Breast cancer prevention in women with a BRCA1 or BRCA2 mutation

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Counselling women about the resources that are available to them to assess their risk of breast cancer and providing advice on appropriate screening and risk-reduction strategies can be challenging for clinicians. This article discusses genetic risk factors for breast cancer, how to take a family history, and how to counsel and organize appropriate referrals for patients who may be at an increased risk of breast cancer because of a mutation in the BRCA1 or BRCA2 gene. In addition, it provides information on counselling women who have been identified as having a mutation in BRCA1 or BRCA2.

Case
A 40-year-old patient informs you that her sister has been diagnosed with breast cancer at the age of 38. The patient’s mother, at age 65, is healthy and has never had a cancer diagnosis. The patient knows of no other family history of breast cancer on her mother’s side of the family; her father’s grandmother possibly had breast cancer, but she died before the patient was born. The patient also mentions a paternal aunt who died of ovarian cancer. She is of Ashkenazi Jewish descent. The patient inquires whether she should be concerned about her sister’s breast cancer diagnosis and if she is too young to begin breast screening. How would you advise her?

Assessing breast cancer risk
Several models are available to help assess a woman’s risk of breast cancer. The Gail Model calculates a woman’s breast cancer risk over the next five years, in addition to her lifetime risk (www.cancer.gov/bcrisktool/). The model considers age, ethnicity, history of breast cancer in first-degree relatives, age of menarche, and previous history of breast biopsies and benign breast disease.

Clinicians should be familiar with the process of taking a detailed family history (pedigree) to assess cancer risk. This involves collecting information with regard to types of cancer, the ages at which cancer diagnoses were made, and the vital status of three generations of relatives within a family. In addition, family ethnicities should be recorded. There are many resources available to help clinicians assess genetic family histories, including a detailed list on the University of Kansas Medical Center website.

Genetic testing for BRCA1 and BRCA2 mutations helps physicians identify women who are at significantly increased risk of developing breast and ovarian cancer. For BRCA1 carriers, the estimated cumulative risks to age 70 years are 65% for breast cancer and 39% for ovarian cancer. The corresponding risks for BRCA2 carriers are 45% for breast cancer and 11% for ovarian cancer.1 In comparison, the average woman in the general population has an 11% lifetime risk of developing breast cancer and a 1.5% risk of developing ovarian cancer (Table 1). After the initial diagnosis of breast cancer in a BRCA1 or BRCA2 carrier, the risk of cancer in the opposite breast (a new primary cancer) increases by approximately 3% per year.2–4

| Table 1: Lifetime breast cancer risk |
|------------------------------------|
|                                    |
|                                     |
| Lifetime breast cancer risk         |
| Median age of breast cancer onset (y) |
| General population                  | 11% | 61   |
| BRCA1                               | 65% | 43   |
| BRCA2                               | 45% | 41   |

About 1 in 200 women in North America carries a BRCA1 or BRCA2 mutation,5–7 but among several ethnic groups the prevalence is considerably higher. Notably, the frequency in those of Ashkenazi Jewish ancestry is 1 in 50.8 Other groups with high frequencies of mutations include women from Iceland9 and Poland.10 These high prevalence rates are explained by the presence of
founder mutations. (Founder mutations are one or more specific mutations in a population that have been inherited from a common ancestor, and that have become amplified through chance effects, often aided by geographic isolation of the population.)

Patients identified as being at increased risk for any familial cancers should be referred for genetic counselling. The Ontario Medical Review published guidelines for the referral of patients with a family history of cancer to cancer genetics clinics (www.oma.org/pcomm/OMR/nov/01genetics.htm). These guidelines identify risk factors for inherited breast and ovarian cancer (Textbox 1). The presence of one or more of these factors in an individual’s personal or family history may suggest an increased risk for hereditary cancer and warrants a referral for genetic counselling. Information on genetic counselling centres within Canada can be found at www.cagc-accg.ca.

Case revisited
The patient’s family history suggests a possible BRCA1 or BRCA2 mutation. She has a sister with premenopausal breast cancer, a paternal grandmother with breast cancer who died at a young age, and a paternal aunt with ovarian cancer. Her Ashkenazi Jewish descent may also increase her risk of a mutation. Information is collected on 3 generations within the family and presented in a genetic pedigree (Figure 1), which proves to be suggestive of hereditary breast cancer. You refer your patient for genetic counselling and testing, and also suggest that her sister with breast cancer seek genetic counselling. Models are available to assess an individual’s risk of having a mutation in the BRCA1 or BRCA2 genes (www4.utsouthwestern.edu/breasthealth/cagene/).

Your patient’s genetic counsellor, using the BRCAPRO model, determines that she has a 30% lifetime risk of breast cancer and a 42% chance of having a BRCA1 or BRCA2 mutation. She then receives genetic testing and is found to have a BRCA1 mutation. Your patient returns to consult you and wants to know what she can do to prevent the development of breast cancer. What would you tell her?

Cancer prevention options
Ultimately, the value of genetic testing for BRCA1 and BRCA2 mutations comes from reducing the number of women who develop breast cancer and the number of women who die of the disease. Women with a BRCA1 or BRCA2 mutation may consider several options for breast cancer prevention. The three main options are prophylactic mastectomy, prophylactic oophorectomy, and chemoprevention (tamoxifen or raloxifene). In addition, a woman may elect to undergo routine screening (secondary prevention) with the goal of detecting any cancers at an early, treatable stage.

Figure 1: A family history of cancer. The patient (arrow) is considered the proband.

Prophylactic mastectomy. The goal of prophylactic mastectomy is to prevent breast cancer, thereby eliminating the potential for metastatic spread and death from the disease. The effectiveness of prophylactic mastectomy in preventing breast cancer in BRCA1 and BRCA2 mutation carriers has been established in a small prospective study and in historical cohort studies of primary and contralateral breast cancers. In the small prospective study of 26 women with a BRCA1 or BRCA2 mutation, observed numbers of cancer were compared to expected numbers of breast cancer based on penetrance estimates. Statistical analysis demonstrated that prophylactic mastectomy offered at least an 89% risk reduction of breast cancer in BRCA1 and BRCA2 carriers. Meijers-Heijboer and colleagues observed no cases of breast cancer over 3 years among 76 women who underwent prophylactic mastectomy. Rebbeck and colleagues observed 2 cases of breast cancer among 191 women after mastectomy, compared to 184 cases among 378 women who did not choose mastectomy (p < 0.0001). Metcalfe and colleagues studied the development of contralateral breast cancer in 491 women treated for hereditary breast cancer using various stand-
ard surgical and adjuvant therapies. Only one contralateral breast cancer was observed among 146 women who had undergone a contralateral mastectomy, versus 33 expected with no contralateral mastectomy ($p < 0.0001$). These studies suggest that the residual breast cancer risk after mastectomy is minimal (less than 5%), and much less than the risk of breast cancer in the general population.

Total mastectomy is currently recommended over subcutaneous or nipple-sparing mastectomy; in the latter procedure, some breast tissue must remain below the nipple-areola complex to maintain the blood and nerve supply, and therefore there is the potential for breast cancer to develop in this residual tissue. However, one systematic review previously reported that in all of the case studies in the literature reporting a failure of a subcutaneous mastectomy in the prevention of breast cancer, the majority of cancers did not occur in this residual tissue. As such, the risks and benefits of both surgical options should be discussed with patients.

Although prophylactic mastectomy offers the best protection against developing breast cancer, it is known that the majority of women in Canada are unwilling to exercise this option.

**Prophylactic oophorectomy.** It has been shown that BRCA1-associated breast cancers are hormonally associated. The purpose of an anti-hormonal therapy is to eliminate or block the effect of ovarian estrogen, and probably progesterone, or to prevent aromatization of androgen to estrogen. Anti-hormonal approaches include therapy with tamoxifen, raloxifene and other selective estrogen receptor modulators (SERMs), ovarian ablation (oophorectomy, radiation or chemical ablation with gonadotropin-releasing hormone [GNRH] agonists) and aromatase inhibition (with an agent such as anastrozole or letrozole). Of these, only tamoxifen and oophorectomy have been well studied in women with BRCA1 or BRCA2 mutations.

The rationale for an anti-hormonal approach comes from the observation that oophorectomy prevents breast cancer in BRCA1 and BRCA2 carriers. Cohort studies estimate the reduction in hereditary breast cancer risk associated with a premenopausal oophorectomy to be about 50%.$^{18-20}$ A recent case-control study reported that this risk reduction may be greater if oophorectomy is performed before age 40 and that the duration of protection is approximately 15 years.$^{21}$ Short-term use of estrogen for menopausal symptom relief in young women after oophorectomy might abrogate some of the breast cancer protection associated with oophorectomy but may be important to a woman’s quality of life. In one study the effectiveness of prophylactic oophorectomy was not reduced by the addition of hormone replacement therapy.$^{20}$ Women who elect for prophylactic mastectomy should receive routine screening for osteoporosis associated with low estrogen.

There are no comparable data on the degree of protection against breast cancer offered by other forms of ovarian ablation such as radiation or GNRH agonists. GNRH agonists are a reversible form of ovarian suppression and thus may be preferred by a woman who wishes to preserve her fertility, but the use of these drugs in BRCA carriers is not widespread and their effectiveness in reducing breast cancer risk is unknown. There remains the concern that these non-surgical approaches to ovarian ablation do not address the risk for ovarian or fallopian tube cancers, which are also elevated in BRCA1 and BRCA2 carriers.

**Selective estrogen receptor modulators.** Tamoxifen is a selective estrogen receptor modulator (SERM) that competes with estrogen for binding to the estrogen receptor. In humans, tamoxifen acts as an estrogen antagonist in breast tissue, inhibiting the growth of estrogen-dependent breast tumours.$^{22}$ On theoretical grounds, tamoxifen should not reduce the incidence of estrogen-receptor (ER) negative breast cancers, and most breast cancers that occur in BRCA1 (but not BRCA2) carriers are ER negative. An attempt to understand the preventative role of tamoxifen was made in the National Surgical Adjuvant Breast and Bowel Project – P1 trial.$^{22}$ In this study, the authors compared the incidence of breast cancer among women who took tamoxifen with the incidence among those who took a placebo. In the cohort of 288 women who developed breast cancer during the study, 8 women were found to have a BRCA1 mutation and 11 were found to have a BRCA2 mutation. When cancer incidence was examined in this group of women with BRCA1 and BRCA2 mutations, it was concluded that tamoxifen was protective against breast cancer in women with a BRCA2 mutation, but not in those with a BRCA1 mutation. No protective effect was seen with tamoxifen for BRCA1 carriers, but the number of cases is too small for the study to be definitive. In a large case-control study, tamoxifen was found to reduce the incidence of contralateral breast cancer in affected BRCA1 and BRCA2 carriers by
about one-half (odds ratio = 0.5; 95% confidence interval 0.30–0.85). If we assume that contralateral cancers in carriers are representative of all new primary breast cancers, the results of this study might be extrapolated to the prevention of first primary breast cancers. But this conclusion would be invalid if the 2 primary cancers were not independent — for example, if tamoxifen were given only to ER positive patients, and if the ER status of bilateral cancers were highly correlated. In a recent study by Weitzel and colleagues, the majority of contralateral breast cancers after ER-positive breast cancer were in fact, estrogen-receptor negative, suggesting that tamoxifen prevents ER-negative contralateral breast cancers.

There are risks associated with taking tamoxifen: for every 10,000 women who take tamoxifen there are 15 endometrial cancers, 2 uterine sarcomas, 4 cerebrovascular events, and 5 pulmonary emboli per year above that expected in those not on tamoxifen.

**Screening.** The goal of screening is to identify breast cancer at a stage when surgical cure is likely. For women in the general population, this outcome would pertain to small (< 1 cm) node-negative tumours with no evidence of distant spread. However, BRCA1-associated breast tumours are typically high grade and are estrogen-receptor negative, which may impart higher risk even when they are detected early. Although several small studies have been done of breast-cancer-specific survival in women with a BRCA1 or BRCA2 mutation, there is little consensus on survival outcomes in this group of women. In one study involving BRCA1 carriers, little correlation was found between tumour size and lymph-node positivity, as would be expected with sporadic breast cancer. About one-third of BRCA1 carriers had lymph node metastases detected at diagnosis, regardless of tumour size, making it difficult to predict the benefit of screening using survival data generated from a comparison group of non-carriers.

A number of advisory groups in the United States and Europe have published recommendations for surveillance for women at hereditary risk for breast cancer and ovarian cancer. In general, these guidelines called for annual mammography beginning around age 25, as well as monthly breast self-examinations (BSE) and clinical breast examination (CBE) once to twice a year.

Certain histological features of BRCA1-associated breast cancer (e.g., the appearance of pushing margins) and high breast density (characteristic of young women) in women with a BRCA1 or BRCA2 mutation may make BRCA-associated tumours difficult to detect mammographically. Studies conducted in the US and in the United Kingdom of women under 50 with a family history of breast cancer reported mammography sensitivities of 63%–70% and 44%, respectively. Goffin and colleagues found that only 2 of 8 breast cancers (25%) in BRCA1 carriers were detectable by mammogram at diagnosis, versus 27 of 35 (77%) among non-carrier controls (p = 0.01). In a large cohort at a single centre (n = 251), of 12 breast tumours diagnosed in BRCA mutation carriers, fewer than half were detected by mammogram.

Breast magnetic resonance imaging (MRI) offers the promise of a greatly improved sensitivity of detection of breast cancers in those at high risk. Early studies reported sensitivities in the range of 100% for invasive breast cancer, but later studies that included ductal carcinoma in situ (DCIS) reported lower sensitivities. In the largest series reported to date, the sensitivity of MRI was 83% for invasive disease but was only 71% overall. However, the benefit attributable to finding cases of DCIS (versus early invasive cancers) has not been established. In a study with longitudinal follow-up, MRI detected 9 breast tumours that were missed by the other screening modalities. Of note, only 2 of the 22 women with breast cancer (9%) detected in this Canadian trial had lymph node metastases. Thus, we feel that MRI has a role in screening BRCA mutations carriers. It is not clear if the addition of mammography to MRI improves the sensitivity of screening.

**Case revisited**

Your patient is BRCA1 positive, and women with a BRCA1 or BRCA2 mutation represent the group at highest risk for breast cancer. She should be made aware of her options to reduce her cancer risk. Prophylactic mastectomy has the greatest likelihood of preventing cancer but is not acceptable to many women. The risk reductions resulting from tamoxifen and prophylactic oophorectomy are lower (approximately 50% risk reduction for each) and are associated with the side effects of hormone withdrawal and infertility. For these reasons, for many women screening is the preferred option.
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