Assessing breast cancer risk

Tailored surveillance and risk-reductive interventions

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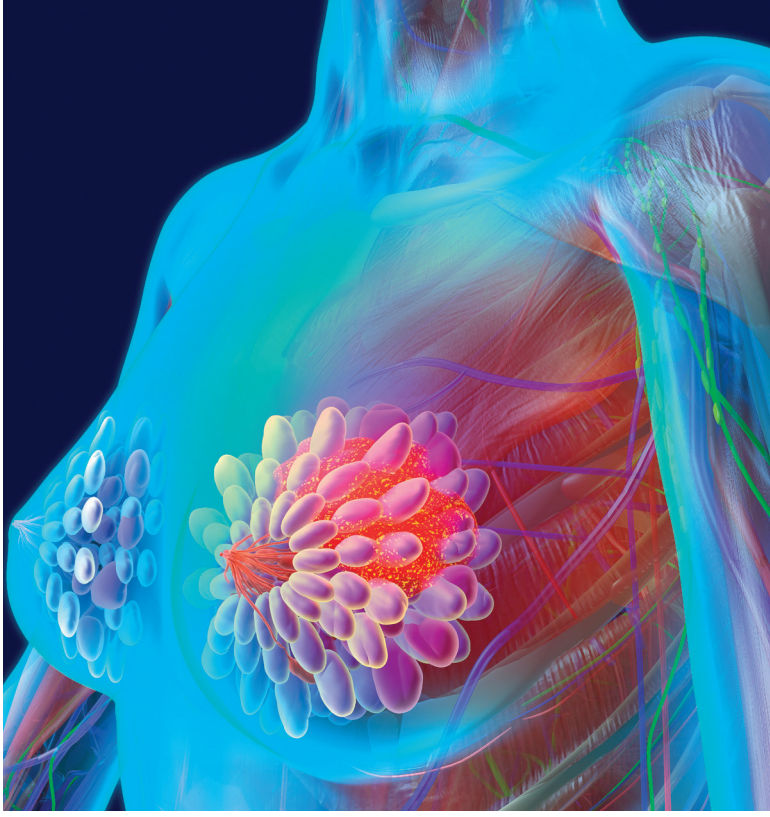

Breast cancer is the most common cancer, affecting one in seven women in Australia. It is important to determine who is at moderate or high risk of breast cancer, as these women require tailored surveillance and consideration of risk-reductive interventions.

Breast cancer is the most common cancer diagnosed in women in Australia.[1] It is also the second most common cause of cancer-related death in women.[1] The lifetime risk of a woman being diagnosed with breast cancer is one in seven. However, some women have a higher risk, which requires tailored surveillance and consideration of risk-reductive interventions. This article discusses how to determine a patient's risk of breast cancer, recommendations for surveillance and options for risk-reductive interventions.

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Risk definition

Lifetime breast cancer risk can be statistically stratified as low (baseline population), moderate or high (Table 1) by using risk-assessment tools.[2] For women who are classified at moderate- or high-risk for breast cancer, routine biennial screening is insufficient. For these women, tailored screening and consideration of risk-reductive interventions are recommended (Tables 2 and 3).[3,4] The recommendation on when to start surveillance varies widely and depends on the risk-assessment tool used or the particular genetic mutation identified.

Risk factors

Genetic mutations

About 5 to 10% of all breast cancers are familial.[5] However, even in patients with a strong family history, a specific genetic mutation is detected in less than 30% of cases.[6] The most common mutations associated with breast cancer are in the genes *BRCA1* and *BRCA2*. Mutations in these genes are thought to cause 3% of all breast cancer diagnoses internationally.[7] Due to their aberrancy, these tumour suppressor genes fail to repair double-stranded DNA breaks, resulting in mutation accumulation, eventually leading to breast cancer. The rates of developing breast cancer by age 70 years in women with mutations in the *BRCA1* or *BRCA2* genes are 55 to 72% and 45 to 69%, respectively.[8] This far exceeds the lifetime risk of about 14% for the baseline population.

Other genetic mutations, including *PALB2*, *ATM* and *CHEK2*, have also been identified as increasing breast cancer risk. All gene mutations have variable penetrance and surveillance recommendations are modified by the risk they confer. Surveillance recommendations are made by eviQ, a free online resource developed in NSW providing evidence-based, consensus driven cancer treatment protocols (including guidelines for specific genetic mutations) to help guide patient care (http://eviq.org.au).

TABLE 1. RISK CLASSIFICATION AND LIFETIME RISK OF BREAST CANCER[2]

Risk classification	Lifetime breast cancer risk
Low	<17%
Moderate	17 to 30%
High	>30%

TABLE 2. CURRENT RECOMMENDATIONS FOR WOMEN WHO HAVE A MEDIUM RISK OF BREAST CANCER[3]

Intervention	Age	Recommendations
Surveillance	All ages	Breast awareness with prompt reporting of persistent or unusual changes to the patient's GP
	40 to 49 years	• Recommend annual mammography • Consider other imaging depending on individual risk factors, such as breast density*
	50 to 60 years	• Recommend mammography second yearly, or annually in women with additional risk factors • Consider other imaging depending on individual risk factors, such as breast density*
	>60 years	Recommend mammography second yearly
Intervention	**Type**	**Recommendations**
Risk-reductive intervention	Surgery	Bilateral risk-reducing mastectomies or bilateral salpingo-oophorectomy are not generally recommended
	Medication†	• Consider use of tamoxifen in premenopausal women from age 35 years • Consider use of aromatase inhibitors or SERMs in postmenopausal women

Abbreviation: SERM = selective oestrogen receptor modulator.

* As age increases, breast density usually decreases, and the frequency and extent of imaging can therefore be reduced or adjusted according to the individual.

† Requires assessment of risks and benefits for an individual by an experienced breast specialist.

Ashkenazi Jewish people

The Ashkenazi Jewish population have a significantly increased risk of carrying *BRCA1* or *BRCA2* gene mutations. About one in 40 Ashkenazi Jewish women have a *BRCA* mutation, compared with one in 400 in the general population. There are three specific *BRCA1/2* pathogenic variants, referred to as BRCA-Jewish founder mutations, which account for more than 90% of the pathogenic variants in this subpopulation.

JeneScreen is an active project that offers genetic testing (free of charge) for *BRCA1/2* mutations in Ashkenazi Jewish women in Sydney or Melbourne, regardless of their family history. This has facilitated the detection of high-risk individuals, many of whom would have otherwise been ineligible for publicly-funded genetic testing.[9]

Family history

Patients often present to a healthcare professional with concerns of developing breast cancer because of a recent diagnosis in a family member. In cases where there is no identified genetic mutation, assessing familial risk can be difficult. The iPrevent online tool (explained in more detail below) provides tailored risk-management information for these patients. Women who have a higher risk of breast cancer compared with the general population are recommended to undergo genetic testing (Box).[10]

Personal history

Multiple factors contribute to an increased risk of developing breast cancer, including increasing age, female gender, high mammographic density, prolonged oestrogen exposure, menstrual cycle beginning before 12 years of age, late menopause, nulliparity and first pregnancy at age above 31 years. In addition, any prior history of breast cancer (both in situ and invasive disease) or a history of diagnosed precursor lesions, such as atypical ductal or lobular hyperplasia, or classic lobular carcinoma in situ, statistically increase the risk of developing breast cancer. Less commonly, a history of mantle radiotherapy before 25 years of age is also a risk factor.

Modifiable risk factors for breast cancer include alcohol consumption, obesity, lack of exercise and the use of menopausal hormone therapy (MHT). The use of MHT (for five years or more) increases breast cancer incidence by about one in every 200 users of oestrogen-only preparations, and up to one in every 50 users of oestrogen plus progestogen preparations.[11] If possible, it is better to use oestrogen-only MHT but this cannot be prescribed for women who have not had a hysterectomy.

Use of hormonal contraception, especially in high-risk patients, also needs to be considered. The relative risk of breast cancer in all current and recent users of hormonal contraception is 1.20.[12] Breast cancer risk increases with duration of hormonal contraception use. This risk increases from 1.09 with less than one year of use to 1.38 with more than 10 years of use.[12] This risk applies to current users and continues for up to 10 years post cessation. This risk is also applicable to newer formulations of hormonal contraception, including progesterone-containing implantable devices.

Risk-assessment tools

iPrevent

iPrevent is an online breast cancer risk-management decision support tool (www.petermac.org/iprevent). It uses a model choice algorithm by selecting one of two validated breast cancer risk-estimation models (International Breast Cancer

TABLE 3. CURRENT RECOMMENDATIONS FOR WOMEN WHO HAVE A HIGH RISK OF BREAST CANCER[4]

Intervention	Age	Recommendations
Surveillance	<40 years	Recommend annual breast MRI* if screening is advised (age to commence depends on validated risk model or presence of confirmed genetic mutation)
	40 to 50 years	• Recommend annual mammography ± tomosynthesis • Recommend annual breast MRI*
	>50 years	• Recommend annual mammography ± tomosynthesis • Consider annual breast MRI* if dense breast tissue† ± tomosynthesis
Intervention	**Type**	**Recommendations**
Risk-reductive intervention	Surgery	• Discuss bilateral risk-reducing mastectomies • Discuss bilateral salpingo-oophorectomy
	Medication‡	• Consider use of tamoxifen in premenopausal women from age 35 years • Consider use of aromatase inhibitors or SERM in postmenopausal women

Abbreviations: MRI = magnetic resonance imaging; SERM = selective oestrogen receptor modulator.

* Only funded in select situations and needs to be ordered by a specialist (MBS Item 63464).
† As age increases, breast density usually decreases, and the frequency and extent of imaging can therefore be reduced or adjusted according to the individual.
‡ Requires assessment of risks and benefits for an individual by an experienced breast specialist.

PATIENTS WITH A FAMILY HISTORY OF CANCER WHO WARRANT REFERRAL FOR GENETIC TESTING[10]

Two first- or second-degree relatives diagnosed with breast or ovarian cancer AND one or more of the following on the same side of the family:*

- additional relative(s) with breast or ovarian cancer
- breast cancer diagnosed before age 50 years
- more than one primary breast cancer in the same person
- breast and ovarian cancer in the same person
- Jewish ancestry
- male breast cancer
- pancreatic cancer
- high-grade (Gleason score >7) or metastatic prostate cancer

* If possible, genetic testing should be performed first on the affected family member.

Intervention study [IBIS] or Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm [BOADICEA] version 3), based on a woman's risk factors. It then provides tailored risk-management information for patients. Overall, it has shown good discriminatory accuracy.[13,14] iPrevent cannot be used for patients who have a history of breast cancer or precursor lesion, have a confirmed cancer gene mutation (except for *BRCA1* and *BRCA2*) or have had chest radiotherapy. iPrevent can be completed online in about 30 minutes and patients can then download a personalised report to take to their appointment to discuss with their healthcare professional.

CanRisk

CanRisk uses the BOADICEA version 6 model to assist healthcare professionals in calculating an individual's future risk of breast and ovarian cancer (www.CanRisk.org). It can be used in patients who have previously been diagnosed with invasive breast cancer and it also integrates polygenic risk scores. Although both CanRisk and iPrevent excel at family history recording, neither includes the risk associated with a prior history of precursor lesion.

IBIS

The IBIS risk-assessment tool, also known as the Tyrer-Cuzick model breast cancer risk-evaluation tool, is used to estimate the likelihood of a woman developing breast cancer specifically within 10 years of her current age and up to 85 years of age (https://ibis.ikonopedia.com). The IBIS tool can be used to determine breast cancer risk in patients with confirmed *BRCA* mutations and previously diagnosed breast precursor lesions, and is more useful in the specialist setting.

Risk-reductive strategies

Simple measures to reduce modifiable risk factors for breast cancer include exercise, weight reduction and decreased use of MHT. Interventional strategies for nonmodifiable risk factors include risk-reductive surgery and use of risk-reductive medications.

Breast risk-reductive surgery

Risk-reductive surgery reduces the risk of breast cancer by at least 90% but is currently only recommended for high-risk patients. The two options for risk-reductive surgery are a mastectomy or mastectomy with reconstruction. Patients can either have implant-based reconstruction (prosthesis) or autologous tissue reconstruction (using the patient's own tissue). If pursuing reconstruction, this can be performed as a skin or nipple-sparing procedure in which there is no increased risk of subsequent breast cancer compared with simple mastectomy.

An implant-based reconstruction can be performed as a single staged operation with insertion of a permanent implant at the time of mastectomy, or as a staged procedure with insertion of an expander at the initial mastectomy, with a subsequent planned operation to exchange the expander for the permanent implant later. The implant pocket can either be placed superficial to the muscle (prepectoral approach)

or deep to the muscle (subpectoral approach) (Figure). Surgeon preference for implant placement varies across Australia. The prepectoral approach reduces postoperative pain but has a risk of rippling, whereas the subpectoral approach has a lower risk of rippling but a higher risk of animation.[15] Postoperatively, there are no significant differences when clinically examining or imaging either technique. It is important for patients to know that these are not lifelong devices (they have a general lifespan of 15 years) and ongoing assessment of the device is required, with potential exchange of the implant in the future.

The most common autologous tissue reconstruction is a deep inferior epigastric perforator flap using abdominal fat for reconstruction. Enough abdominal fat is required to recreate both breasts. This procedure provides reliable long-term results for patients, with excellent long-term satisfaction and good cosmesis.

It is important that patients are aware that there is still a risk of developing breast cancer in the future after having risk-reductive surgery, albeit small. This risk is far less than the baseline population risk.

Ovarian risk-reductive surgery

Patients with *BRCA1/2* mutations have a higher risk of both breast and ovarian cancers. By age 70 years, the risk of developing ovarian cancer is about 39 to 44% for patients with the *BRCA1* mutation and about 11 to 17% for *BRCA2* mutation.[8] It is currently recommended that bilateral salpingo-oophorectomy should be performed between the ages of 35 and 40 years for patients with *BRCA1* mutation and 40 and 45 years for those with *BRCA2* mutations to reduce ovarian cancer risk, although the optimal timing should be individualised. Patients can take MHT after bilateral salpingo-oophorectomy, without increasing their risk of breast cancer, for a period of about five years to minimise side effects. Previously, risk-reducing bilateral salpingo-oophorectomy was recommended for premenopausal patients with *BRCA* mutations as a means to reduce breast cancer risk; however, most recent evidence has failed to corroborate this.[16]

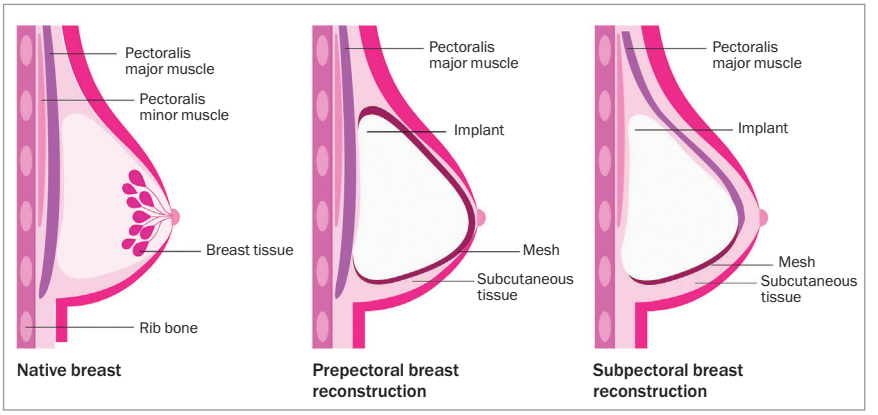

Figure. Implant-based reconstruction options postmastectomy.
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Risk-reductive medications

The two main classes of risk-reductive medication for breast cancer are selective oestrogen receptor modulators (SERMs e.g. tamoxifen and raloxifene) and aromatase inhibitors (e.g. letrozole and anastrozole, which are both used off-label for breast cancer prevention). SERMs have an anti-estrogenic effect on breast tissue and can be used in both pre- and postmenopausal women.[17] However, they have predominantly oestrogenic effects on the uterus and liver. Key side effects are venous thromboembolism, endometrial hyperplasia and hepatotoxicity. Aromatase inhibitors reduce oestrogen synthesis by blocking the aromatase enzyme, which converts androgens into oestrogens. They are only effective in postmenopausal women. Side effects include arthralgia, fatigue and osteoporosis. Decision making regarding which class of medication to use depends on a patient's menopausal state, as well as any relevant contraindications. Currently, only tamoxifen is PBS listed for reduction of breast cancer risk in patients at moderate to high risk, and costs about AU$25 per month. These drugs can reduce breast cancer risk in high-risk women by about 30 to 60%.[18] Discussions about risk-reductive medications should take place in consultation with a breast specialist.

The BRCA-P trial is an international breast cancer prevention clinical trial investigating whether the use of denosumab, a monoclonal antibody that inhibits nuclear factor kappa-B ligand, is a safe and effective option for preventing breast cancer in women with a confirmed *BRCA1* gene mutation who have not had breast risk-reductive surgery (www.breastcancertrials.org.au/trials/brca-p/). Eligible patients will be randomised to either placebo or denosumab for five years.

Conclusion

Breast cancer is the most common cancer affecting women in Australia. Biennial screening mammography for women aged 50 to 74 years has been shown to be appropriate for those at population level risk; however, it is insufficient in moderate- and high-risk groups. It is important to understand who is, or might be, at high risk of breast cancer to ensure they have appropriate tailored breast cancer surveillance. Risk-reductive strategies are recommended for patients at moderate- or high-risk of beast cancer and should be discussed in consultation with a breast specialist. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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