CLINICAL REVIEW

Women at High Risk for Breast Cancer—What the Primary Care Provider Needs to Know

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Until recently, the assessment made by the primary care provider regarding screening for breast cancer was generally limited to decisions about when to initiate mammography. Early diagnosis was stressed as the best protection against breast cancer morbidity. However, there have been recent developments in the ability to predict and modify breast cancer risk. It is therefore important for the primary care provider to be able to identify women at higher risk for breast cancer and be familiar with issues regarding screening and risk reduction. Recent data regarding the evaluation of breast cancer risk, newer screening strategies for high-risk women, and medical and surgical approaches to reduce breast cancer risk and are discussed in this article. (J Am Board Fam Med 2009;22:43–50.)

Each year 170,000 women are diagnosed with breast cancer; screening for breast cancer is one of the topics that primary care providers should address with their patients. Screening for breast cancer has been extensively endorsed and most women in the United States more than 40 years old participate in screening activities.[1,2] In the community mammography remains the main screening tool.[3] However, there have been several important developments in the ability to predict and modify breast cancer risk. Recently, data have become available regarding the evaluation of risk, screening strategies for high- risk women, and medical and surgical approaches that can decrease breast cancer risk. Women who are concerned about their risk for breast cancer and should be counseled and managed appropriately; it is important for primary care providers to be familiar with these issues.

Evaluation of Breast Cancer Risk

Average Risk

The National Cancer Institute's Surveillance, Epidemiology, and End Results program estimates that, based on breast cancer statistics from 2001 through 2003, 12.7% of women born in the United States today will develop breast cancer sometime during their lifetime. This average risk of approximately 12% is often expressed as "1 in 8," whereas the chance that a woman will never have breast cancer is 87.3%, or "7 in 8" women.[4]

Identification of Women at Higher Risk for Breast Cancer

Several approaches are available for identifying women with a higher than average risk of breast cancer. These include an assessment of family history with genetic testing consideration; a review of clinical history, including prior breast biopsies; and the evaluation of mammographic density.

Family History

Many women will have a family history of breast cancer but, among the majority of these women, the risk does not increase substantially and is associated with, at the most, a doubling of the lifetime risk. Only 1% to 2% of breast cancer cases are caused by the inheritance of an autosomal dominant, high-penetrance gene, conferring up to an 85% lifetime risk of breast cancer. In some families, there is also a high risk of ovarian cancer. Features of the family history that suggest cancer may be caused by such a high-penetrance gene include:[5–8]

- Two or more first-degree (parent, sibling, or child) or second-degree (grandmother, grand-

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daughter, aunt, niece, half-sibling) relatives with breast or ovarian cancer.

- Breast cancer occurring before the age of 50 (premenopausal) in a close relative.
- Family history of both breast and ovarian cancer.
- One or more relatives with 2 cancers (breast and ovarian cancer or 2 independent breast cancers).
- Male relatives with breast cancer.
- Two breast cancer susceptibility genes, BRCA1 and BRCA2, have recently been identified; these genes are responsible for approximately 40% of cases of inherited breast cancer. In patients with BRCA1 mutations, the average cumulative risk of developing cancer by the age of 70 ranges between 55% and 85% for breast cancer and between 16% and 60% for ovarian cancer. In BRCA 2-mutation carriers, the risks range between 37% and 85% for breast cancer and between 11% and 27% for ovarian cancer.[9]

Clinical History and Significance of Previous Breast Biopsies

Studies have shown an increased cancer risk in young survivors after radiation treatment. Among women with Hodgkin's disease who received mantle field radiation treatment, the risk of breast cancer increases significantly 15 to 30 years after radiation therapy.[10]

The best-characterized premalignant lesions are atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS). LCIS and ALH, together described as lobular neoplasia, are associated with substantially increased risk of subsequent breast cancer, with lifetime risk estimates ranging from 10% to 20%.[11] ADH is part of the continuum of ductal proliferative breast diseases, ranging from usual ductal hyperplasia to ductal carcinoma in situ (DCIS). The literature review by Arpino et al[11] suggests a 4- to 5-fold increased risk of invasive breast cancer in women with ADH at a median follow-up of 17 years, which is doubled if the woman has an associated family history of breast cancer.

Once thought to be a precursor to invasive carcinoma, LCIS is now considered to be a marker of increased risk for breast cancer. In most cases it is characteristically multifocal and bilateral. More than 50% of patients with LCIS have multiple foci in the ipsilateral breast, and approximately 30% of patients have LCIS in the contralateral breast.[12,13]

LCIS is considered a marker of increased risk of cancer in either breast. In contrast, DCIS (also called intraductal carcinoma) represents the stage of breast cancer development in which most of the molecular changes that characterize invasive breast cancer are already present even though the lesion has not assumed a fully malignant phenotype.[14] DCIS is a precursor to invasive cancer and is therefore not discussed in this review.

A systematic review of published studies done by the Agency for Health care Research and Quality revealed that within 5 years after LCIS diagnosis, 4.2% to 9.3% of patients were diagnosed with breast cancer. In studies that followed patients for more than 5 years, the incidence of cancer was 7.7% to 26.3%.[15]

Mammographic Density

Extensive mammographic density is strongly associated with the risk of breast cancer, with age and mutations in the breast cancer gene being the only other factors associated with a greater risk. A meta-analysis of 42 studies showed that women in the highest quartile of mammographic density have a risk of breast cancer that is approximately 4 to 6 times higher than that of women of similar age in the lowest quartile.[16] In a recent study, Boyd et al[17] also reported an association between breast cancer and extensive mammographic density even when the density was observed as much as 8 years before a breast cancer diagnosis. This finding indicates that the association between extensive mammographic density and an increased risk of breast cancer is not only because of a masking effect of the breast density, which could obscure a cancer, but also because of a biologic connection between breast density and breast cancer.

Breast density is not currently used routinely when assessing breast cancer risk. In the future, however, measures of mammographic density could be useful in assessing the risk of breast cancer and in guiding measures to prevent breast cancer.

Risk Assessment Tools

The use of breast cancer risk assessment tools in the evaluation of risk is a good way for physicians to engage their patients in a discussion of factors that may contribute to their increased risk. These models incorporate family history, which is the main determinant of risk, but some of these models incorporate other risk factors, such as previous ab-

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normal breast biopsies and reproductive history (these are discussed below). Women who are assessed in primary care settings as being high risk by the use of any one of these models should be offered a referral to centers that have expertise in high-risk breast cancer for genetic counseling and a more definitive assessment of risk.

Breast Cancer Risk Assessment Tool

This is an interactive tool designed by the National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project (NSABP) to estimate a woman's risk of developing invasive breast cancer. This is available on the National Cancer Institute's Web site (http://www.cancer.gov/bcrisktool/).

This tool was developed from the original Gail model and includes the following risk factors: current age, race, age at menarche, age at first live birth, the number of first-degree relatives with breast cancer, the number of previous breast biopsy examinations, and presence of atypical hyperplasia. The model predicts a woman's likelihood of having a breast cancer diagnosis within the next 5 years and within her lifetime (up to the age of 90).[18,19] Although this prediction model has been validated in large populations, one of the limitations of this model is that it is not good at predicting individual risk.[20] In addition, this model does not take into consideration the paternal family history, second-degree relatives, or the age at onset in affected relatives. Both of these factors are significant in predicting hereditary breast cancer risk.

Claus Model

The Claus model (http://www4.utsouthwestern.edu/breasthealth/cagene/default.asp) estimates the probability that a woman will develop breast cancer based on her family history of cancer; it incorporates more extensive family history but excludes other risk factors.[6] Risk tables have been published by Claus et al and the risks can be calculated as lifetime probabilities of developing cancer or an estimated risk that a woman will develop cancer over 10-year intervals. It should be emphasized that the Claus model may be used only for women with at least one female first- or second-degree relative with breast cancer; this model does not take into account other risk factors that have been associated with breast cancer, such as age of menarche, age at first live birth, or a family history of ovarian cancer.

Genetic Testing and BRCAPRO

Although less than 10% of all breast cancers are linked to genetic mutations, such as BRCA-1 and BRCA-2, women who carry these mutations are at very high risk for breast cancer. The information provided by genetic testing is invaluable when making informed decisions related to breast cancer risk management. Universal genetic testing has some major drawbacks, namely the high cost and the frequency of mutations of uncertain clinical significance that occur in unselected families. The American Society of Clinical Oncology has devised guidelines suggesting that it is reasonable to consider testing of women whose mutation probability is greater than 10%.[21]

The BRCAPRO is a program that calculates the probability that a particular family member carries a germ-line mutation of the BRCA1 and BRCA2 genes (http://www4.utsouthwestern.edu/breasthealth/cagene/default.asp). The calculations are based on Bayes' rules of determination of the probability of a mutation, given family history.[22] Women who are identified in primary care settings to be at high risk should be referred to genetic counseling for a more definitive risk assessment. Risk assessment tools are recommended as an adjuvant to genetic counseling. Genetic counseling is recommended before mutation testing. Data are not available to determine the optimal age to test.

Screening Strategies in High-Risk Women

Mammography has been proven to detect breast cancer at an early stage. However, for women with an increased risk of breast cancer, newer screening technologies are available for earlier detection, particularly in women younger than 40 years for whom mammography is less sensitive. Contrast-enhanced magnetic resonance imaging (MRI) has been shown to have a high sensitivity (86% to 100%) for detecting breast cancer in high-risk asymptomatic and symptomatic women, although reports of specificity have been more variable (37% to 97%).[23–27] The American Cancer Society now recommends MRI screening in addition to mammograms for women who meet at least one of the following conditions[28]:

- they have a BRCA1 or BRCA2 mutation;
- they have a first-degree relative (parent, sibling, child) with a BRCA1 or BRCA2 mutation (even if they have yet to be tested themselves);

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- their lifetime risk of breast cancer has been scored at 20% to 25% or greater (as defined by BRCAPRO or other accepted risk assessment tools that look at family history and other factors);
- they had radiation to the chest between the ages of 10 and 30; or
- they have clinical syndromes that place them at high risk, such as Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome; or they may have one of these syndromes based on a history in a first-degree relative.

There is still not enough evidence for or against recommending MRI screening in women who[28]:

- have a 15% to 20% lifetime risk of breast cancer based on one of several accepted risk assessment tools that look at family history and other factors;
- have LCIS or ALH;
- have ADH;
- have very dense breasts or unevenly dense breasts on a mammogram; or
- have already had breast cancer, including DCIS.

Screening MRIs are not recommended for women with a lifetime risk of breast cancer below 15%.

Although an MRI is a more sensitive test, it may still miss some cancers that a mammogram would detect. An MRI should therefore be used in addition to, not instead of, a screening mammogram.

For most high-risk women, screening with MRI and mammograms should begin at the age of 30 and continue for as long as the woman is in good health. Because evidence is limited regarding the best age at which to start screening, this decision should be based on shared decision-making between patients and their health care providers, taking into account individual patient circumstances and preferences. Recommendations for screening in high-risk women are summarized in Table 1.

Reducing Risk

Several nonpharmacological interventions have been studied. Regular exercise may reduce breast cancer risk, although the mechanism is unknown.[29] Reduction in body weight and decreasing or stopping alcohol consumption may reduce breast cancer risk in postmenopausal women.[30,31] Dietary folate seems to protect against the increased risk of breast cancer caused by alcohol intake.[32,33] Although not statistically significant, the Women's Health Initiative found that a low-fat diet was associated with a 9% reduction in the risk of breast cancer.[34] Observational studies also suggest that vitamin D and calcium might be involved in the development of breast cancer. Of the 13 studies of breast cancer, 9 reported a favorable association of vitamin D markers or sunlight with cancer risk, including one where the association was limited to premenopausal women; 1 study reported a favorable trend of borderline statistical significance and 3 found no association.[35] None reported adverse effects. However, there are no data from randomized controlled trials ensuring adequate vitamin D intake could reduce the risk of breast cancer. It is important to discuss these with women, but they need to be aware that lifestyle changes alone should not be relied on as the only risk reduction strategies.

Hormonal Interventions

Use of Selective Estrogen Receptor Modulators

The links between hormones and breast cancer has long been recognized. The identification of the estrogen receptor provided a successful target for the treatment and prevention of breast cancer. Selective estrogen receptor modulators (SERMs), which antagonize estrogens in some tissues and mimic their action in others, play a key role in chemoprevention. Tamoxifen acts as an estrogen antagonist in breast tissue and as an estrogen agonist in the endometrium. Conversely, raloxifene behaves as an estrogen antagonist in both the breast and the endometrium. Differences in their molecular and 3-dimensional structures affect the transcriptional activity of the activated estrogen receptor.

The National Surgical Adjuvant Breast and Bowel Project (NSABP P-1) Breast Cancer Prevention Trial evaluated the use of tamoxifen for the prevention of breast cancer in high-risk women who were either pre- or postmenopausal. The study found that tamoxifen, when given for 5 years, decreased the risk for developing invasive breast cancer by 49% in women who were at an increased risk for developing breast cancer. Those with atypical hyperplasia derived the largest risk reduction: 85%.[36] Significant adverse effects are associated with tamoxifen, including hot flashes, endometrial

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Table 1. Breast Cancer Screening for Women at Increased Risk

	Symptom Category	Screening Follow-up
NCCN guidelines*	Prior thoracic RT	Periodic breast self-exam encouraged (<25 years old) Annual clinical breast exam (>25 years old) Annual mammogram (8–10 years after RT or 40 years, whichever first)
	5-year risk of invasive breast cancer ≥1.7%†	Periodic breast self-exam encouraged Clinical breast exam every 6 to 12 months (35 years old)
	Genetic high risk	Monthly self breast exam (18 years old) Bimonthly clinical breast exam (25 years old) Annual mammogram (20–25 years old) Annual MRI (25 years old)
ACS guidelines‡	<15% lifetime risk	MRI not recommended
	15% to 20% lifetime risk	Should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram.
	>20% lifetime risk	Annual mammogram and annual MRI
USPSTF§	Women who are at increased risk for breast cancer (for example, those with a family history of breast cancer in a mother or sister, a previous breast biopsy revealing atypical hyperplasia, or first childbirth after age 30) The USPSTF did not examine whether women should be screened for genetic mutations (BRCA1 and BRCA2) that increase the risk of developing breast cancer, or whether women with genetic mutations might benefit from earlier or more frequent screening for breast cancer.	More likely to benefit from regular mammography than women at lower risk. The recommendation for women to begin routine screening in their 40s is strengthened by a family history of breast cancer having been diagnosed before menopause.

*From National Comprehensive Cancer Network. Clinical practice guidelines in oncology, 2007. Available at http://www.nccn.org.
†Risk based on the breast cancer risk assessment tool.
‡From Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75–89.
§From US Preventive Services Task Force. Screening for breast cancer: recommendations and rationale. Ann Intern Med 2002;137(5 Part 1):344–6.
RT, radiation therapy; MRI, magnetic resonance imaging.

cancer, and venous thrombolembolism. Women may perceive these risks as outweighing the potential benefits and may opt not to take tamoxifen.[37] Tamoxifen was the first drug approved for chemoprevention of breast cancer.

Recent evidence suggests a similar magnitude of benefit from the related drug raloxifene. In the NSABP P-2 Study of Tamoxifen and Raloxifene trial, tamoxifen and raloxifene had equivalent effects in reducing risk of invasive breast cancer in all examined high-risk women who were postmenopausal, including women with a history of atypical hyperplasia or LCIS, who had the highest annual rates of invasive breast cancer.[38] There were fewer noninvasive cancers in the women who took tamoxifen, although this was not statistically significant. Comparisons of raloxifene with tamoxifen show equal efficacy as a chemopreventive agent for breast cancer, but there were fewer thromboembolic disorders, endometrial cancers, hysterectomies, cataracts, and cataract surgeries in women taking raloxifene. Raloxifene was approved for the prevention of invasive breast cancer in high-risk postmenopausal women in 2007.

Women should be offered chemoprevention with SERMs only after a shared decision-making process that involves careful consideration of the risks and benefits. Data are currently needed regarding the optimal time to initiate chemoprevention in women identified as high risk.

Aromatase Inhibitors

The aromatase enzyme is required for the last step in estrogen biosynthesis. The third-generation aromatase inhibitors, which include exemestane, anastrozole, and letrozole, are potent and selective inhibitors of aromatase activity. The effect of aromatase inhibitors, as measured by the degree of aromatase inhibition, is approximately 98% for each of the third-generation agents.

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Interest in the use of the drugs for chemoprevention developed from the findings of the Anastrozole, Tamoxifen Alone and in Combination trial.[39] Postmenopausal women with early-stage breast cancer who were using anastrozole alone had a 58% reduction in contralateral invasive breast cancer. The second International Breast Cancer Intervention prevention trial began in 2003 and compares anastrozole to placebo in 6000 postmenopausal women with an increased risk of breast cancer as well as women with mammographic density covering at least 50% of the breast.[40]

Surgical Interventions

Cancer prediction models work well for populations but are not good at predicting individual risk. In a patient who has no evidence of breast cancer but who is at high risk, bilateral mastectomy is an option for risk reduction. Bilateral prophylactic mastectomy has been reported to reduce breast cancer incidence more than 95%.[41–45]

A recent position statement by the American Society of Surgical Oncology suggests bilateral prophylactic mastectomy may be considered in the following patients without a cancer diagnosis who are at high risk because of[46]:

- the presence of BRCA mutations or other genetic susceptibility genes;
- a strong family history of breast cancer; cancer in multiple first-degree relatives and/or multiple successive generations of family members with breast and/or ovarian cancer;
- histologic risk factors: ADH, ALH, or LCIS confirmed on biopsy (these changes are especially significant if they are present in a patient with a strong family history of breast cancer); or
- difficult surveillance; a clinically and mammographically dense breast may make surveillance difficult.

Patients considering prophylactic mastectomy should also be informed about the potential benefits and risks of immediate reconstruction. The position statement recommended that these patients are best evaluated by a multidisciplinary team, which may include a surgeon, a medical oncologist, a pathologist, and a genetic counselor. It is important for these patients to be aware of potential risks and benefits of prophylactic mastectomy as well as the fact that the procedure does not provide 100% protection against the development of breast cancer. Additional factors to consider include patient age and other comorbidities.

Prophylactic Salpingo-oophorectomy

Bilateral prophylactic salpingo-oophorectomy is widely used for cancer risk reduction in premenopausal women with BRCA1/2 mutations.[47–49] Bilateral prophylactic salpingo-oophorectomy significantly reduces breast cancer risk by approximately 50% and ovarian cancer risk by 80% to 95% but may be accompanied by menopausal symptoms, increased cardiovascular risk, impaired quality of life, and accelerated bone loss.[49] Therefore, decisions regarding the timing of bilateral prophylactic salpingo-oophorectomy and the use of hormone replacement therapy after bilateral prophylactic salpingo-oophorectomy must be made only after consultation with a multidisciplinary team.

A thorough discussion with the patient of alternative approaches including close surveillance, risk-reduction strategies including chemoprevention, and participation in clinical trials is necessary to provide the patient with the full spectrum of risk-reduction options.

Conclusions

Most women will not develop breast cancer during their lifetime. However recent data can help identify the subset of women who are at higher risk for breast cancer. Furthermore, improved screening strategies and treatment options are now available that could decrease the risk for these women.

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