Menopausal symptom management considerations in patients at high risk for breast cancer

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Educational objectives: At the conclusion of this educational activity, participants should be able to:

1. Describe breast cancer risk assessment, risk factors of significance, and options for risk reduction.
2. Discuss factors to consider when balancing breast cancer risk with menopausal symptom relief.
3. Discuss pharmacologic management of menopausal vasomotor symptoms for patients with significant breast cancer risk.

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Women experiencing menopausal symptoms who are also at elevated risk for developing breast cancer can pose a unique management dilemma for clinicians. This article provides a review of breast cancer risk factors, including those of particular importance, options for breast cancer risk management, and factors to consider when balancing risk with menopausal symptom relief utilizing hormone therapy.

KEY WORDS: **Breast cancer, breast cancer risk, menopause, menopausal symptom management**

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Women having menopausal symptoms often rely on their women's health providers for compassionate, timely, and evidence-based care. For women who are at increased risk for developing breast cancer, it is imperative that their providers are knowledgeable about how breast cancer risk reduction strategies may impact menopausal symptoms and how menopausal symptom management recommendations may impact breast cancer risk. This article focuses on select breast cancer risk factors that pose unique challenges for providers, specifically when considering menopausal symptom management with the use of hormone therapy. Breast cancer risk assessment, options for breast cancer risk reduction, and factors to consider when balancing risk with menopausal symptom relief are discussed.

Breast cancer risk assessment

There are a variety of modifiable and nonmodifiable risk factors for the development of breast cancer, although certain factors impact menopausal management decision making far more than others (*Table 1*, *Table 2*).[1] One of the first steps in addressing these concerns is to determine which patients are at significantly elevated breast cancer risk.

Collecting a detailed personal and family history, reviewing the most current breast imaging findings, obtaining pathology reports from prior breast biopsies, and performing genetic evaluation and testing, as appropriate, are all part of comprehensive breast cancer risk assessment. In addition, easily accessible tools are available in the clinic setting to assess breast cancer risk. Two of the most utilized tools are the modified Gail model, also known as the Breast Cancer Risk Assessment Tool, which has been validated across multiple ethnic groups, and the Tyrer-Cuzick (IBIS) Breast Cancer Risk Evaluation Tool, which is well calibrated in most racial /ethnic groups.[2,3] The models incorporate a variety of factors that impact risk, and provide 5-year, 10-year, and/or lifetime risk percentages for developing the disease.

Table 1. Modifiable risk factors[1]

- Alcohol consumption
- Obesity
- Sedentary lifestyle
- Nulliparity
- Oral contraceptive use
- Menopausal hormone therapy

Table 2. Nonmodifiable risk factors[1]

- Assigned female at birth
- Older age
- Certain inherited genetic mutations
- Family history of breast or other cancers
- Personal history of breast cancer
- Race and ethnicity
- Dense breast tissue
- Certain benign breast conditions
- Early menarche
- Late menopause
- Prior chest wall radiation

Risk factors of significance

Risk factors such as breast biopsy findings of atypical hyperplasia (ductal/lobular) or lobular carcinoma in situ (LCIS), genetic mutation carriers of high- or moderate-penetrance breast cancer susceptibility genes (ie, *BRCA1/2*), or those with prior thoracic radiation exposure are so significant that they warrant intervention based on any one of those discoveries alone. In addition, guidelines suggest that women with an elevated 5-year, 10-year, and/or lifetime risk of developing breast cancer be considered for medical management change.[2,4–7]

Atypical hyperplasia

Atypical hyperplasia of the breast is a benign (noncancerous) condition in which there is an overgrowth of cells lining the breast ducts or breast lobules. In both atypical ductal hyperplasia and atypical lobular hyperplasia, the cells appear microscopically abnormal.[8] Atypical hyperplasia carries with it a fourfold increase in breast cancer risk and a projected cumulative breast cancer incidence of 30% at 25 years.[9,10]

Lobular carcinoma in situ

Similar to atypical lobular hyperplasia, LCIS is an overgrowth of abnormal cells in the lobules of the breast. With LCIS, however, there are

predominantly more abnormally appearing cells than with atypical lobular hyperplasia.[11] Lobular carcinoma in situ is associated with a 7- to 12-fold increase in breast cancer risk, with a corresponding breast cancer risk of 26% at 15 years.[12,13]

Genetic mutation carriers

Women with genetic mutations in high- or moderate-penetrance breast cancer susceptibility genes are at significant, though varying degrees of, breast cancer risk. Mutations in *BRCA1* and *BRCA2* are associated with the highest risks for developing breast cancer, conferring lifetime risks of breast cancer of up to 87%.[14] *BRCA* mutation carriers also bear a significant risk of ovarian and other cancers.

Prior thoracic radiation exposure

Women who received thoracic radiation treatment at a young age, particularly between the ages of 10 and 30 years, are at significantly elevated risk for developing breast cancer later in life. The estimated cumulative absolute risk of breast cancer at age 55 is approximately 29%.[4]

Elevated risk model findings

Guideline recommendations from the American Cancer Society, the American Society of Clinical Oncology, the National Comprehensive Cancer Network (NCCN), and the United States Preventive Services Task Force all provide direction on the use of breast cancer risk assessment tools to determine whether increased breast cancer surveillance and/or breast cancer risk-reducing medications should be considered.

Increased breast cancer surveillance is recommended for women with a 5-year modified-Gail model risk of 1.7% or greater and/or a remaining lifetime risk of 20% or greater using a model that is heavily weighted in family history, such as the Tyrer-Cuzick model. When considering risk-reducing therapy (particularly challenging if a patient is experiencing menopausal symptoms that warrant intervention), having a 5-year modified Gail model risk of 1.7% or greater meets eligibility criteria for risk-reducing medications for women at least age 35 years who do not have contraindications to the medication being considered. Having a 5-year modified Gail model risk of 3% or greater or a 10-year Tyrer-Cuzick model risk of 5% or greater, however, is when risk-reducing medications are guideline recommended.[2,4–7]

High-risk management considerations

Often, management of patients at high risk for breast cancer encompasses a multimodal approach of both preventive and early identification strategies, including increased surveillance, risk-reducing medications, lifestyle modification, and the option of preventive surgery (in select high-risk patients). The purpose of medication intervention, lifestyle modification, and preventive surgery is to reduce breast cancer risk. The goal of increased breast surveillance is to identify breast cancer at its earliest and most treatable stage. Collaboration with or referral to a high-risk breast specialist or medical oncologist is often helpful to engage patients in a conversation about their particular breast cancer risk and would include a detailed discussion of both breast cancer surveillance and risk-reduction options.

Risk reduction

All patients should be provided counseling on lifestyle modification including limiting or avoiding alcohol; weight management and the importance of avoiding obesity, especially in the postmenopausal period; and the importance of exercise. These are all important aspects of risk management. Consumption of just one alcoholic beverage per day equates to a 7% to 10% increase in breast cancer risk, and that risk changes to a 20% increase in risk with the consumption of 2 to 3 alcoholic beverages per day. Physical activity reduces risk. The current exercise recommendations include 150 to 300 minutes of moderate or 75 to 150 minutes of intense exercise per week, equating to a 20% lower risk of breast cancer.[15]

Collectively, the breast cancer risk

factors of atypical hyperplasia, LCIS, having a calculated modified Gail model 5-year risk of 3% or greater, or having a calculated Tyrer-Cuzick model 10-year risk of 5% or greater, are all associated with a recommendation for risk-reducing medications. Risk-reducing medications also are a consideration for risk reduction in *BRCA* mutation carriers.

Risk-reducing medications, also referred to as endocrine therapy (previously known as chemoprevention), are extremely effective in reducing breast cancer risk, especially for those with atypical hyperplasia and LCIS. Risk-reducing medications include selective estrogen receptor modulators (SERMS) and aromatase inhibitors. Two SERMs, tamoxifen and raloxifene, are approved by the US Food and Drug Administration for breast cancer prevention. The aromatase inhibitors, exemestane and anastrozole, are guideline supported and commonly prescribed for prevention, although not FDA approved for that purpose. Endocrine therapy has been shown to reduce breast cancer risk in patients with atypical hyperplasia by 86% and in those with LCIS by 50%.[2]

Regarding risk model findings, a modified Gail model 5-year risk of at least 3% or a Tyrer-Cuzick model 10-year risk of at least 5% are thresholds by which patients are most likely to derive more benefit than harm from risk-reducing medications.[5,6] For *BRCA* mutation carriers, risk reduction includes the option of risk-reducing mastectomy. Additionally, there is some evidence to suggest that risk-reducing medications, specifically SERMS, may be effective in reducing breast cancer risk, although the data are limited. There is more evidence to support the use of SERMs for risk reduction in *BRCA2* mutation carriers, as opposed to *BRCA1* mutation carriers, as *BRCA2*-associated breast cancer is most likely to be estrogen receptor positive, whereas *BRCA1* is not.[16]

The purpose of medication intervention, lifestyle modification, and preventive surgery is to reduce breast cancer risk. The goal of increased breast surveillance is to identify breast cancer at its earliest and most treatable stage.

Prior to starting endocrine therapy, numerous additional factors need to be taken into consideration, including a determination of pre- versus postmenopausal status, contraindications to use, risks and side effects of the medication, and overall estimated risk-reduction benefit.[2,5,6] Women's health providers do not typically prescribe endocrine therapy for risk reduction as most eligible patients are offered these medications only after a careful discussion with a medical oncologist or high-risk breast specialist. However, as some of the medications have menopausal symptom-related side effects, women's health providers should be knowledgeable about risk-reduction medications as to be optimally positioned to answer patient questions and navigate through symptom management.

Menopausal symptom management considerations

Within a shared decision-making framework, how is the management of those with significant breast cancer risk balanced with menopause symptom management? Also, what if a consideration for menopause symptom management is hormone therapy (HT)? The North American Menopause Society states that while using the best available evidence, providers should individualize treatment while maximizing benefits and minimizing risks, and that for women younger than age 60 years or within 10 years of menopause onset with no contraindications, the benefit/risk ratio is favorable for HT to manage bothersome vasomotor symptoms.[17,18] For menopausal symptom management, there are varying formulations, routes of delivery, and intended durations of use of estrogen and progestin, as well as patient characteristics, to consider. All may play a role in the effects of hormone therapy on breast tissue.[16] Although there are data that show no additive effect of certain underlying breast cancer risk factors and hormone therapy use on breast cancer incidence, for some women, it may be important to consider alternatives to hormone therapy based on the risk/benefit calculation or for those who have clear contraindications to their use.[17,18]

For patients taking risk-reducing medications, guidelines such as the NCCN recommend against the use of HT for menopausal symptom management.[2] Having atypical hyperplasia or LCIS are strong indications to begin a risk-reducing agent, so patients with a history of biopsy results revealing

Table 3. Weighing the risks and benefits: Important questions for shared decision making

- What is the patient's breast cancer risk?
- What are the underlying factors and how significant are those factors on breast cancer risk?
- Are there comorbidities to consider?
- Are there contraindications to risk–reducing medications or to HT?
- What are the patient's menopausal symptoms?
- How severe are the patient's symptoms?
- What has been prescribed to manage symptoms and how long has the strategy been in place?
- For patients currently taking HT, has there been a dose adjustment, change of preparation, or route?
- How long has the patient been taking HT?
- Are there acceptable alternatives to HT to alleviate symptoms?
- Have lifestyle modifications been employed and were they successful or not?
- What does the patient desire?

HT, hormone therapy.

Table 4. Nonhormonal treatment options for vasomotor symptoms[19]

Medication	Dose	FDA approved
Paroxetine	7.5 mg/day	Yes
Venlafaxine	37.5 mg–75 mg/day	No
Fezolinetant	45 mg/day	Yes
Gabapentin	600–900 mg/day	No
Clonidine	0.1 mg/day	No

those findings may also want to consider alternatives to hormone therapy for the management of menopausal symptoms. *BRCA* mutation carriers bear a significant risk of ovarian cancer, in addition to breast and other cancers. Due to the ovarian cancer risk, premenopausal risk-reducing bilateral salpingo-oophorectomy is part of the management recommendations. As menopausal symptoms associated with oophorectomy occurring in the premenopausal period are often more significant than in the postmenopausal period, national guideline recommendations for *BRCA* mutation carriers do include guidance on hormone replacement therapy (HRT). Guidelines state that HRT can be considered for premenopausal patients who have undergone risk-reducing salpingo-oophorectomy who are personally unaffected by breast cancer and do not have any other contraindications to HRT.[16] Evidence has shown that hormone therapy use does not further increase the risk of breast cancer in women after oophorectomy due to a *BRCA1* or *BRCA2* mutation.[15] Typically in such instances, short-term HRT for menopausal symptom management is prescribed at the lowest effective dose for the shortest amount of time and may continue as needed until age of natural menopause (~ age 50). To aid in shared decision making when navigating risk with menopausal symptom management, there are several questions to contemplate when determining the best approach to care, as outlined in *Table 3*.

For women who have contraindications to hormone therapy, vasomotor symptom management may include a discussion of other treatment modalities, many of which are nonhormonal. Selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentin, clonidine, and a new medication, fezolinetant, which is a neurokinin 3 (NK3) receptor agonist, have all been shown to be effective alternatives to HT for the management of vasomotor symptoms associated with menopause. Two medications are approved for the management of menopausal vasomotor symptoms by the FDA.[19,20] *Table 4* outlines these options for treatment, which may be considered after carefully weighing their risks, benefits, contraindications, and side effects balanced with the patient's breast cancer risk. Careful attention should be paid to those who are candidates for or are already prescribed risk-reducing agents, as some menopausal treatment options, including nonhormonal options are contraindicated or cautioned against in those scenarios.

For women who are currently taking breast cancer risk-reducing medications, side effects can include the onset or exacerbation of menopausal symptoms such as hot flashes. Management considerations include a change in risk-reduction agent, a change in medication dose, addition of a nonhormonal agent to combat symptoms, or possibly a discontinuation of the medication if symptoms

are severe. Those decisions are most often made by the patients' medical oncologist or high-risk breast specialist, both of whom are well versed in breast cancer risk management.

One must be aware that some medications for the treatment of vasomotor symptoms can interact with and/or potentially diminish the effectiveness of the risk-reducing agent. Estrogens and progestins are not recommended for the treatment of vasomotor symptoms due to their potential for interaction. Careful consideration is needed with the accompanying use of tamoxifen and SSRIs, especially paroxetine and fluoxetine, as these medications can diminish tamoxifen's effectiveness. Venlafaxine or citalopram, however, appear to be safer alternatives to paroxetine and fluoxetine as they have less impact on tamoxifen metabolism.[2] Caution is advised when considering any concomitant medication use with a risk-reducing agent. As most patients at significant breast cancer risk are cared for by a multidisciplinary healthcare team, it is recommended that the women's health provider discuss any change to the treatment plan in collaboration with the patient's high-risk breast specialist.

Conclusion

Menopausal symptom management is a common aspect of caring for patients in women's health practice. Management can be complicated when risk factors for other conditions exist, especially breast cancer. Understanding which breast cancer risk factors warrant intervention and the types of intervention recommended can help the clinician navigate the decision tree of balancing breast cancer risk with menopause symptom management in a shared decision-making framework with their patients. ■

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