Preventing Breast Cancer Through Identification and Pharmacologic Management of High-Risk Patients

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Abstract

Breast cancer remains the most common cancer in women in the United States. For certain women at high risk for breast cancer, endocrine therapy (ET) can greatly decrease the risk. Tools such as the Breast Cancer Risk Assessment Tool (or Gail Model) and the International Breast Cancer Intervention Study risk calculator are available to help identify women at increased risk for breast cancer. Physician awareness of family history, reproductive and lifestyle factors, dense breast tissue, and history of benign proliferative breast disease are important when identifying high-risk women. The updated US Preventive Services Task Force and American Society of Clinical Oncology guidelines encourage primary care providers to identify at-risk women and offer risk-reducing medications. Among the various ETs, which include tamoxifen, raloxifene, anastrozole, and exemestane, tamoxifen is the only
Breast cancer remains the most common cancer in women in the United States and the second most common cause of cancer death overall in women. One in 8 women will have breast cancer in their lifetime, at a median age of 62 years. Only 5% to 10% of breast cancers occur because of an inherited genetic variant; therefore, health care providers must be aware of not only a woman’s family history of breast cancer but also contributing personal risk factors when determining whether a woman is at increased risk for breast cancer. Although there is no standardized approach to assessing breast cancer risk, risk calculators are available to identify women at high risk for breast cancer. The most commonly used tools include the Breast Cancer Risk Assessment Tool (BCRAT, or Gail Model) (https://bcrisktool.cancer.gov/index.html) and the International Breast Cancer Intervention Study (IBIS) risk calculator (http://ems-trials.org/riskevaluator). Alternatively, providers can use the combination of a woman’s known breast cancer risk factors to guide risk management decisions.

Primary care providers are on the front lines of care. A proactive approach to identifying individual women at increased risk for breast cancer is imperative because these women benefit from genetic testing, high-risk breast imaging surveillance, preventive endocrine therapy (ET) interventions, and lifestyle education. The purpose of this review is to provide a simplified approach for the busy primary care provider to assess breast cancer risk and offer a risk-reducing medication by using a framework of shared decision making.

IDENTIFYING WOMEN AT HIGH RISK FOR BREAST CANCER

Breast cancer risk prediction models are individualized statistical methods that estimate a woman’s probability of breast cancer development on the basis of disease-specific risk factors. Multiple models are available to guide clinical decision making; however, available models are limited in calibration and discriminatory accuracy and can be time-consuming. Validated risk calculator tools with the highest predictive value are preferred. The BCRAT and IBIS risk calculators are included in the current evidence-based guidelines, including those from the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network, and US Preventive Services Task Force, to assist in identifying high-risk women.

The BCRAT incorporates current age, age at menarche, age at first childbirth, breast cancer history in first-degree relatives, history of breast biopsies, and history of atypical hyperplasia. Risk may be underestimated if breast biopsy results with atypical hyperplasia are included. This model is not intended for women with a history of carcinoma in situ, mantle (chest) irradiation, or a known inherited breast cancer gene variant. A 2018 review by Al-Ajmi et al found that the BCRAT had good calibration but was limited when predicting individual risk of breast cancer development. In general, a BCRAT 5-year risk of at least 1.7% is considered high risk, and risk-reducing medications could be considered in women at low risk for medication adverse effects. However, the US Preventive Services Task Force guidelines state that an estimated 5-year risk of at least 3% is considered substantial risk, and ET should be recommended for eligible women unless a contraindication to ET outweighs the benefit.

The IBIS v.8.0 model is among the best-calibrated breast cancer risk models available; however, it, too, has modest discriminatory accuracy. It combines classical breast cancer risk factors plus breast density and allows for a more detailed family history entry, including
affected first-, second-, and third-degree relatives plus their age at diagnosis. It can provide a 10-year and a lifetime calculated breast cancer risk (http://ems-trials.org/riskevaluator). Risk may be overestimated with inclusion of breast biopsy results of atypical hyperplasia or lobular carcinoma in situ (LCIS) for those with very dense parenchyma on mammography and for Hispanic women. The ASCO 2019 guidelines for use of ET state that for select women with an IBIS 10-year risk estimate of 5%, the benefits of ET outweigh the risks, similar to having a BCRAT 5-year risk estimate of 3% or more.10

Atypical ductal hyperplasia confers a future risk of breast cancer to either breast of approximately 1% to 2% per year or approximately 25% to 30% at 25 years of follow-up. Such cumulative incidence data are preferred because commonly used breast cancer risk models, such as the BCRAT or IBIS model, do not accurately predict risk for individual women with atypical hyperplasia. Lobular carcinoma in situ confers a 2% risk per year, and in general, this confers about a 20% lifetime risk.12,13 Recognizing the benefit of ET is imperative in this population.

Women with known genetic variants conferring an increased risk of breast cancer, such as BRCA 1/2 (for expansion of gene symbols, use search tool at www.genenames.org), are at the highest risk for breast cancer. Additionally, women who received mantle (chest) irradiation between the ages of 10 and 30 years have a substantial increase in breast cancer risk.

For primary care providers, a barrier to prescribing ET includes lack of an easily accessible and user-friendly risk assessment strategy. The 2019 US Preventive Services Task Force Medication Use to Reduce Breast Cancer Recommendation Statement and the 2019 ASCO Clinical Practice Guideline Update support the use of a simplified, efficient approach to breast cancer risk assessment to guide ET eligibility. The approach can be used in a busy primary care setting with limited time to assess risk with standardized risk calculators. In general, high risk includes women aged 35 years and older without a personal history of ductal carcinoma in situ or invasive breast cancer who have a combination of risk factors, including those commonly used in breast cancer risk assessment models or breast cancer risk reduction trials. Collecting a family history and identifying factors that confer a strong family history are important. A strong family history includes the following factors: a close relative (first or second degree) with breast cancer diagnosed before age 45 years, 2 first-degree relatives with breast cancer diagnosed at any age, multiple affected relatives over several generations on the same side of the family, bilateral breast cancer, or male breast cancer. In addition, women with an estimated relative risk of at least 4 times the population risk for their age if 40 to 44 years old, or 2 times their age if 45 to 69 years old, are at high risk for breast cancer and should receive appropriate risk reduction counseling. These estimates confer essentially the same risk as a calculated 5-year risk of 3% or more, a 10-year risk of 5% or more, or a lifetime risk of 20% or more. Women with a combination of lifestyle and reproductive risk factors such as obesity, older age, early menarche (onset at age ≤10 years), nulliparity or late age of first parity (age ≥30 years), prolonged combined menopausal hormone therapy (>3 years of use after the expected age of the onset of menopause), and increased breast density are eligible for ET counseling.

ENDOCRINE THERAPY AS A RISK-REDUCING MEASURE
Medications to reduce breast cancer risk are greatly underused despite multiple evidence-based publications reporting their efficacy for decreasing breast cancer risk in high-risk women. It is estimated that less than 4% of eligible women accept use of ET. This low rate of usage by eligible patients is multifactorial and includes limited benefit-risk understanding; concerns for adverse effects, lack of knowledge, and limited time for risk assessment and medication counseling; and a public misconception that ET is a chemotherapeutic agent with cytotoxic properties.14,15 The age range to
consider initiating ET is 35 to 70 years, but it may be used earlier in women with atypical hyperplasia, LCIS, previous mantle irradiation, or known high-risk breast cancer genetic variants. Endocrine therapy options are summarized in the Table.

**Selective Estrogen Receptor Modulators:**

**Tamoxifen and Raloxifene**

Tamoxifen selectively blocks estrogen in the breasts but acts like estrogen in other tissues such as bone and uterus. Tamoxifen is US Food and Drug Administration—approved for breast cancer risk reduction in premenopausal and postmenopausal women older than 35 years with a BCRAT 5-year risk of more than 1.7%. In the National Surgical Adjuvant Breast and Bowel Project P-1 study,\(^{16}\) 5 years of standard therapy with tamoxifen 20 mg/d decreased the risk of invasive estrogen receptor—positive breast cancer by approximately 50% in high-risk women, by 86% in those with atypical hyperplasia, and by 56% in those with LCIS. The IBIS-I breast cancer prevention trial\(^ {17}\) reported an extended long-term benefit after completion of 5 years of tamoxifen treatment. No studies to date have found a survival benefit with tamoxifen. Recently, a study of tamoxifen 5 mg/d vs placebo in patients with atypical hyperplasia or ductal carcinoma in situ by DeCensi et al\(^ {18}\) found a 50% decreased risk of invasive cancer with fewer adverse effects than standard-dose

<table>
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<th>TABLE. Comparison of Risk-Reducing Treatment Options</th>
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<td><strong>Characteristic</strong></td>
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AI, aromatase inhibitor; DVT, deep vein thrombosis; FDA, US Food and Drug Administration; PE, pulmonary embolism.
tamoxifen. The study dose was given for 3 years rather than the conventional 5 years, and women at high risk because of a family history of breast cancer were excluded. Although 5-mg tablets are not currently available in the United States, taking 10 mg every other day has these same theoretical benefits and is an option. \(^{18}\)

Data specifically addressing the use of tamoxifen in women with BRCA1 and BRCA2 variants are limited. However, in a small prospective study, tamoxifen reduced breast cancer occurrence by approximately 60% in BRCA2 variant carriers but did not reduce breast cancer occurrence in BRCA1 carriers, possibly because breast cancers that develop in BRCA1 carriers tend to be hormone receptor negative. \(^{19}\)

Risks and adverse effects of tamoxifen therapy should be discussed with the patient before drug initiation. Tamoxifen is associated with a small to moderate increased risk of venous thromboembolism events, with a higher risk in older women (4-7 events per 1000 over 5 years). Menstrual irregularities can occur, and women taking tamoxifen should be educated to report any abnormal vaginal symptoms (eg, bloody discharge, spotting, and leukorrhea). Any new vaginal symptoms or persistent bleeding requires a gynecologic evaluation. Tamoxifen is a teratogen; therefore, contraception is strongly recommended for premenopausal women. The addition of oral hormonal contraception may further increase thrombotic risk, whereas certain intrauterine devices have less thrombotic risk. Tamoxifen is associated with an increased risk of venous thromboembolism but less than that for tamoxifen. There is no increased risk of endometrial cancer. \(^{22}\) There is no information on raloxifene and reduced breast cancer risk in postmenopausal women with a BRCA1 or BRCA2 pathogenic variant.

Until recently, no clinical trials had addressed the efficacy of ET in women who received mantle irradiation between ages 10 and 30 years. A phase IIb trial from 2020 has found that low-dose tamoxifen citrate for breast cancer risk reduction in radiation-induced cancer survivors was effective in reducing established biomarkers of risk, including breast density. \(^{23}\)

Aromatase Inhibitors: Exemestane and Anastrozole

Aromatase inhibitors (AIs), including anastrozole and exemestane, are effective in reducing estrogen by blocking the enzyme aromatase, which is responsible for the peripheral conversion of androgens to estrogen. These medications substantially decrease the risk of breast cancer in postmenopausal women. In the MAP.3 study of
more than 4500 patients, exemestane 25 mg/d substantially decreased the risk of breast cancer by 65%. Adverse effects noted in this study were hot flashes, fatigue, sweating, insomnia, and arthralgia.24 The IBIS-II trial25 reported that anastrozole 1 mg/d also decreased breast cancer risk, with similar adverse effects to exemestane. Both medications have been found to decrease bone mineral density; however, prevention trials report no increase in fractures.25

Studies are underway on the use of AIs to reduce the risk of primary breast cancer for patients with BRCA pathogenic variants. The most up-to-date guidelines regarding which genetic syndromes are associated with an increased breast cancer risk are available through the National Comprehensive Cancer Network (https://www.nccn.org/professionals/physician_gls/default.aspx).

Choosing ET: A Simplified Individualized Approach
The choice of ET should be individualized in women at increased risk for breast cancer (Figure). Specific examples are given in the Supplemental Table (available online at http://www.mayoclincproceedings.org).

MANAGING ET ADVERSE EFFECTS
Common adverse effects associated with ET include hot flashes, vaginal dryness, joint pain, and osteoporosis risk. If adverse effects of ET are not effectively managed, poor adherence to ET may result. Options for nonhormonal vasomotor management include cognitive behavioral therapy, venlafaxine, gabapentin, oxybutynin, acupuncture, exercise, and avoiding spicy foods, caffeine, and alcohol.26-28 Women experiencing vaginal dryness and atrophy can be offered low-dose intravaginal estrogen options and/or over-the-counter vaginal moisturizers.29 Women with an intact uterus who are using local vaginal estrogen therapy do not require progesterone. Several large breast cancer prevention trials (NSABP Study of Tamoxifen and Raloxifene and Mammary Prevention 3) permitted vaginal estrogen for the management of vaginal dryness in study participants.
Joint pain can be bothersome and decreases the quality of life for about 30% of women taking AIs. Regular exercise and use of nonsteroidal anti-inflammatory drugs can be helpful in managing symptoms. Acupuncture has also been found to be effective. Baseline monitoring of bone mineral density is recommended before initiating AI therapy in postmenopausal women. Bone mineral density testing should be offered every 1 to 2 years, depending on fracture risk. It may be necessary to initiate bone-modifying therapy if osteopenia is present (T score > −2.0), and the benefits of continuing AI outweigh the risk of bone loss. If severe osteoporosis is present, a selective estrogen receptor modulator is preferred. The importance of adequate calcium and vitamin D intake, weight-bearing exercise, resistance training, minimization of alcohol, and smoking cessation for bone health should also be discussed with women.

FUTURE DIRECTIONS
Recently, panels of single-nucleotide polymorphisms (SNPs), also known as single-nucleotide variants, have been used in various settings to promote an individualized approach to decision making. These SNPs are identified and used to calculate a polygenic risk score incorporating individual patient characteristics. Through genomewide association studies, certain SNPs have been identified that decrease or increase the personal risk of breast cancer. This personalized information may also be used in the future for helping patients make informed personalized decisions and improve usage of ET.

CONCLUSION
Women identified as being at high risk for invasive breast cancer—on the basis of a strong family history, combination of hormonal or reproductive risk factors, or history of a high-risk pathologic lesion—should be offered ET. Informing women about their individualized risk vs benefit of ET, and weighing their personal values through shared decision making, is encouraged. Health care providers are key stakeholders in educating women about the importance of adopting a healthy lifestyle for primary prevention of breast cancer. This includes weight management, regular physical activity, plant-based nutrition, and avoidance of toxic substances such as tobacco and alcohol. In the future, combined assessment of SNPs and use of risk calculators to determine polygenic risk scores may be used to influence decision making and consideration of ET use and to potentially decrease the incidence of breast cancer.

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SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: AI = aromatase inhibitor; ASCO = American Society of Clinical Oncology; BCRAT = Breast Cancer Risk Assessment Tool; ET = endocrine therapy; IBIS = International Breast Cancer Intervention Study; LCIS = lobular carcinoma in situ; SNP = single-nucleotide polymorphism

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