A Family Affair? Breast Cancer Genetics

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Breast cancer is the most frequently diagnosed cancer in Canadian women. Fortunately, with enhanced screening and treatment, the mortality rate is falling. Most of the recently-observed decreases in fatality rates are due to improved treatment (*i.e.*, antiestrogens such as tamoxifen [for women with estrogen-positive breast cancer]) and combination chemotherapy with well-established agents, such as doxorubicin and cyclophosphamide, as well as newer drugs (*e.g.*, the taxanes). However, breast cancer remains the major cause of death for women between the ages of 40 and 50 years. Nevertheless, the risk of a 40-year-old woman dying of breast cancer over a 10 year period is one in 500.

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The most important risk factor to consider for breast cancer is age as most cases of breast cancer are diagnosed in women > 50 years. Indeed, the risk for breast cancer by age 50 is around 2%, whereas the risk for the next 20 years increases by a further 5%. That is, the risks to age 50, 70 and 95 years are roughly 2%, 7% and 11%, respectively. Therefore, it can be seen that in the entire population, breast cancer diagnosed in those < 50-years-of-age is a relatively rare event. Nevertheless, in terms of the number of potential years of life lost, breast cancer, diagnosed in young women, has a more devastating effect than breast cancer diagnosed in older women. This is because younger women have potentially more years of life to lose than older women and their cancers tend to be more aggressive and more fatal. The most important risk factor for breast cancer after age at diagnosis is a positive family history of breast cancer.

What is the role of the FP in advising a woman regarding her genetic risk for breast cancer?

Family history

The first important step to identify an at-risk woman is to take a brief, focused family history. It is important to recognize that the family history includes both sides of the family (*i.e.*, that occurring on the father's side, as well as on the mother's) and both must be considered. The ages at diagnoses should be noted and a family history of other cancers, particularly ovarian cancer, should also be documented.

In general, if there are three or more cases of breast cancer in a family, with an average age of diagnosis at < 50 years, or two women diagnosed with ovarian cancer at any age, then hereditary breast/ovarian cancer is likely present in the family. These families are rare. It is more likely that the woman coming to your clinic will have a much lower level of risk. To address this, the McGill University Program in Cancer Genetics has created referral guidelines (www.mcgill.ca/cancergenetics/) which will inform the referring doctor of the likely result of a referral to cancer genetics services. They are not meant to serve as indicators for which patients to refer, as this may depend upon circumstances. In Montreal, cancer genetics clinics are offered at the McGill University Health Centre (Montreal General Hospital), the Jewish General Hospital (Segal Cancer Centre) and at the Centre Hospitalier de l'Université de Montréal (Hôtel-Dieu campus).

Is all familial breast cancer due to known genetic factors?

Although there are several important breast cancer genes, such as the first breast cancer susceptibility gene (BReast CAncer 1) and BRCA2,[1] most familial breast cancer cannot be explained by currently known genes. This means that only a minority of individuals and families will be suitable for genetic testing. Those that are will be offered counselling sessions before and after genetic testing and psychological support.

Those that are not offered testing will be given a personalized risk assessment and advice regarding prevention and screening practices. For example, post-menopausal women with a family history of breast cancer may be eligible for entry into clinical trials that evaluate the role of drugs that are known to reduce the incidence of breast cancer, such as:

- tamoxifen,
- raloxifene, or
- the newer aromatase inhibitors:
  - anastrazole and
  - letrozole.[2]

Younger women are currently not eligible for such prevention trials. If they have a strong family history of early-onset breast cancer, they may be offered genetic testing, which is carried out after a simple blood draw. In Montreal, some testing is done at the McGill University Health Centre, but often the blood sample is sent to the US for complete analysis. The Quebec government covers the cost, which averages at $3,500 Canadian.

How high are the risks?

There is still some debate as to the risks for breast and ovarian cancer for carriers of BRCA1 and BRCA2 mutations, but the average risks to age 70 are 50% to 60% for breast cancer and 20% to 40% for ovarian cancer.[3] These compare with general population risks of 7% and 1.5% for breast and ovarian cancer, respectively.

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What can be done for the woman at high-risk?

Prevention is the mainstay of management of women at very high-risk of breast cancer. By high-risk, we mean risks of at least 1% per year. Women who carry mutations in BRCA1 or BRCA2 genes, who are > 35-years-of-age, have risks of this magnitude.

Surgery

Prevention can be medical, as discussed above, or surgical (*i.e.*, preventive surgery). The issues surrounding prophylactic surgery are too complex to be discussed in this brief overview, but approximately 20% to 30% of North American women who carry BRCA1 or BRCA2 mutations, who have not had breast cancer, opt to undergo a bilateral preventive mastectomy. This is a much less popular choice in most European countries.

Preventive oophorectomy is a much more popular choice for women who are no longer considering having additional children.

MRI scan

Those who decide not to undergo mastectomy are offered annual screening using MRI scans, a technique that is much better than a mammograph at detecting breast cancers in high-risk women, such as BRCA1 or BRCA2 mutation carriers.[4]

Psychological support

Psychological support is important for high-risk women, as the familial burden of breast cancer can take a psychological toll on women who are at-risk.[5] Individual psychotherapeutic support may be helpful as well. In the last few years, a charity has been established that focuses specifically on the needs of women and families who have a strong family history of breast cancer. The triple aims of the Hereditary Breast and Ovarian Cancer Foundation (www.hboc.ca) are awareness, action and research. A biennial conference is available in Montreal for both health professionals and the lay public (www.odon.ca/brca/), where all the issues touched upon in this overview will be dealt with in great detail.

The most important risk factor for breast cancer is age.

Conclusion

Breast cancer is the most common cancer diagnosis in Canadian women. Along with improvements in treatment and methods of prevention, diagnosing breast cancer early is a major challenge. Identifying women who are at very high-risk of breast (and ovarian) cancer is an important aspect of this challenge and FPs can play a vital role as first-line healthcare practitioners.

Cancer genetics services are available in most major cities in Canada and are equipped to provide a timely service to women at-risk. The challenge is identifying these women. The FP is the ideal person to do this. Dx

References
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