Identification and management of women with a family history of breast cancer

Practical guide for clinicians

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Abstract

Objective To summarize the best evidence on strategies to identify and manage women with a family history of breast cancer.

Sources of information A PubMed search was conducted using the search terms *breast cancer, guidelines, risk, family history, management,* and *magnetic resonance imaging screening* from 2000 to 2016. Most evidence is level II.

Main message Taking a good family history is essential when assessing breast cancer risk in order to identify women suitable for referral to a genetic counselor for possible genetic testing. Offering risk-reducing surgery (bilateral prophylactic mastectomy, bilateral salpingo-oophorectomy) to women with *BRCA* genetic mutations can save lives. All women with a family history of breast cancer should be encouraged to stay active and limit alcohol intake to less than 1 drink per day; some will qualify for chemoprevention. Women with a 20% to 25% or greater lifetime risk of breast cancer should be offered enhanced screening with annual magnetic resonance imaging in addition to mammography.

Conclusion Healthy living and chemoprevention (for suitable women) could reduce breast cancer incidence; enhanced screening could result in earlier detection. Referring women who carry *BRCA* mutations for risk-reducing surgery will save lives.

EDITOR'S KEY POINTS

- Although family physicians believe that they are best suited to taking family histories and stratifying their patients' risk of breast cancer, many think that they lack knowledge in this area.
- Taking a family history helps identify *BRCA* mutation carriers. A good family history assessment should include at least all first-degree relatives from both sides of the family, ethnicity, and the age of diagnosis of affected relatives. Screening tools can help identify those women who should be referred for genetic counseling or enhanced screening.
- Women at substantially increased risk might have cancers detected earlier by enhanced screening with annual magnetic resonance imaging in addition to mammography, and risk-reducing surgeries in *BRCA* mutation carriers save lives. Physical activity and moderating alcohol intake reduce breast cancer risk and should be encouraged.

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About 1 in 9 Canadian women will get breast cancer in her lifetime and 1 in 30 will die of the disease.[1] Collecting an accurate personal and family history is helpful to identify individuals at increased risk of common health conditions, including cancer.[2] Family physicians generally collect family history at the first visit[3] or as part of a periodic health assessment using a Preventive Care Checklist Form.[4] With the identification of genetic mutations that substantially increase women's risk of not only breast but also ovarian cancer, and with the availability of enhanced screening for high-risk women, family physicians are well positioned to prevent breast cancer or facilitate earlier diagnosis. Women referred for annual screening with magnetic resonance imaging (MRI) in addition to mammography might have their cancers detected earlier.[5] Carriers of *BRCA* mutations who opt for risk-reducing surgeries (mastectomy, salpingo-oophorectomy) are less likely to die of breast or ovarian cancer.[6-8]

Case

A 50-year-old woman with a family history of breast cancer presented to her family doctor requesting referral for high-risk breast screening. Her mother was diagnosed with breast cancer at age 75 and her maternal grandmother at age 60.

She had menarche at age 14, delivered her first of 4 children at 29, and has had 2 previous benign breast biopsies. She is active and drinks less than 1 alcoholic drink per day. She is premenopausal, is of Scottish descent, and has no current breast symptoms.

Her doctor advises her that she is not at high enough risk to be considered for MRI screening in addition to mammography. She reassures her that her recent mammogram findings were within normal limits. Determined, the woman seeks a second opinion from another family doctor who refers her to the Ontario Breast Screening Program, which screens women at high risk of breast cancer. The genetic counselor tells her by telephone that, although she does not meet the criteria for *BRCA* testing, she has a greater than 25% lifetime risk of breast cancer and an MRI is offered. The nurse navigator calls to arrange the MRI to correlate with day 7 to 13 of her menstrual cycle. The MRI finds an indeterminate enhancement in the right breast. A targeted ultrasound shows an irregular lesion with spiculated borders. Ultrasound-guided core biopsy reveals an invasive mammary carcinoma.

Sources of information

A PubMed search was performed from 2000 to 2016. Search terms included *breast cancer, guidelines, risk, family history, magnetic resonance imaging screening,* and *management*. Canadian Task Force on Preventive Health Care (CTFPHC) and US Preventive Services Task Force recommendations supplemented by leading site-specific national guidelines were reviewed. Further sources were identified from references with a focus on Canadian data. Most evidence is level II.

Main message

Why is family history important? Cancers tend to cluster in some families, likely owing to interactions between lifestyle factors and variations in genetic code. Women with 1 first-degree relative with breast cancer have a 2-fold increased risk of breast cancer; if that relative had her cancer diagnosed before menopause, the increased risk is 3-fold.[9]

Certain families with multiple relatives with early onset breast, ovarian, or other cancers might have a genetic mutation that predisposes them to early onset cancer. The most common mutations are seen in the *BRCA1* or *BRCA2* genes. A defect in one of these genes impairs its ability to function as a tumour suppressor by repairing damaged DNA. Lifetime risks in the general population are 12% for breast cancer and 1.3% for ovarian cancer,[10] but a woman with a *BRCA1* mutation has a 57% to 65% likelihood of breast cancer by age 70 and a 39% risk of ovarian cancer. A woman with a *BRCA2* mutation has a 45% to 55% risk of breast cancer by age 70 and an 11% to 17% risk of ovarian cancer.[11]

About 5% to 10% of breast cancer is hereditary (due to a single gene mutation),[12] with *BRCA* mutations accounting for about 30% of these high-risk breast cancer families.[13] These *BRCA* mutations occur in between 1 in 300 and 1 in 500 women in the general population[14-17] but in 1 in 50 women of Ashkenazi Jewish ethnicity.[18]

Association with breast cancer has been reported for a number of other gene mutations (eg, *TP53* and Li-Fraumeni cancer syndrome; *CDHI* and *PTEN* and Cowden disease; *STK11* and Peutz-Jeghers syndrome). These syndromes have other features aside from breast cancer and will be considered by genetics specialists.[19]

What is a good family history assessment? At the very least a good family history assessment should include all first-degree relatives from both sides of the family, ethnicity, and the age of diagnosis of affected relatives.[20] Patients in primary care settings more accurately report the absence of disease in relatives than the presence of disease, and reporting accuracy is higher when providing information about first-degree relatives compared with more distant relatives (level II evidence, longitudinal studies across different conditions).[21]

Who should be referred for consideration of genetic testing? The CTFPHC has not made a recommendation with respect to family history, and the National Institute for Health and Care Excellence guidelines[22] suggest taking a family history only if a woman presents with breast symptoms or has concerns about relatives with breast cancer, despite survey evidence that family physicians favour a more proactive role.[23] The US Preventive Services Task Force recommends that primary care providers screen women with a family history of breast, ovarian, tubal, or peritoneal cancer with 1 of 5 "at risk" screening tools to determine eligibility for referral for consideration of genetic testing (grade B recommendation).[24] It also recommends against routine genetic counseling or *BRCA* testing for women with a family history not suggestive of a mutation (grade D recommendation).[24]

These tools include screening for the family history factors listed in **Box 1**—factors that are known to increase the likelihood of a family carrying a *BRCA* mutation. The Referral Screening Tool (81% sensitivity, 92% specificity)[25] and the FHS-7 (Family Health Screening–7) tool (sensitivity 87.6%, specificity 56.4%)[26] are the simplest to use and can be completed by the patient or clinician.

For those in high-risk families with histories suggestive of a mutation, discussion about referral to genetic counseling should start after age 18,[18] and family histories should be updated every 5 to 10 years.[27]

Who qualifies for enhanced screening? Women at considerably increased risk of breast cancer might benefit from enhanced screening with annual MRI in

Box 1. Factors seen in families with a BRCA mutation

The following factors are more common in families with a *BRCA* mutation:

- Breast cancer diagnosed before the age of 50 (especially younger than 35)
- Ovarian cancer at any age (epithelial)
- Bilateral breast cancer in the same woman
- Both breast and ovarian cancer in the same woman or the same family
- Multiple breast cancers on the same side of the family (paternal or maternal)
- Male breast cancer
- Ashkenazi Jewish ethnicity

addition to mammography starting at age 25 to 30. Magnetic resonance imaging is a more sensitive test than mammography for detecting invasive cancers in young *BRCA* mutation carriers.[28] A systematic review of 11 prospective non-randomized MRI screening studies in high-risk women revealed the overall sensitivity of mammography alone to be 39% while that of mammography and MRI combined was 94%.[29] Patients should be cautioned about higher false-positive rates (23% vs 5%) (level II evidence).[29] There have been no randomized trials to determine whether MRI for breast screening affects survival.

The American Cancer Society recommends enhanced screening for the following groups: *BRCA* carriers, untested first-degree relatives of a carrier, a woman with a history of therapeutic chest wall radiation between the ages of 10 and 30, or anyone with a lifetime risk of breast cancer of 20% to 25% or greater, calculated using risk assessment tools (level II evidence from non-randomized screening trials and observational studies).[30] A commonly used, validated risk assessment tool is the International Breast Intervention Study risk tool, also called the *Tyrer-Cuzick model*. It can be accessed online at **www.ems-trials.org/riskevaluator**.[31] This risk model combines family history and age of onset of cancers, with height, weight, reproductive history, hormone use, and history of any atypical breast biopsies. The National Comprehensive Cancer Network guidelines suggest an annual clinical breast examination in addition to enhanced screening for these groups (level III evidence, expert opinion).[32]

Ontario introduced one of the first organized high-risk breast cancer screening programs in July 2011, the Ontario Breast Screening Program, which offers high-risk screening (no clinical breast examination) to women aged 30 to 69 who meet category A criteria consistent with the American Cancer Society recommendations, except that a minimum 25% lifetime risk is required rather than 20% to 25%. Published first-year results show higher cancer detection rates most significant in *BRCA* mutation carriers (detection rate for known *BRCA* carriers of 30.8 per 1000 initial screening examinations [95% CI 19.4 to 43.7], compared with a detection rate of 6.9 per 1000 [95% CI 3.0 to 13.5] for those with a family history and ≥ 25% risk [$P < .001$]).[5]

The Ontario Breast Screening Program referral form also has category B criteria such that women who are untested first-degree relatives of a *BRCA* mutation carrier or women with a personal or family history suggestive of a mutation might be referred for consideration of genetic counseling and testing (**www.cancercare.on.ca/obsphighrisk**).

In a high-risk screening program in British Columbia, the incremental cost-effectiveness ratio of annual MRI and mammographic screening for *BRCA* carriers compared with annual mammography alone was calculated to be $50 900 per quality-adjusted life-year gained.[33]

Who should be referred for risk-reducing surgery? Carriers of *BRCA* mutations should be offered bilateral prophylactic mastectomy (BPM) with reconstruction and risk-reducing salpingo-oophorectomy (RRSO) after childbearing is complete and before menopause.[34] A BPM in a mutation carrier does not eliminate breast cancer risk, but risk is reduced by more than 90% (level II evidence from cohort studies of high-risk women and *BRCA* mutation carriers).[35-37] Women having this surgery should be offered reconstruction and empathic support. Hartman et al determined that 6 high-risk women would need to be treated with BPM to prevent 1 breast cancer.[35]

An RRSO in a mutation carrier reduces the risk of dying of breast cancer by 50% to 56% (level II evidence from an international case-control study and a meta-analysis),[6-8] reduces the risk of dying of ovarian cancer by 80%, and reduces all-cause mortality by 77% (level II evidence from an observational study of *BRCA* mutation carriers).[8] As there is no effective early detection strategy for ovarian cancer, which generally presents at an advanced stage, this demonstrates how a thorough family history and referral for genetic testing can save lives. Women can be offered hormone replacement therapy for management of menopausal symptoms after RRSO.[38] After RRSO most women maintain their previous level of physical and health-related quality of life with reduced worry about ovarian cancer.[27]

What other risk-reducing strategies can we offer? There is sufficient evidence to encourage physical activity in all women with a family history of breast cancer not only for reduction in breast cancer risk, but also for cardiovascular benefits. Women who walk briskly for 30 minutes 5 times per week have an 18% reduction in breast cancer risk, with even more active women having up to a 25% reduction.[39,40] It seems prudent to advise women to limit alcohol intake to less than 1 drink per day on average, given that alcohol at levels of 2 to 3 drinks per day increases risk by 43% (level II evidence from cohort studies).[41]

Chemoprevention has been shown to reduce breast cancers in high-risk women. Both selective estrogen receptor modulators, including tamoxifen and raloxifene, and aromatase inhibitors, including exemestane and anastrozole, have proven efficacy (level I from randomized controlled trials).[42-45] There are limited data on the effectiveness of chemoprevention in mutation carriers. Chemoprevention should be considered for women younger than age 50 with a high-risk family history or a history of atypical hyperplasia, as they have the most favourable risk-benefit ratio.[46] The CTFPHC guideline supports counseling women at high risk about chemoprevention (grade B recommendation).[47] Interested women could be referred to oncologists for a more in-depth discussion.

What about potential harms? Studies of collecting family history do not suggest adverse effects but also do not provide definitive evidence that taking a family history is harmless.[48] One randomized controlled trial evaluating taking a family history as part of a periodic health examination in a family practice setting showed an initial increase in anxiety in the intervention group at weeks 1 and 2 but no difference at 3 months (level I evidence).[49] Enhanced screening with MRI in addition to mammography results in more recalls, most of which are false positives, with associated patient anxiety and costs to the health care system. Most patients do not experience serious psychosocial distress as a result of receiving genetic test results, but some experience symptoms of anxiety and depression.[50]

Conclusion

Our case illustrates how taking a good family history might allow earlier diagnosis of breast cancer. Carroll and colleagues (**page e626**) remind us that family physicians believe that they are ideally suited to have discussions around family history owing to their existing trusting relationships with their patients: "If we don't do it, who will? ... [A]nd who's going to know their history better than us?"[51] Our case reminds us that not all cancers are seen on mammogram and that for women at substantially increased risk an MRI can add value.

Family physicians have an opportunity to make a difference for women with a family history of breast cancer. All women should be encouraged to be physically active and limit their alcohol intake. Women younger than age 50 with a strong family history of breast cancer or with a history of atypical hyperplasia should be considered for chemoprevention. By taking a good family history, updating it regularly, and offering referral to genetic counselors for possible mutation carriers and enhanced surveillance to those with a lifetime risk of 25% or greater, breast cancers will be diagnosed earlier. Risk-reducing surgery for *BRCA* carriers will save lives. For additional information on hereditary breast cancer or to locate a genetics clinic in Canada, visit **www.geneticseducation.ca**.

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Contributors
Both authors contributed to the literature review and analysis, and to preparing the manuscript for submission.

Competing interests
None declared

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