Reducing the risk of breast cancer: A personalized approach

Although primary care physicians often use the same screening schedule and preventive measures for all the women they see, optimal breast cancer risk reduction requires an individualized approach.

One woman in 8 will develop invasive breast cancer over the course of her life. Apart from being female, age is the most significant risk factor.

Providers face many decisions regarding breast cancer screening. At what age should breast imaging be initiated? How frequently should clinical breast exams and mammography be performed? When should chemoprevention be considered? The answers to these questions depend on an understanding of the individual patient’s risk for developing breast cancer.

A family physician is ideally positioned to individualize breast care, based on a thorough patient and family history, physical examination, and appropriate use of a validated risk assessment tool. Yet all too often, physicians use a one-size-fits-all approach.

The time required to take a thorough history is an obvious obstacle to individualized care. Physician lack of knowledge of the benefits and adverse effects of approved breast cancer risk-reduction strategies is a problem, as well—one that this review can help to address.

Identifying patients at risk
Among the known risk factors for breast cancer, some are modifiable (use of oral contraceptives and alcohol consumption, for example); others, such as family history and age at which menopause occurs, are not (TABLE 1). Aging itself confers the greatest risk: The incidence of breast cancer comes close to doubling at each 10-year interval before menopause and continues to climb, but more slowly, thereafter.

Estrogen exposure: The risk is cumulative
A number of studies have linked early onset of menarche (<12 years of age) and late menopause (>55 years) to an in-
Lifestyle modification, imaging, and chemoprevention, as needed, can reduce the likelihood of breast cancer for women at all levels of risk.

Genetic mutations and breast cancer risk
An estimated 5% to 10% of breast cancers are inherited. Genetic susceptibility is generally transmitted as an autosomal dominant trait.

There are 2 known breast cancer genes, BRCA1 and BRCA2, located on the long arm of chromosomes 17 and 13, respectively. The genes themselves encode tumor suppressor proteins. Mutations in these genes impair the DNA repair process, resulting in increased risk.

The chance of carrying a mutation in either BRCA1 or BRCA2 is estimated at one in 500 to 800 in women of Northern/Western European descent. Among Ashkenazi Jews, however, the frequency is about one in 50.

A thorough family history that takes into account both the number of affected relatives and their age at diagnosis (TABLE 2) is helpful in determining whether a patient is at low, high, or very high risk of carrying a genetic mutation. Women who have no first-degree relative with breast cancer—or a relative who was diagnosed with breast cancer after age 50—are at low risk, while those with at least one first-degree relative diagnosed with breast cancer before the age of 50 would be categorized as high risk.

A woman with a family history of early-
onset breast or ovarian cancer or a relative who developed both breast and ovarian cancer, bilateral breast cancer, or male breast cancer would be classified as very high risk for a genetic mutation, as would a patient with 2 or more family members affected by breast or ovarian cancer.

Ashkenazi Jewish heritage and a relative who was diagnosed with ovarian or breast cancer indicate an increased likelihood of a BRCA mutation, as well. Other genetic conditions, with mutations that are distinct from the BRCA genes, have also been linked to breast cancer, but occur less frequently.

BRCA gene testing can confirm very high risk status, prompting the initiation of preventive measures and facilitating early detection. Such testing can also identify—and relieve the anxiety of—noncarriers in high-risk families. Recently published guidelines from the US Preventive Services Task Force (USPSTF) support testing in women with suspicious family histories with a grade B recommendation, indicating that there is at least fair evidence that testing improves important health outcomes and that the benefits of testing outweigh the harms.

The downside of specific BRCA gene testing for patients who find that they do not have this genetic mutation may include a false sense of security and the failure to identify any other genetic mutations. Patients who learn that they do carry a BRCA gene mutation could face psychosocial or economic harm associated with aggressive surveillance and surgical intervention.

Tools can quantify 5-year, 10-year, and lifetime risk
A number of breast cancer risk assessment tools have been developed to help clinicians individualize patient care. None provides the basis for an all-encompassing approach to breast cancer risk or a comprehensive patient discussion of preventive strategies. We have found that, when used in combination, 2 or more predictive models can complement each other and guide the development of a targeted risk reduction approach.

When to use a predictive tool
It is not necessary to use a predictive model for patients at low risk for breast cancer. The tools detailed in TABLE 3 are better suited to women who have a suspicious family history, a history of precancerous breast lesions, or known reproductive risks. Although each model has limitations, it is important that you have a working knowledge of circumstances that favor one tool over another. For instance, the Gail model, the most widely used, can help determine if a particular patient is a candidate for chemoprevention. Others, such as the Tyrer-Cuzick model and the Claus model, are useful in deciding whether a patient is a candidate for breast magnetic resonance imaging (MRI) as an adjunct to mammography screening. Another useful tool is the BRCAPRO, which is used primarily by genetic counselors to assess the likelihood that a patient carries a BRCA1 or BRCA2 mutation and would benefit from genetic testing.

Managing patients at all risk levels
Although patients with average, high, or very high risk will all be managed differently, evidence suggests that lifestyle modification as needed, imaging, and chemoprevention, in some cases, can reduce the likelihood of breast cancer for women at all levels of risk.

For women with an average risk (a 5-year Gail model score ≤1.66% and no significant family history), a discussion of the benefits and risks, as well as the limitations,
Talk to patients at average risk for breast cancer about the benefits and risks of initiating mammography at age 40 vs age 50 and annual vs biennial screening.

of annual screening mammography beginning at age 40 vs age 50 is in order. Several major organizations, the American College of Obstetricians and Gynecologists and American Cancer Society (ACS) among them, have guidelines that support annual mammography beginning at 40 years but do not specify at what age to discontinue screening. In contrast, the USPSTF recommends biennial mammography between the ages of 50 and 74 years (See “The mammography controversy: When should you screen?” J Fam Pract. 2011;60:524-531).

How to proceed? Talk to patients in the 40- to 50-year age range about the benefits and risks of earlier, more frequent screening vs waiting until 50 to start mammography and opting for screening every 2 years. Breast health awareness and the role of clinical breast exams also should be included in a balanced discussion of early detection of breast cancer. A review of the patient’s reproductive status and use of hormone preparations is appropriate, as well.4,5

For very high-risk patients (those with a family history that strongly suggests a genetic predisposition, a confirmed gene mutation, evidence of hereditary breast and ovarian cancer, or a personal history of chest wall irradiation between the ages of 10 and 30 years), a discussion of more aggressive risk-reduction strategies is recommended.4 A clinical breast exam and mammogram should be performed beginning at age 25—or 5 to 10 years before the earliest age at which a first-degree relative was diagnosed.

Starting at age 30, patients at very high risk should undergo annual mammography and breast MRI, either simultaneously or staggered every 6 months, along with a twice-yearly clinical breast exam.14 Breast health awareness and lifestyle modification should be emphasized, and the benefits and risks of chemoprevention should be discussed. Surgical risk-reduction strategies, such as prophylactic mastectomy and oophorectomy, should also be discussed, along with the offer of a referral to a surgeon for consultation.5

What to tell patients about chemoprevention

The USPSTF has issued a grade B recommendation to a discussion of chemoprevention for women who are at high risk for breast cancer and low risk for an adverse event.30 Counseling a patient regarding the risks and

| TABLE 2 |
| Genetic counseling for patients at high risk8,15 |

<table>
<thead>
<tr>
<th>Indication for referral</th>
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<tbody>
<tr>
<td>Known mutation in breast cancer susceptibility</td>
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<tr>
<td>At-risk race/ethnicity: Ashkenazi Jews</td>
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<tr>
<td>Family history (any of the following):</td>
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<tr>
<td>— Two cases of primary breast cancer on the same side of the family</td>
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<tr>
<td>— Primary ovarian cancer on either side of family</td>
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<tr>
<td>— Male breast cancer</td>
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<tr>
<td>— Combination of breast cancer with thyroid cancer, sarcoma, endometrial cancer, pancreatic cancer, brain tumor, gastric cancers, unusual skin changes, leukemia, or lymphoma on the same side of the family</td>
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</table>
benefits of chemoprevention will depend on her age, comorbidities, whether or not she has had a hysterectomy, and her willingness to take the suggested medication.

**Selective estrogen receptor modulators (SERMs).** The American Society of Clinical Oncology Clinical Practice Guideline Update has reviewed the benefits and potential adverse effects of the SERMs tamoxifen and raloxifene. The Society supports the use of tamoxifen in pre- and postmenopausal women for breast cancer risk reduction; it also supports the use of raloxifene for postmenopausal women, the only patient population for which raloxifene has been approved.37

In a review of 7 placebo-controlled, randomized clinical trials and one head-to-head trial, both drugs reduced the risk for invasive, estrogen receptor–positive breast cancer by about 40% compared with placebo. Breast cancer deaths, however, did not decrease.31

Both tamoxifen and raloxifene were found to increase bone mineral density and reduce fracture risk.31 Thromboembolic events—which occurred less frequently with raloxifene than tamoxifen—was the chief adverse effect, with an incidence of 0.4% to 0.7%. In addition, fewer cases of endometrial cancer were reported with raloxifene compared with tamoxifen, making raloxifene the preferred treatment for postmenopausal women with an intact uterus.31

The National Surgical Adjuvant Breast and Bowel Project STAR study—one of the

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**TABLE 3**

**Breast cancer risk assessment tools: What you need to know**5,14,16-23

<table>
<thead>
<tr>
<th>Tool</th>
<th>Intended use</th>
<th>Criteria considered</th>
<th>Results</th>
<th>Limitations</th>
<th>Validation</th>
<th>How to access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gail model</td>
<td>Assess eligibility for chemoprevention in women &gt;35 years</td>
<td>Reproductive history, history of breast biopsies, first-degree relatives with breast cancer</td>
<td>Estimates 5-year and lifetime risk for invasive breast cancer</td>
<td>Can overestimate risk in patients with previous biopsy and atypical hyperplasia results and family history</td>
<td>Validated in independent projects; widely used to define excess risk; modified model for minorities validated</td>
<td>Available at <a href="http://www.cancer.gov/bcrisktool/">http://www.cancer.gov/bcrisktool/</a></td>
</tr>
<tr>
<td>Tyrer-Cuzick* model</td>
<td>Assess need for breast MRI</td>
<td>Hormonal and reproductive history, history of breast biopsies, number and age of onset of first- and second-degree relatives with breast cancer</td>
<td>Estimates 10-year and lifetime risk for invasive breast cancer</td>
<td>Potential for significant overestimation of risk in patients with atypical hyperplasia findings on breast biopsy</td>
<td>Not validated</td>
<td>Go to <a href="http://www.ems-trials.org/riskevaluator">http://www.ems-trials.org/riskevaluator</a> Click on “software downloads” to select the appropriate version</td>
</tr>
<tr>
<td>Claus model</td>
<td>Assess need for breast MRI</td>
<td>Age of onset of first- and second-degree relatives with history of breast cancer</td>
<td>Estimates incremental 10-year and lifetime risk for invasive breast cancer</td>
<td>Looks only at family history, without considering hormonal or reproductive risk factors</td>
<td>Validation does not extend to minorities</td>
<td>Tables found in Cancer (1994;73:643-651) available at no charge from <a href="http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1097-0142/issues">http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1097-0142/issues</a></td>
</tr>
<tr>
<td>BRCAPro</td>
<td>Determine whether genetic testing is indicated</td>
<td>Family history of breast and ovarian cancer</td>
<td>Estimates likelihood of genetic mutation</td>
<td>Time-consuming; requires highly detailed family history</td>
<td>Validation does not extend to minorities</td>
<td>Not widely available; used primarily by genetic counselors</td>
</tr>
</tbody>
</table>

*Also known as the IBIS model.

IBIS, International Breast Cancer Intervention Study; MRI, magnetic resonance imaging.
trials included in the review—initially reported that tamoxifen and raloxifene were equivalent in reducing breast cancer risk in postmenopausal women at increased risk.\textsuperscript{28} In an updated analysis based on 81 months of use, however, tamoxifen resulted in a 50% reduction in the incidence of breast cancer vs a reduction of 38% for raloxifene.\textsuperscript{32}

The greater reduction in breast cancer risk seen with tamoxifen comes at a potential cost. Tamoxifen was found to have a worse adverse effect profile, leading to a higher risk for endometrial hyperplasia and hysterectomy, as well as thromboembolic events. The difference in all-cause mortality, however, was not statistically significant.\textsuperscript{32}

Aromatase inhibitor therapy. The National Cancer Institute of Canada recently published a major chemoprevention trial, evaluating the effectiveness of aromatase inhibition in breast cancer risk reduction.\textsuperscript{29} This randomized, double-blind trial of exemestane vs placebo included more than 4500 women with a median follow-up of 3 years, and found that the exemestane reduced the incidence of invasive breast cancer in postmenopausal women at moderate risk by 65% (hazard ratio=0.35; 95% confidence interval, 0.18-0.70; \(P=0.002\)).\textsuperscript{29}

IBIS-II, a multicenter study in the United Kingdom, randomly assigned 6000 women at increased risk for breast cancer to placebo or anastrozole, an alternative aromatase inhibitor. This trial is ongoing, and breast cancer incidence is the primary endpoint.\textsuperscript{33} Aromatase inhibitors have not been approved by the US Food and Drug Administration for breast cancer prevention.\textsuperscript{34}

Weighing the benefits of surgery
For women who have a strong family history of breast cancer or are known carriers of a BRCA1 or BRCA gene mutation, the already high risk of developing breast cancer increases as they age. Prophylactic surgery—risk-reduction mastectomy (RRM) and/or bilateral salpingo-oophorectomy (RRSO)—has been found to lower the risk.\textsuperscript{5,36,37}

RRM can reduce the risk of breast cancer by as much as 90% for such patients;\textsuperscript{38,39} RRSO yields similar results, reducing the risk of ovarian cancer by 80% to 95% and the risk of breast cancer by 40% to 59%, provided the surgery is performed before the patient is 50 years old.\textsuperscript{36,37}

These potential benefits must be weighed against the harm associated with surgically induced menopause, with the attendant risks of cardiovascular disease, osteoporosis, and menopausal symptoms.\textsuperscript{40} Notably, hormone therapy use after RRSO in women with a gene mutation has not been found to increase the risk of breast cancer. In fact, it may be associ-
ated with a decreased risk. In general, short-term use of low-dose estrogen—up to the age of 51 or 52 years—is considered to be safe for this population, but long-term data on breast cancer risk are lacking.

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References