An approach to the patient with a family history of breast cancer

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This eleventh article in our series on breast disease discusses the management of a patient with a family history of breast disease. Apart from increasing age and female gender, family history is the most important risk factor for breast cancer. However, women with a family history of breast cancer often overestimate their risk of developing the disease. Much of the clinician's role is to reassure the patient and clarify the risk based on a careful assessment of the family history.

Apart from increasing age and female gender, family history is the most important risk factor for breast cancer. Women with a family history of breast cancer, however, often overestimate their risk of developing the disease. Most women with a family history of breast cancer do not have a much higher than average risk of developing breast cancer, even if they have an affected first degree relative. As breast cancer is so common, a family history of breast cancer often occurs simply by chance. It is estimated that less than 5% of women diagnosed with breast cancer have a strong genetic predisposition.[1] Much of the clinician's role, therefore, is to reassure the patient by taking a good family history and then clarifying the risk based on a careful assessment of the family history.

For the few patients at potentially high risk of breast cancer (about 1% of the female population), management involves discussing the option of testing the family for inherited germline mutations in tumour suppressor genes such as BRCA1 and BRCA2 that may cause a high risk of breast cancer and epithelial ovarian cancer. Some patients with a strong family history and those who test positive for these mutations may elect options to reduce their risk of developing breast cancer, such as risk reducing mastectomy, salpingo-oophorectomy, or preventive medication. Close monitoring with mammography and the use of screening for ovarian cancer are also important areas for discussion with such patients.

Taking a family history

Taking a good family history is extremely important. Essential information to collect about the family is listed in *Table 1*. It is important to ask about all relatives, affected and unaffected by cancer, over three generations. Even though breast cancer may be the focus, all cancers in the family must be documented, even if they seem unrelated. Keep in mind that maternal and paternal family histories are equally important, even for cancers that mostly affect females such as breast and ovarian cancer. Germline mutations may pass down through the maternal or paternal sides of the family, though males will be infrequently affected. A generation of affected individuals may therefore appear to be 'skipped' in one family line if an unaffected male passes on a breast cancer gene mutation. Although only one in a hundred new diagnoses of breast cancer occurs in males, the risk of male breast cancer is increased in some families with a genetic predisposition. Features of the family history that suggest the presence of a germline mutation in a breast/ovarian cancer susceptibility gene are listed in *Table 2*.

Categories of risk

The risk of breast cancer conferred by a positive family history is dependent on the number of relatives affected by breast and/or ovarian cancer, their age at diagnosis, and how closely related they are to the unaffected person. The National Breast Cancer Centre (NBCC) has developed three categories of risk based on family history (see *Patient education* this issue. Also available at www.nbcc.org.au/resources/resource.php?code=BOG). More detailed tables are also available.[2] The aim of taking a family history is to determine which of these risk categories an unaffected person falls into. The category gives a guide to screening recommendations based on level of risk and to the appropriateness of referral

to a family cancer clinic for consideration of genetic testing. It should be noted that, in the absence of evidence, category specific recommendations for breast screening have been developed using a consensus approach.

Inherited gene mutations

Cancer is a genetic disease associated with mutations in genes that normally act to control cell growth, proliferation and DNA repair. Genetic mutations usually occur in somatic cells over the course of a lifetime and cancer is usually due to a series of acquired mutations in genes that control cell growth, eventually allowing cells with these accumulated faults to grow in an uncontrolled fashion. Up to 95% of all cancers are caused by these somatic mutations in cancer associated genes. As these faults occur in somatic cells (such as the cells lining breast ducts), they cannot be inherited.

However, some rare families have an inherited mutation in one of these same genes. In these cases, some of the family members start life with a defective copy of a particular tumour suppressor gene (the 'first hit') present in every cell of the body. In order for cancer to develop, the second (normal) copy of the gene must be inactivated, either through mutation or through mechanisms of gene silencing (the 'second hit'), and further genetic changes also need to occur in the breast tissue. In the majority of women with breast cancer these two hits occur in the breast tissue through life (and cannot be passed on). In a person with a rare genetic susceptibility to the disease, the 'first hit' has already been inherited either in the egg or the sperm (germline mutation). This gene mutation affects all the cells in the body. People who inherit a germline mutation in a cancer associated gene are therefore at increased risk of developing cancer. In addition, a germline mutation can be passed on to the next generation. For each of their offspring (male or female) there is a 50% chance they will inherit the mutated copy of the gene.

Germline mutations associated with inherited susceptibility to breast and ovarian cancer

Several genes have been identified in which germline mutations are associated with a high risk of breast cancer, invasive epithelial ovarian cancer (especially of the serous subtype) and cancer of the fallopian tube. The first gene to be discovered was BRCA1 on chromosome 17. Since then, BRCA2 and other cancer susceptibility genes have been identified. People who have an inherited fault in these genes are gene mutation 'carriers', with an increased risk of developing cancer. Inherited faults in BRCA1 and BRCA2 are more common in individuals of Ashkenazi Jewish heritage. Features of cancer in BRCA1 and BRCA2 gene mutation carriers are listed in *Table 3*.[3]

Genetic testing

Genetic testing may be offered to an individual or family where there is a personal or family history with features suggesting genetic cancer susceptibility. Testing should only be performed in a setting where the test can be adequately interpreted and the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer. Genetic testing should only be done with pre- and post-test counselling. This should include discussion of the possible risks and benefits

Table 1. Taking a family history: essential information to collect

- Ask about all relatives over three generations, affected and unaffected by cancer
- Maternal and paternal family history are equally important, even for breast and ovarian cancer
- Document all cancers on both sides of the family and age at diagnosis
- Ethnic background (especially Ashkenazi Jewish origin)

Table 2. Features of the family history that suggest genetic susceptibility to breast and ovarian cancer

- Several family members on one side of the family in different generations affected by breast and/or ovarian cancer
- Women who develop breast cancer before the age of 40 years
- Women who develop bilateral breast cancer
- Women who develop both breast and ovarian cancer
- Men as well as women who develop breast cancer
- Ashkenazi Jewish origin

Table 3. Features of cancer in carriers of BRCA1 and BRCA2 mutations[3]

	Features of breast cancer	Susceptibility to other cancers
BRCA1	High grade cancer	Breast cancer
	High mitotic rate	Cancer of ovaries and fallopian tubes
	Tend to be oestrogen receptor negative	Prostate cancer
BRCA2	No special phenotype	Breast cancer
		Cancer of ovaries and fallopian tubes
		Breast cancer in males
		Prostate cancer
		Pancreatic, gallbladder/bile duct cancers
		Melanoma

of early detection of cancer and prevention modalities.[4] Guidelines recommend against routine referral for genetic counselling or routine breast cancer susceptibility genetic testing for women whose family history does not strongly suggest a mutation in BRCA1 or BRCA2.[5]

The initial step in genetic testing is usually to take blood from one of the family members affected by breast or ovarian cancer (although sometimes an unaffected obligate carrier may be tested instead). The decision concerning which genes to test is based on the family history. This first phase, the 'mutation search', must be done with full informed consent. Pretest counselling must cover the potential harms, benefits and limitations of testing. The laboratory then searches the large BRCA1 and BRCA2 genes to determine whether a causative gene mutation can be found. This search may take some months. A causative gene mutation cannot be found in every family tested as mutations may be missed or may be present in other genes not yet identified. Therefore, if the family history is strong and the genetic test (mutation search) fails to identify a gene mutation in an affected family member, that test result should be considered 'inconclusive' and all relatives remain at potentially high risk. Sometimes the laboratory will identify an unclassified variant – a change in the genetic code that is not definitely tied to a genetic susceptibility (yet), and this should also be considered an inconclusive result at this stage.

Only when a causative mutation in BRCA1 or BRCA2 has been identified can other at risk adult family members (male and female) then be offered 'predictive' genetic testing. Predictive tests are relatively cheap and quick, with results generally available in 4–6 weeks. Once the family gene mutation has been identified in the mutation search phase, others in the family can be tested for the presence or absence of that same gene fault, giving a more reliable estimate of their future cancer risk.

In families of Ashkenazi Jewish background, genetic testing for breast cancer susceptibility is simpler. There are three specific mutations that account for most inherited cases of breast/ovarian cancer in these families and the phase of 'mutation search' is considerably shorter. In Jewish families, sometimes an unaffected person with a family history of breast/ovarian cancer can be tested just for the three specific 'Jewish' mutations.

The risk of cancer associated with a BRCA1 or BRCA2 (or other) gene mutation and the approach to that risk requires discussion

Table 4. Screening for breast and ovarian cancer in BRCA mutation carriers

Breast cancer screening

- includes yearly mammography with or without breast ultrasound
- usually starts 5–10 years earlier than the youngest age of diagnosis of breast cancer in the family

- Mammographic screening
  - is less sensitive in women with gene mutations relative to women at average population risk[5,9]
  - women should be advised to promptly report any breast changes even if having annual mammography
- Breast MRI
  - is proving useful in detecting clinically and mammographically occult breast cancers in women at high risk
  - however the effect on breast cancer mortality has not been studied in appropriately designed screening trials and it is not yet routinely available
- Ductal lavage
  - is currently being investigated in research studies

Ovarian cancer screening

- Transvaginal ultrasound (annual)
  - has not been proven to reduce mortality from this cancer
  - however it is usually recommended for women at potentially high risk who have not had preventive surgery, starting at age 35 or 40 years, depending on the gene involved and the family history
- CA-125 (annual) measurement
  - has not been proven to reduce mortality from this cancer
  - may be added after menopause
  - results may be unpredictable in premenopausal women

Figure 1. Annual mammography is recommended in women carrying the gene mutations BRCA1 and BRCA2 but there is some evidence that it may be less sensitive in these women than in the general population

before testing. Those found not to carry the family mutation at predictive testing should be considered to be at average risk of cancer. Importantly, their offspring are also not at high risk.

Family cancer clinics

Family cancer clinics provide cancer risk assessment, surveillance advice, prevention strategies, and genetic counselling and testing for cancer susceptibility. Family cancer services are usually in institutions with a public sector comprehensive cancer service forming a key part of the multidisciplinary approach to cancer care. These services can be found via the Cancer Council Helpline (13 11 20) and at www.genetics.com.au. Outreach clinics and telehealth are conducted in some rural areas with outreach counsellors assessing family history and liaising with central family cancer clinics.

Risk and management issues for high risk women

If a woman is found to carry a germline mutation in BRCA1, it will mean a high, but not certain, risk of breast cancer as well as an increased risk of cancer of the ovaries and fallopian tubes. Each child of a mutation carrier (male or female) also has a 50% chance of having inherited the mutation.

There has been conflicting evidence as to the exact risk of cancer in BRCA1 and BRCA2 carriers. In a meta-analysis that included data from 22 studies, the average cumulative risks in BRCA1 mutation carriers by age 70 years were 65% for breast cancer, and 39% for ovarian cancer. Corresponding estimates for BRCA2 mutation carriers were 45% for breast cancer and 11% for ovarian cancer. Risks of developing a second contralateral breast cancer have been reported to be 50–64% by the age of 70 years.[6] Precise protocols on the management of these patients remain controversial.

Management options for affected and unaffected women at genetic risk are complex, requiring the interaction of the specialist in cancer genetics with the breast surgeon, plastic surgeon, gynaecological oncologist, oncologist, endocrinologist, and the patient's general practitioner. The approach should be multidisciplinary, and may be coordinated through a family cancer clinic.

Options for managing women who test positive for a gene mutation are:

- screening of the breasts and ovaries (*Table 4, Figure 1*)
- risk reduction measures (*Table 5*)
  - risk reducing mastectomy (reduces the risk of breast cancer)
  - risk reducing salpingo-oophorectomy (reduces the risk of cancer of the ovaries and fallopian tubes and also of breast cancer if premenopausal at time of surgery)
  - preventive medication (tamoxifen or aromatase inhibitor: may reduce the risk of breast cancer in some women but these agents are not available [for prevention] in Australia outside research trials).

Table 5. Measures to reduce the risk of cancer in BRCA gene mutation carriers

Risk reducing salpingo-oophorectomy

- Only proven method of reducing the risk of ovarian cancer and cancer of the fallopian tube
- Small residual risk of primary peritoneal carcinomatosis after surgery
- After premenopausal oophorectomy there may also be a 50% reduction of risk of breast cancer in women carrying BRCA1 or BRCA2 mutations
- In women who carry germline mutations in BRCA1 or BRCA2, risk reducing bilateral salpingo-oophorectomy lowers the risk of epithelial ovarian cancer (and cancer of the fallopian tube) by at least 90%
- These findings support the practice of offering risk reducing bilateral salpingo-oophorectomy to carriers of these mutations after childbearing is completed
- The current practice, based on risk estimates derived from BRCA families, is to offer surgery at 35–40 years of age in BRCA1 mutation carriers, and 40–45 years in BRCA2 carriers
- Decisions about timing of surgery also need to take into account the family history of ovarian cancer, particularly the earliest age at diagnosis in an affected family member

Risk reducing mastectomy

- For carriers of gene mutations associated with a high risk of breast cancer, the procedure results in a 90% reduction of risk of breast cancer[10,11]
- Surgery cannot reduce cancer risk to zero
- Risk reducing bilateral mastectomy, with or without reconstruction, needs to be discussed as an option in the context of risk counselling and management
- Is aimed at macroscopically removing as much breast tissue as possible. No axillary dissection is required
- Discuss options for reconstruction, either immediate or delayed

Preventive tamoxifen

- Has been shown to reduce short term risk of breast cancer in well women at increased risk of breast cancer.[12] However, the effect of tamoxifen on mortality from breast cancer has not yet been defined, and tamoxifen is associated with venous thrombo-embolic events and endometrial cancer
- Tamoxifen fails to prevent oestrogen receptor negative breast cancer, a subtype that occurs more commonly in BRCA1 mutation carriers
- Therefore tamoxifen cannot at this time be routinely recommended as a preventive agent in women at high risk

Preventive surgery

Surgery – breast

Risk reducing bilateral mastectomy will reduce the risk of developing breast cancer

but does not reduce the risk to zero.[7] Risk reducing mastectomy is not a decision that a woman can come to easily without significant preoperative counselling. For many women the breasts define their femininity and concerns about social interactions, relationships and personal psychological adjustment are important considerations. The option of breast reconstruction can be discussed. Unlike women with newly diagnosed breast cancer, women considering risk reducing mastectomy can be encouraged to take their time in making decisions and spend as much time as they feel is necessary to understand the surgery and its implications. Many younger women choose to complete their families before considering prophylactic surgery. Most women with partners wish to include them in their decision making. Most women want to at least discuss immediate breast reconstruction. Treatment teams need to offer the full range of options.

Surgery – ovaries and fallopian tubes

Risk reducing bilateral salpingo-oophorectomy is a procedure sometimes more easily accepted by the high risk woman, particularly if she is postmenopausal. The symptoms of menopause for the premenopausal woman however, can be quite severe, especially when occurring abruptly following ovarian surgery. For most women, salpingo-oophorectomy is relatively straightforward and can be performed laparoscopically. Oophorectomy also confers up to a 50% reduction in breast cancer risk for the premenopausal woman who has not already undergone prophylactic mastectomy.[8] Sometimes, after surgical menopause in younger women, use of hormone therapy may need to be considered on an individual basis, but this does not negate the breast cancer risk reduction afforded by oophorectomy.

Conclusion

Most cases of breast cancer are not associated with a genetic predisposition. The role of the GP is to document the family history and to determine in which of the three risk categories the patient belongs. The category determines the screening recommendations. For the few women (about 5% of the population) that fall into the moderately increased risk or potentially high risk categories, referral to a family cancer clinic may be worthwhile. The clinic can examine the risk in more detail and offer genetic testing and risk reduction measures if indicated.

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