potentially useful modality when women are pregnant or breast-feeding and other screening modalities are contra-indicated. It is generally recommended that CBE be carried out every six to 12 months in high risk women. While there is no evidence of survival benefits from breast self-examinations, women should be encouraged to be aware of how their breasts look and feel, and report any changes promptly.

Ovarian cancer screening/surveillance

Despite mounting evidence from observational studies that it is of no benefit, ovarian screening is sometimes considered for high risk women who have not undergone RRBSO.⁷⁸ Screening tests usually consist of trans-vaginal ultrasonography with serum CA125 levels.⁷⁸⁻⁸¹ Women who choose ovarian screening rather than RRBSO should be fully informed of the lack of evidence for any benefit.

Lifestyle factors

Lifestyle and environmental factors may modify breast cancer risk, although the effects are modest compared with surgery or chemoprevention. Current evidence is limited for several reasons. Most studies of modifiers of cancer risk in high risk women have been retrospective, prevalent case control designs, which have a high likelihood of systematic biases, including recall and survivorship bias. The few prospective studies are small or cobbled together from multiple institutions, using non-systematic and non-uniform follow-up strategies. Non-random loss to follow-up is a major potential source of bias in these studies. Additionally, most studies have focused on mutation carriers rather than the much larger population of women who have a strong family history but lack an identified gene mutation.

Parity

Increasing parity and early age at first childbirth are protective in the general population against breast cancer development. While several studies have investigated the effect of parity and age at first birth on breast cancer risk in BRCA1 and BRCA2 mutation carriers, results have been inconsistent.⁸²⁻⁸⁷ However, the advantage of early childbearing for mutation carriers is that it allows earlier use of other effective risk management strategies such as risk reducing surgery and chemoprevention.

Breastfeeding

In the general population, a woman's breast cancer risk reduces by about 4% for every 12 months of breastfeeding.⁸⁸ Several studies of mutation carriers have shown a reduction in breast cancer risk associated with breastfeeding.^{85,86,89} The single study which did not show any risk reduction was inadequately powered to exclude benefit.⁸⁴ Women who are at high risk should breastfeed for as long as practical and preferably beyond one year.

Oral contraceptive use

Use of the combined oral contraceptive pill reduces ovarian cancer risk in the general population and in BRCA1 and BRCA2 mutation carriers. Whether oral contraceptive pill use affects breast cancer in high risk individuals remains controversial. A meta-analysis of 54 studies showed that current oral contraceptive pill use is associated with a 24% increase in breast cancer risk, but the risks were similar for those with and without a family history of breast cancer.⁹⁰ Two other studies have not demonstrated a significant effect of oral contraceptive pill use on breast cancer risk in women with a family history.^{91,92} Conversely, one study showed a three-fold increase in breast cancer risk among women who used the oral contraceptive pill and had a first degree relative with breast cancer.⁹³

In BRCA mutation carriers, two studies have shown no increase in risk in BRCA1 carriers who used oral contraceptive pills for at least one year,^{94,95} and one showed an increased risk of about 20% in ever-users of oral contraceptive pill.⁹⁶ Of these three studies, two showed no effect of oral contraceptive pills on breast cancer risk in BRCA2 mutations, however one showed

an increased risk for BRCA2 carriers after at least five years of use. Thus, at this stage, there is no consistent evidence to suggest that the oral contraceptive pill is either safe or contra-indicated in women at high risk for breast cancer.

Obesity

There is clear evidence in the general population that obesity is associated with significantly increased breast cancer risk.^{97,98} Data on the effect of weight control on breast cancer risk in mutation carriers is very limited, however the published data does suggest that this may be an important area of risk management.^{99,100}

Alcohol consumption

Alcohol is clearly associated with breast cancer risk in the general population, with risk increasing by about 9% per daily standard drink.¹⁰¹⁻¹⁰⁴ Few studies have addressed the influence of alcohol in high risk women. One study found a 2.4-fold increase in breast cancer risk in daily drinkers with a strong family history of breast cancer.¹⁰⁵ Conversely, the only published study in mutation carriers showed no increased risk of breast cancer associated with alcohol consumption in carriers aged less than 50.¹⁰⁶ Given the other adverse health effects of excessive alcohol, it may be prudent to recommend that high risk women drink no more than one standard drink per day.

What about risk management in high-risk women with cancer?

Women with a personal diagnosis of breast cancer may be identified as belonging to a high risk family. Risk management for such women should consider the risk for a subsequent breast cancer or ovarian cancer and the competing risk of dying from their prior cancer, which attenuates the prevention benefits. Referral to a family cancer centre for urgent genetic testing may be appropriate in planning both loco-regional and systemic management. For women who carry a mutation in BRCA1 or BRCA2, the risk of a second breast cancer is around 40%^{107,108} and ovarian cancer risk is also increased.¹⁰⁹

The most effective preventative strategy against development of a new breast cancer in BRCA1/2 positive individuals with a prior history of breast cancer, is complete mastectomy (if the previous operation on the affected breast was less than a mastectomy) with contralateral mastectomy, which reduces the risk of contralateral breast cancer by 90%.¹¹⁰ In mutation carriers with a low risk of systemic recurrence of their prior breast cancer, this operation should be considered prior to adjuvant breast irradiation, as the latter can limit the reconstructive options. Similarly, RRSO should be considered if the prognosis from the breast cancer is reasonably good; additionally, the subsequent oestrogen deprivation may be an effective adjuvant therapy in pre-menopausal hormone receptor positive women.¹¹¹ Conversely, in women who are at high risk for systemic recurrence, it may be pertinent to wait two to five years before proceeding with risk reducing surgery, which will be of no benefit if her previous cancer recurs systemically. However, these decisions

are complex and should involve the input of experts in breast cancer genetics, the treating oncologist and the woman herself.

If risk reducing mastectomy is not performed, secondary chemoprevention may be considered. Tamoxifen appears to reduce contralateral breast cancer risk by about 50% in mutation carriers, including BRCA1 carriers (who usually do not receive adjuvant tamoxifen for treatment of their hormone receptor negative breast cancers).¹¹²

Management of subsequent breast cancer risk in women with prior ovarian cancer will be highly influenced by the stage and prognosis of the ovarian cancer. For women with advanced ovarian cancer, where the five-year survival rates are low (even taking into account the possible better survival from ovarian cancer in BRCA mutation carriers), management of breast cancer risk with screening and/or chemoprevention may be preferable to BRRM, whereas BRRM may be appropriate for women with early stage ovarian cancer.

Conclusion

The management of women at high risk of breast and ovarian cancer is complex and requires individualisation based on a woman's age, childbearing potential, personal risk and wishes. The great promise of predictive genetic testing for cancer predisposition in improving public health will only be realised with widespread implementation of evidence-based risk reduction strategies by the oncology and genetics community.

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