Management of Menopausal Symptoms in Breast Cancer Patients

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Abstract

As the number of breast cancer survivors increases in the United States, many of these women will suffer from climacteric symptoms and a reduced quality of life as a result of adjuvant therapy, chemotherapy, or natural menopause. As such, physicians caring for breast cancer survivors should address survivorship issues related to hypoestrogenism. This article reviews hormonal and nonhormonal evidence-based treatment options for breast cancer patients with common menopausal symptoms, focusing on vasomotor symptoms and the genitourinary syndrome of menopause. Specific attention is given to the safety profile of both systemic and vaginal hormonal therapy in this specific patient population.

Introduction

In the United States (U.S.), breast cancer is the second most common cancer with American women having a 12 percent average lifetime risk of developing breast cancer.¹ The American
Cancer Society estimates that about 266,120 new cases of invasive breast cancer will be diagnosed in women in 2018.\textsuperscript{1} Although breast cancer is the second leading cause of cancer related deaths in women, death rates from female breast cancer dropped 38 percent from 1989 to 2015, resulting in more than 3.1 million breast cancer survivors in the U.S. With 23 percent of breast cancer cases being diagnosed in women younger than age 50, in combination with improved breast cancer survival rates, knowledgeable and up-to-date physicians will be positioned to help patients with a personal history of breast cancer manage menopausal symptoms.\textsuperscript{1} Breast cancer patients may undergo spontaneous menopause or they may experience induced menopause secondary to chemotherapy. Cancer treatment should address female-specific survivorship issues, including the hypoestrogenic-related adverse effects of cancer therapies or of natural menopause in survivors.

**Management of Vasomotor Symptoms in Breast Cancer Patients**

Vasomotor symptoms (VMS) represent the most bothersome symptoms of menopause and are the most common reason women seek medical care at the time of the menopausal transition. Often referred to as hot flushes or night sweats by patients, VMS are associated with a sudden sensation of extreme heat in the upper body. Other manifestations of VMS include perspiration, flushing, chills, clamminess, anxiety, sleep disruption, and heart palpitations.\textsuperscript{2,3} A cohort study revealed that the median duration of moderate-to-severe VMS is 10.2 years, with the most common age of onset being 45-49 years of age.\textsuperscript{4} The impact that VMS have on a woman’s quality of life, as well as the prolonged duration of VMS for some women, underscores the importance of treating these common symptoms both in the general population of menopausal women as well as in breast cancer survivors.

Despite limited supporting data, various behavioral and lifestyle measures can be recommended to all patients experiencing bothersome VMS. Possible lifestyle solutions include portable fans, maintaining a low ambient temperature, wearing layered clothing, avoiding consumption of tobacco, alcohol, caffeine, and spicy food, and consuming cool drinks. The effectiveness of alternative techniques including acupuncture, reflexology, exercise, yoga, paced respiration, relaxation training, and mindfulness-based stress reduction has not been established.\textsuperscript{2,3}
Numerous randomized controlled trials have demonstrated that systemic hormone therapy (HT), with estrogen alone or a combination of estrogen with progestin, is the most effective treatment for menopausal VMS. A variety of systemic estrogen preparations are available, including oral formulations, transdermal HT in the forms of patches, gels, emulsions, or sprays, and a systemic vaginal ring. The goal of menopausal HT is to use the appropriate type, dose, formulation, route of administration, and duration of HT to meet the patient’s individualized treatment goals.

In women with an intact uterus, treatment with estrogen alone is associated with an elevated risk of endometrial neoplasia; when adequate progestogen is combined with estrogen, the risk of endometrial neoplasia is not higher than in untreated women. As such, it is imperative that all women with an intact uterus be prescribed combination HT consisting of estrogen combined with progestational protection or oral conjugated estrogen combined with the selective estrogen receptor modulator (SERM) bazedoxifene (Duavee®). In contrast, estrogen-only HT is appropriate for women who have undergone hysterectomy.

Findings from the Women’s Health Initiative (WHI) Hormone Therapy randomized clinical trials have helped physicians better understand the benefits and risks of systemic HT. The goal of the WHI study was to assess the effects of postmenopausal HT use among healthy menopausal women aged 50-79 years on the risk of coronary heart disease, fractures, and breast cancer. The WHI study included a trial of combined estrogen-progestin HT in women who had an intact uterus at baseline (n= ~17,000) and a trial of estrogen-alone HT in women who had undergone prior hysterectomy at baseline (n= ~11,000). After an average of five years of combined HT use, a slightly increased risk of breast cancer, coronary heart disease, stroke, and venous thromboembolic events and a decreased risk of fractures and colon cancer were observed. Among women receiving estrogen-alone HT, an increased risk of thromboembolic events was noted without an increased risk of cardiovascular events or breast cancer. Importantly, results for breast cancer differed in the two trials, with an increased risk of breast cancer noted in the combined HT trial and a reduced risk in the estrogen-alone HT trial. A 2013 report reviewed WHI findings from both trials, including post-intervention follow-up stratified by age. Absolute risks of adverse events related to HT were substantially lower and tended to be small for younger
women (ages 50-59) than for older women. After study medications were stopped, some elevation in breast cancer risk persisted in the combined HT trial (cumulative HR over 13 years 1.28, 95% CI 1.11-1.48). The attributable risk with combined HT is less than one additional case of breast cancer diagnosed per 1,000 users of combined HT annually. In contrast, a significantly reduced risk of breast cancer (HR 0.79, 95% CI 0.65-0.97) was noted in the estrogen-alone HT trial.²

While combined HT appears to modestly increase the risk of breast cancer in healthy women, the effect of HT on risk of recurrent breast cancer in breast cancer survivors is less clear. The U.S. Food and Drug Administration (FDA) lists a personal history of breast cancer as a contraindication to the use of HT because of theoretic concerns that estrogen will stimulate recurrence. Multiple observational studies⁷,⁸,⁹,¹⁰,¹¹,¹² and a systematic review of four studies¹³ suggest that HT in breast cancer survivors does not increase the risk of recurrence and may even be beneficial. A meta-analysis of eight observational studies (n=3710, mean age range 47-64.7 years) showed a decreased risk of breast cancer recurrence in women taking HT during a mean follow up of 57.1 months (RR 0.64, 95% CI 0.65-0.82).¹⁴ However, observational studies may be subject to selection bias by including only women with better prognosis disease.

Randomized clinical trial data regarding the impact of systemic HT on risk of breast cancer recurrence are limited and their findings are inconclusive. Two Swedish randomized clinical trials, both initiated in 1997, examined the use of HT in breast cancer survivors and demonstrated conflicting results. The larger study was the Hormonal Replacement Therapy After Breast Cancer – Is It Safe? (HABITS) trial, which provided follow-up data on 442 women with previously treated breast cancer who were randomized to either HT (n=221) versus nonhormonal symptom management (n=221). The HABITS trial was stopped early in 2003 due to an increase in breast cancer events in the HT arm. With median follow-up of four years, new breast cancer events occurred almost twice as often in the HT group compared with the nonhormone group (39 of 221 in the HT arm versus 17 of 221 in control arm, HR 2.4, 95% CI 1.3-4.2). The cumulative incidence of a breast cancer event in the HT and nonhormone groups at five years was estimated at 22 percent and 8 percent, respectively. However, no elevated breast-cancer specific or overall mortality was noted in the HABITS trial.¹⁵
A similar randomized clinical trial in Stockholm was also terminated early in 2003 based upon the results of the HABITS trial. After 10.8 years of follow-up in the Stockholm study, there was no significant difference in new breast cancer events, with 60 new breast cancer events in the HT group versus 48 in the control group (HR 1.3, 95% CI 0.9-1.9). However, there was an increased risk of contralateral breast cancer with HT use, with 14 contralateral breast cancers in the HT group and 4 in the control group (HR 3.6, 95% CI 1.2-10.9).\textsuperscript{16}

Several factors limit the clinical application of these two Swedish studies to U.S. breast cancer survivors, including the small number of events in both trials and 52 percent of study participants in the Stockholm trial concomitantly used tamoxifen with HT (a practice not commonly employed in the United States). Although the data are not entirely consistent, the increase in breast cancer recurrence risk observed in the HABITS trial is of concern.\textsuperscript{2,15,16} A pooled analysis of results, while showing statistically significant heterogeneity of results, concluded that use of HT after breast cancer was linked to significantly higher recurrence rates (HR 1.8, 95% CI 1.03-3.10).\textsuperscript{17}

Given the uncertainty regarding the effect of systemic HT on risk of breast cancer recurrence, expert guidelines recommend the first-line use of nonhormonal therapies for controlling VMS in women with a personal history of breast cancer.\textsuperscript{2,15,16} When faced with a decision regarding whether to start off-label use of HT in patients with a personal history of breast cancer, the patient and her physician should consider the stage and receptor status of the cancer and then weigh the quality of life expectations against the potential risk of recurrence. Some women with early stage breast cancer and bothersome menopausal symptoms may decide, after discussion with their oncologist, that the benefits of off-label systemic HT use may outweigh the potential risks. After tamoxifen or aromatase therapy has been completed, some women at low risk of recurrence may choose to use systemic HT after discussion with their oncologist.

Although not as effective as estrogen therapy, several nonhormonal options are available for the treatment of menopausal VMS. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and some anticonvulsant medications are effective
for the nonhormonal treatment of VMS. In randomized controlled trials, escitalopram, citalopram, venlafaxine, desvenlafaxine, gabapentin, and pregabalin have been effective in treating VMS. However, low-dose paroxetine mesylate (7.5 mg/d) is the only nonhormonal therapy that is FDA approved for the treatment of VMS. Paroxetine mesylate and venlafaxine represent the antidepressants best studied in the treatment of VMS, with lower doses than those used to treat psychiatric disorders being effective.\textsuperscript{2} When prescribing antidepressants to women concomitantly using tamoxifen, clinicians should be aware that SSRIs inhibit the hepatic enzyme Cyp2d6, an enzyme which converts tamoxifen to its biologically active version. Therefore, paroxetine and fluoxetine should not be used by women taking tamoxifen. In contrast, venlafaxine, desvenlafaxine, gabapentin, and pregabalin do not inhibit the hepatic enzyme Cyp2d6 and are therefore appropriate nonhormonal treatment options for bothersome VMS in women taking tamoxifen.\textsuperscript{2}

Bioidentical hormones are chemically similar or structurally identical to those produced by the human body. Bioidentical hormones include commercially available products approved by the FDA (micronized progesterone and estradiol) and compounded preparations that are not regulated by the FDA.\textsuperscript{3} The use of compounded bioidentical hormone therapy (cBHT) is increasing among perimenopausal and postmenopausal women, with an estimated 2.5 million U.S. women using these formulations.\textsuperscript{2} Virtually every medical society that provides clinical guidance regarding management of the menopausal transition recommends against prescribing cBHT, citing the following concerns: nonuniform dosing, inconsistencies in manufacturing standards and state regulatory oversight, the potential for product contamination and/or impurities, lack of patient package inserts regarding anticipated risks, and lack of scientific evidence for efficacy or safety.\textsuperscript{18}

Despite the lack of data demonstrating efficacy in the treatment of VMS, over the counter supplements have been used for the management of VMS. A 2010 Cochrane meta-analysis of 30 placebo-controlled trials of high doses of phytoestrogens for the treatment of VMS found no evidence of benefit.\textsuperscript{19} There is currently insufficient data to support the use of herbal remedies including black cohosh, ginseng, St. John’s wort, ginko biloba, and Chinese herbal medicine treatments.\textsuperscript{3}
Management of Genitourinary Syndrome of Menopause in Breast Cancer Patients

Genitourinary syndrome of menopause (GSM) is a common and progressive condition that adversely affects the health, sexuality, and quality of life of many menopausal women. GSM is defined as a set of clinical exam findings and bothersome symptoms associated with estrogen deficiency involving changes to the labia, introitus, clitoris, vagina, urethra, and bladder. Common symptoms of this condition include genital irritation, burning, and dryness, urinary urgency, dysuria, and recurrent urinary tract infections, and sexual symptoms of pain and dryness. Physical examination findings are consistent with vulvovaginal atrophy and include loss of fat pad in the mons and labia majora, labial thinning, narrowing of the introitus (particularly in the absence of penetrative sexual activity), decreased width and depth of the vagina, pale vulvar and vaginal tissue, loss of vaginal rugae resulting in smooth, shiny, and dry appearing vaginal epithelium, attenuated vaginal fornices resulting in a cervix flush with the vaginal apex, and inflammation of the vaginal mucosa resulting in erythema and friability. Women may experience all or some of the signs and symptoms, which must be bothersome for the syndrome to be diagnosed. Without active management, GSM often worsens over time. Additionally, hypoestrogenic women of any age may experience these symptoms, including women with a personal history of breast cancer who are estrogen deficient secondary to chemotherapy or radiation.²

Nonhormonal approaches represent first-line choices for managing GSM symptoms experienced by women during or after treatment for breast cancer.²⁰ Women with GSM should be counseled that regular sexual activity may help address symptoms and prevent progression of disease. Use of over-the-counter nonhormonal vaginal lubricants for sexual activity and/or regular use of longer-acting vaginal moisturizers may be effective initial treatment options for women with GSM.² Additionally, for women with insertional dyspareunia, 4% aqueous lidocaine applied to the vulvar vestibule prior to vaginal penetration can reduce sexual discomfort.

Pelvic floor physical therapy (PT) and use of graduated vaginal dilators (often under pelvic floor PT guidance) can be highly effective in treating GSM. Combining pelvic floor PT with
pharmacologic treatment of atrophic epithelial changes may be necessary for women with severe symptoms.

For breast cancer survivors with GSM who remain symptomatic despite use of nonhormonal treatments, consideration should be given to the off-label use of highly effective low-dose vaginal estrogen therapy (ET). Vaginal estrogen delivers a low dose of hormone to the local vaginal tissue with minimal systemic absorption. Use of low-dose vaginal ET is associated with serum estrogen levels that are within the normal postmenopausal range, resulting in a high degree of safety. Estrogen decreases the vaginal pH, improves elasticity and thickness of vulvovaginal tissues, and restores vaginal blood flow. Several formulations of low-dose vaginal ET are currently available in the U.S. including vaginal estradiol tablets, two creams, and a vaginal ring. Systematic reviews have noted that the tablets, vaginal ring, and creams have comparable efficacy in treating vulvovaginal symptoms. Women should be advised to use the lowest dose necessary for symptom relief, as systemic absorption is dose-dependent. Studies show that the use of low-dose vaginal estrogens do not result in sustained serum estrogen levels exceeding the normal postmenopausal range, with the vaginal ring and tablets having the lowest rates of systemic absorption. Systemic estrogen impact is more variable with the creams than with the tablet or ring. Accordingly, when prescribing low-dose vaginal estrogen off-label to women with a history of breast cancer, the authors prefer the E2 ring or tablet over estrogen creams. However, it should be noted that the threshold for systemic estrogen levels associated with breast cancer recurrence risk has yet to be determined and the clinical relevance of even very small increases in circulating estrogen levels with low-dose vaginal estrogen products in women with breast cancer remains unclear.

Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use low-dose vaginal ET for treatment of GSM. A nested case-control analysis of a cohort study of women with breast cancer who either did or did not use vaginal estrogen showed no increased risk of breast cancer recurrence in vaginal estrogen users. In another study, the risk of recurrence in women who used vaginal cream was not increased, irrespective of the total dose prescribed.
The decision to use vaginal ET in breast cancer survivors may be made in coordination with the patient’s oncologist. Additionally, it should be preceded by an informed decision-making and consent process in which the patient has the information and resources to consider the benefits and potential risks of off-label low-dose vaginal ET. When the decision is made to use vaginal ET, it should be prescribed at the lowest effective dose and for a limited time period until symptoms improve.\textsuperscript{20}

Special consideration should be taken regarding the use of vaginal ET in women with breast cancer who use aromatase inhibitors (AIs). AIs block 95 percent of estrogen synthesis and are associated with circulating estradiol levels lower than 1 pg/mL.\textsuperscript{22} Studies have demonstrated an initial increase of serum estradiol with the use of low-dose vaginal estrogen among women taking an AI, although these levels were not sustained over time and increased cancer recurrence was not noted.\textsuperscript{20} However, any rise above baseline serum estradiol levels may affect AI efficacy.\textsuperscript{22}

The use of vaginal ET may be appropriate for women with GSM who use tamoxifen. Low and temporary increases of plasma estrogen do not appear to increase recurrence risk in women using tamoxifen because of a competitive interaction with the estrogen receptor. Because of these effects, women on AIs with GSM refractory to nonhormonal approaches may benefit from the short-term use of low-dose vaginal ET with tamoxifen to improve symptoms, followed by a return to normal AI therapy for the duration of the treatment course.\textsuperscript{20}

It should be noted that the FDA package labeling for low-dose vaginal estrogen products includes the same boxed warning that accompanies all systemic HT products regarding risk of cardiovascular disorders, endometrial cancer, breast cancer, and probable dementia. This warning is not evidence-based and adversely affects women’s health and quality of life by discouraging use of these highly effective therapies.\textsuperscript{22}

Intravaginal use of the hormone dehydroepiandrosterone (DHEA) (Intrarosa®, Prasterone) is also approved for the treatment of GSM. Using the provided applicator, patients administer one 6.5 mg prasterone vaginal insert once daily at bedtime. Intravaginal DHEA has not been studied
in women with a history of breast cancer nor in those patients currently taking AIs.

For women with GSM who prefer an oral agent, ospemifene (Osphena®, 60 mg daily) is a SERM approved for the treatment of GSM. As with the SERMs tamoxifen and raloxifene, ospemifene may increase the risk of venous thromboembolism and VMS. Ospemifene has not been assessed in women with a history of breast cancer; thus, no recommendations can be given for its use in this population.\(^2\)

**Conclusion:**

The number of breast cancer survivors is steadily increasing due to early detection and improved therapies. Many of these women will suffer from climacteric symptoms and a reduced quality of life as a consequence of adjuvant therapy, chemotherapy, or natural menopause. As such, it is imperative that breast cancer treatment address survivorship issues related to hypoestrogenism.

The guidance provided in this review will help physicians safely improve the quality of life for their patients who are breast cancer survivors.

**References:**


1. The median duration of moderate-to-severe vasomotor symptoms is __________.
   A. 2-3 years  
   B. 5 years  
   C. 10 years

2. True or False: When prescribing hormone therapy (HT) to women with bothersome menopausal symptoms who are free of contraindications to HT, one should prescribe combination HT consisting of estrogen combined with progestational protection if the uterus is intact or estrogen-only hormone if there has been a prior hysterectomy.
   A. True  
   B. False

3. True or False: Findings from the Women’s Health Initiative (WHI) Hormone Therapy randomized clinical trial demonstrated an increased risk of breast cancer in the estrogen-alone hormone therapy trial and a reduced risk of breast cancer in the combined estrogen-progestogen hormone therapy trial.
   A. True  
   B. False

4. True or False: Nonhormonal therapies are considered first-line therapies for controlling vasomotor symptoms in women with a personal history of breast cancer.
   A. True  
   B. False

5. Which of the following medications is approved by the Food and Drug Administration for the treatment of vasomotor symptoms?
   A. Fluoxetine  
   B. Venlafaxine  
   C. Paroxetine mesylate  
   D. Desvenlafaxine

6. Which of the following is the most appropriate nonhormonal treatment option for bothersome vasomotor symptoms in a patient who is also taking tamoxifen?
   A. Paroxetine  
   B. Venlafaxine  
   C. Fluoxetine

(test continued on next page)
7. True or False: Virtually every medical society that provides clinical guidance regarding management of the menopausal transition recommends against prescribing compounded bioidentical hormone therapy due to concerns regarding nonuniform dosing, inconsistencies in manufacturing standards and state regulatory oversight, the potential for product contamination and/or impurities, lack of patient package inserts regarding anticipated risks, and lack of scientific evidence for efficacy or safety.
   A. True
   B. False

8. All of the following statements regarding the genitourinary syndrome of menopause (GSM) are true except:
   A. GSM can involve changes to the labia, introitus, clitoris, vagina, urethra and bladder
   B. Common symptoms may include recurrent urinary tract infections and sexual symptoms of pain and dryness
   C. Physical exam findings may include a decreased width and depth of the vagina and pale appearing vulvar and vaginal tissue
   D. Without active management, GSM most often spontaneously resolves

9. In women without vasomotor symptoms, all of the following are considered first-line treatment options for the genitourinary syndrome of menopause (GSM) except:
   A. Regular sexual activity
   B. Oral estradiol tablets
   C. Vaginal moisturizer
   D. Use of vaginal dilators
   E. Pelvic floor physical therapy

10. True or False: Data do not suggest that the use of low dose vaginal estrogen for treatment of genitourinary syndrome of menopause increases the risk of cancer recurrence among breast cancer survivors.
    A. True
    B. False

EVALUATION:
1. What will you do differently as a result of this information?
   ________________________________________________________________
   ________________________________________________________________
   ________________________________________________________________

2. How will you apply what you learned to your practice?
   ________________________________________________________________
   ________________________________________________________________
   ________________________________________________________________

Please evaluate this article. Circle one number using this scale: 1= Strongly Agree to 5= Strongly Disagree

The article met the stated objectives: 1 2 3 4 5
The article was appropriate to my practice: 1 2 3 4 5
The topic was current and well presented: 1 2 3 4 5