Breast cancer risk management for moderate-risk and high-risk women

An accurate assessment of breast cancer risk can help women make important health care decisions.

ABSTRACT: Because breast cancer is the number one cause of death for women between age 35 and 54 years, an accurate assessment of risk is important. Knowing whether her risk is high, moderate, or low allows a woman to make decisions regarding appropriate risk-reducing interventions, strategies, and lifestyle changes. For high-risk women, management options include intense screening and surveillance protocols or prophylactic mastectomy. Genetic testing for mutations in BRCA1 and BRCA2 may be important to stratify risk for individuals and families. For moderate-risk women, breast screening is an appropriate strategy. Both groups of women are suitable for breast cancer prevention trials. Women in all risk groups can benefit from a lifestyle that includes moderate exercise, a low-fat high-fibre diet, and low alcohol consumption.

Breast cancer is the most frequently diagnosed cancer in Canadian women. Each year in British Columbia, 2700 new cases of breast cancer will be diagnosed and 640 women will die of this disease. There is much fear and anxiety regarding breast cancer because it is the number one cause of death for women between age 35 and 54. It often affects women in the prime of their lives and therefore has additional significant implications for families, friends, colleagues, and society in general. Breast cancer advocacy has increased awareness, research, and funding, which in turn have resulted in earlier detection, more successful treatments, and improved survival.

An accurate assessment of risk is important for individual women to enable them to make decisions regarding appropriate risk-reducing interventions, strategies, and lifestyle changes.

Risk assessment
Risk assessment is based on personal risk factors and family history of breast cancer. Strong risk factors (risk greater than four times normal) are family history of premenopausal bilateral breast cancer or premenopausal breast cancer in a mother and sister, breast and ovarian cancer in close relatives, evidence of genetic susceptibility in mutations of BRCA1 or BRCA2, personal history of lobular carcinoma in situ, atypical hyperplasia, and mammographic density occupying more than 75% of the breast volume.

Moderate risk factors (risk greater than two to four times normal) are older age, North American and northern European residence, family history of premenopausal breast cancer, personal history of breast cancer, hyperplasia without atypia, and mammographic density occupying more than 50% of the breast volume.

Weak risk factors (risk up to two times normal) are family history of postmenopausal breast cancer, high socioeconomic status, nulliparity, later age at first birth (>30 years versus <20 years), later age at menopause.

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High-risk women

Women who have a family history of multiple (three or more) relatives with breast cancer, especially premenopausal or bilateral breast cancer, should be referred to the Hereditary Cancer Program (HCP) of the British Columbia Cancer Agency (BCCA) for genetic counseling. The family history often includes ovarian cancer. After consultation with a genetic counselor or medical geneticist, a patient will be offered genetic testing for BRCA1 and BRCA2 if appropriate. BRCA1 and BRCA2 are very important but relatively uncommon genes that account for 5% to 10% of all breast cancers. The counseling includes education regarding basic genetics and risk assessment for an inherited predisposition for breast and ovarian cancer. The risks, benefits, and limitations of genetic testing, including the psychosocial, legal, and ethical implications, are discussed. Women who test positive for a mutation in BRCA1 or BRCA2 have a 70% to 80% lifetime risk of developing breast cancer and a 20% to 40% lifetime risk of developing ovarian cancer. A true-negative test occurs only when there is a known mutation in the family and an individual is found to be negative for the family mutation. When a mutation is not found in a family, the result is uninformative. It could be due to a false-negative, as the sensitivity of the testing method is 90% to 95%, or because a mutation exists in an as-yet unidentified breast cancer gene, or because a mutation truly does not exist in that family. These families are still at moderate risk for breast cancer, as 30% may have a cluster of breast cancers due to an interaction of multiple factors not attributable to BRCA1 or BRCA2.

Women who are carriers of BRCA1 or BRCA2 mutations (and have no prior history of breast or ovarian cancer) can be referred to the Hereditary Cancer Program High-Risk Clinic, where they will be seen every 6 months for a general physical examination that pays particular attention to the breast and regional lymph nodes. These women are taught breast self-examination and encouraged to perform this monthly. Annual mammograms are performed from age 25 or from the age that is 10 years younger than the age of the relative with the earliest breast cancer diagnosis in the family. In addition, we are investigating the use of annual breast ultrasound and magnetic resonance imaging as screening modalities in an attempt to increase the early detection rate. The latter two investigations are not indicated for screening in the general population, but may be useful in specific clinical scenarios in the diagnostic workup of a suspicious mass.

Women are advised that they may wish to consider prophylactic mastectomy as a successful risk-reducing strategy. Recent data show prophylactic mastectomy confers a greater than 90% reduction in breast cancer risk. No recommendation is made for or against prophylactic surgery, as it is recognized to be a very personal decision. Many factors contribute to this decision, including underlying personality traits and family experience of breast cancer. As part of the decision-making process, we discuss the implications of disturbance in body image, potential impact on sexuality, psychosocial sequelae, including depression, and the risks and morbidity of surgery. There is no optimal time to perform the surgery, but greater benefit is derived from performing the surgery earlier rather than later. All women considering prophylactic surgery are encouraged to review reconstruction options with a plastic surgeon prior to making a final decision. These women are also at increased risk for ovarian cancer and having a prophylactic bilateral salpingo-oophorectomy may decrease the risk of ovarian cancer by 90%; this surgery can also result in a decreased breast cancer risk of 50%.

Women who have previously been diagnosed with breast or ovarian cancer and are subsequently found to have a mutation in BRCA1 or BRCA2 should have screening and follow-up recommendations made by their oncologist, as the long-term prognosis and risk of metastatic disease must be taken into consideration.

It should be noted that BRCA1 and BRCA2 testing have resumed at the BC Cancer Agency. (Testing was suspended from July 2001 to February 2003 because of the BC government’s concern that genetic testing could infringe upon the patent of Myriad Genetics. BC was the only province to suspend testing.) The testing is fully covered by the Medical Services Plan, as are the screening tests and prophylactic surgeries. The waiting time for a genetic counseling appointment is 6 months. The wait for a genetic test result is an additional 6 months. For individuals who do not meet the HCP criteria for testing, private testing may be obtained through Myriad Genetics at a cost of $3800.

Moderate-risk women

These women have a number of risk factors but do not fall into the high-risk category. For example, a moderate-risk woman has two rather than three postmenopausal relatives with breast cancer. For women aged 40 to 79 who have at least a 10-year life expectancy, annual screening with...
mammography and a physical examination is recommended. This differs from the current screening recommendations for the general female population who are at low or average risk for breast cancer.

**Low-risk women**

The Screening Mammography Program of BC (SMPBC) recommends that women aged 50 to 79 with a life expectancy of at least 10 years should have a mammogram every 2 years.\(^\text{11}\) The Canadian Task Force on Preventive Health recommends that women aged 40 to 49 should discuss the pros and cons of screening with their family physicians. If they then choose to have a screening mammogram, this should be done annually.\(^\text{12}\)

**Men at risk**

Breast cancer is rare in men and accounts for less than 1% of all cancers in men. In 2002, there were 23 men diagnosed with breast cancer in BC. Although male breast cancer is seen in families with a BRCA1 mutation, it occurs more frequently in families with BRCA2 mutations.\(^\text{13}\) In these families, the risk of male breast cancer before the age of 80 was recently estimated at 6.9%. This is 80 to 100 times higher than the risk in the general population. BRCA2 mutations account for 15% of all male breast cancers. For men with BRCA mutations, there is no standard recommendation for breast cancer screening, such as mammography or breast self-examination. Men with BRCA mutations should be made aware of their increased risk and encouraged to seek prompt medical attention for any abnormalities.

**Chemoprevention**

Tamoxifen is the only drug that has been proven to decrease the risk of in situ and invasive breast cancer in healthy moderate-risk or high-risk women. Several other drugs are under investigation, including raloxifene, which has been evaluated in trials for the treatment and prevention of osteoporosis.\(^\text{14-17}\)

The NSABP Breast Cancer Prevention Trial (BCPT) began in 1992 and involved 13,338 North American women who were randomly assigned to either tamoxifen or placebo.\(^\text{14}\) Compared with women in the general population, women in the BCPT were at a three to five times higher risk for developing breast cancer. After a median follow-up of 54 months, a 49% reduction in the incidence of breast cancer (two-sided t test, \(P<.00001\)) was seen across all age groups in the tamoxifen arm (Table 1). This was significant for cancers that were greater than 2 cm in size, lymph node negative, and estrogen receptor (ER) positive. The most significant reduction in the incidence of invasive cancers in the tamoxifen group was seen for women who had a previous diagnosis of lobular carcinoma in situ or atypical hyperplasia. The chief adverse events recorded were endometrial cancers and vascular events (Table 2).

Two additional tamoxifen chemoprevention studies\(^\text{18,19}\) were both negative in early publication. Both studies had fewer patients, a higher non-compliance rate, and were confounded with the inclusion of a significant percentage of women also taking hormone replacement therapy. A subsequent update of the Italian randomized trial showed a reduction in ER-positive breast cancers in high-risk women taking tamoxifen but no benefit for low-risk women.\(^\text{20}\)

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**Table 1. Incidence of breast cancer (per 1000 women per year) in NSABP Breast Cancer Prevention Trial.**

<table>
<thead>
<tr>
<th>Age</th>
<th>General population</th>
<th>Placebo group</th>
<th>Tamoxifen group</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49</td>
<td>1.5</td>
<td>6.7</td>
<td>3.77</td>
</tr>
<tr>
<td>50–59</td>
<td>2.5</td>
<td>6.28</td>
<td>3.10</td>
</tr>
<tr>
<td>≥60</td>
<td>3.5</td>
<td>7.33</td>
<td>3.33</td>
</tr>
<tr>
<td>Any age, with lobular carcinoma in situ</td>
<td>N/A</td>
<td>12.99</td>
<td>5.69</td>
</tr>
<tr>
<td>Any age, with atypical hyperplasia</td>
<td>N/A</td>
<td>10.11</td>
<td>1.43</td>
</tr>
</tbody>
</table>

**Table 2. Adverse events (per 1000 women per year) in NSABP Breast Cancer Prevention Trial.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Endometrial cancer</th>
<th>Vascular events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo group</td>
<td>Tamoxifen group</td>
</tr>
<tr>
<td>≤49</td>
<td>1.09</td>
<td>1.32</td>
</tr>
<tr>
<td>≥50</td>
<td>0.76</td>
<td>3.05</td>
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</tbody>
</table>
Managing your breast cancer risk

High-risk women
Your physician may refer you to the British Columbia Cancer Agency Hereditary Cancer Program for genetic risk assessment for breast cancer. For women who proceed to genetic testing and are found to have mutations in BRCA1 or BRCA2 (genes known to account for some breast cancers), an intense screening program of annual mammography, breast ultrasound, and magnetic resonance imaging may be appropriate. Chemoprevention may be discussed as an option. Some women may choose to have both breasts surgically removed to prevent cancer.

Moderate-risk women
40 to 79 years: You should visit a Screening Mammography Program of BC clinic annually. You might also consider participating in breast cancer prevention studies. If you are very concerned about your breast cancer risk, you may find genetic counseling helpful.

Low-risk women
Your physician will probably suggest that you follow screening guidelines for the general population, as described below.

40 to 49 years: Discuss pros and cons of mammography screening with your physician. If you wish to proceed, you should visit a Screening Mammography Program of BC clinic annually and have a physical exam annually.

50 to 79 years: You should have a screening mammogram every 2 years and a physical exam annually.

Chemoprevention should only be considered after an informed discussion of the risks versus the benefits. For example, a woman who has lobular carcinoma in situ has a 1% per annum risk of developing invasive breast cancer over 30 years. Therefore, if she took tamoxifen for a period of 5 years, at the end of 10 years she would reduce her risk of breast cancer from 10% to 5%.

Tamoxifen is prescribed at 20 mg once a day orally, for 5 years. Common side effects are hot flashes and vaginal symptoms (discharge, dryness, or itching). There were no differences in the incidence of nausea, skin rashes, depression, weight gain, and weight loss reported in the tamoxifen and placebo groups. Risks also include an increased incidence of endometrial cancer, stroke, deep venous thrombosis, pulmonary embolism, and cataracts requiring surgery. The benefits are breast cancer risk reduction and a trend toward fewer bone fractures.

The STAR Trial (Study of Tamoxifen and Raloxifene) is an ongoing breast cancer prevention study. This study is close to completing accrual and will involve 19 000 postmenopausal women at high risk of breast cancer from the United States, Puerto Rico, and Canada. The women are randomly selected to receive either tamoxifen or raloxifene. Both are selective ER modulators. Raloxifene has been evaluated in clinical trials for the prevention and treatment of osteoporosis. In these trials, it was observed to reduce the incidence of breast cancer and did not appear to cause endometrial cancer. Side effects of raloxifene include hot flashes, leg cramps, and an increased risk of deep venous thrombosis and pulmonary embolism. For breast cancer prevention, raloxifene should only be prescribed in the context of a clinical trial. Close to 100 British Columbia women have already entered this study.

New directions
Several breast cancer prevention studies are currently underway in Europe and the United Kingdom. These randomized controlled trials are studying postmenopausal women and comparing an aromatase inhibitor such as anastrozole or exemestane with a placebo. Other trials are comparing tamoxifen with an aromatase inhibitor. As ovarian function declines, the relative proportion of estrogens synthesized in extragonadal sites increases and nonovarian estrogens predominate in the circulation. The aromatase inhibitors work by blocking the conversion of the androgenic precursors testosterone and androstenedione to estradiol and estrone. A new Canadian breast cancer prevention study, NCIC MAP3, has been proposed. This will be a three-arm study of placebo versus exemestane (aromatase inhibitor) versus exemestane and celecoxib (COX-2 inhibitor). The next large-scale North American study to be undertaken will probably compare one of the selective ER modulators, tamoxifen or raloxifene, with an aromatase inhibitor.

The COX-2 inhibitors are also being studied on their own or in combination with either a selective ER modulator or an aromatase inhibitor. For ER-negative cancers, there is some interesting and preliminary research in animals and phase 1 trials involving retinoids and tyrosine kinase inhibitors.

Summary
A detailed family history is an important step in the evaluation of an individual woman’s risk of developing breast cancer. For high-risk women who have an inherited predisposition due to mutations in BRCA1 or BRCA2, genetic testing will stratify that person’s risk further. The decision-making process is often complex and emotional and families can benefit from
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being seen in the Hereditary Cancer Program at BCCA. Moderate-risk women should be encouraged to have an increased awareness of their risk and could benefit from participating regularly in breast screening programs as well as clinical trials evaluating breast cancer risk-reducing strategies. Low-risk women should follow the breast screening guidelines for the general population. All women should be advised that there are beneficial effects from a lifestyle that includes moderate exercise, a low-fat high-fibre diet, and low alcohol consumption.

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Competing interests
None declared.

References