CME CREDIT

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Managing menopause after breast cancer: Balancing risks and benefits

ABSTRACT

Many women now survive breast cancer, but find themselves at increased risk of menopausal complications. How to manage menopause after breast cancer is a complex issue, given that estrogen has a role in the development of breast cancer and valid concerns exist about estrogen replacement therapy in patients who have had breast cancer. This article explores the relationship between estrogens and breast cancer and discusses management options for a variety of menopausal complications in breast cancer survivors.

KEY POINTS

Hormonal factors influence both breast cancer development and breast cancer recurrence.

Nonhormonal interventions may successfully alleviate a variety of menopausal symptoms and associated disease processes.

Evidence of benefit of estrogen replacement comes from observational, not randomized, studies

Further study of the safety of estrogen replacement therapy in breast cancer survivors is needed.

ONE OF THE MOST COMPLEX ISSUES facing breast cancer survivors and their physicians is how to manage menopause and its complications. Most breast cancer patients are postmenopausal at the time of diagnosis, many enter menopause prematurely as a side effect of breast cancer treatment, and all who survive long-term ultimately become menopausal.

Yet, because of concerns about increasing the risk of breast cancer recurrence, estrogen replacement therapy is generally discouraged in women with a history of breast cancer. Women successfully treated for breast cancer are therefore at risk for a variety of complications of menopause, including osteoporosis, accelerated heart disease, and genitourinary and vasomotor symptoms. Infertility may also be a concern for younger patients. Menopausal health concerns and symptoms are therefore important issues for breast cancer patients of all ages and require individualized management approaches.

The problem is common. Breast cancer is diagnosed in approximately 180,000 women each year in the United States. Most present with early-stage disease, and many survive long-term after treatment. There are nearly 2.5 million breast cancer patients and survivors in the United States.[1] And as therapy for breast cancer continues to improve, the long-term care of survivors gains increasing importance.

ROLE OF HORMONES IN BREAST CANCER

Hormonal factors are clearly implicated in the development of breast cancer, and hormonal manipulations are frequently effective in its treatment. Women who go through menarche

at a relatively young age, or go through menopause at a relatively advanced age, or never have children—ie, who are exposed longer to estrogen through the natural menstrual cycle—have an increased risk of breast cancer. In addition, postmenopausal hormone replacement therapy appears to increase breast cancer risk, although modestly.[2–4] Moreover, women with breast cancer can reduce their risk of recurrence by having their ovaries removed if they are premenopausal or by taking the antiestrogen drug tamoxifen regardless of their age.[5,6]

BREAST CANCER TREATMENT CAN CAUSE PREMATURE MENOPAUSE

Premature menopause is the most common long-term complication of adjuvant chemotherapy for breast cancer.

The incidence of ovarian toxicity with adjuvant chemotherapy appears to be higher in older patients and with higher doses of alkylating agents such as cyclophosphamide. After a 6-month course of classic CMF chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), approximately 40% of women age 40 or younger become amenorrheic, compared with approximately 76% of women over the age of 40.[7] A 3-month course of standard AC chemotherapy (doxorubicin and cyclophosphamide), in which patients receive a significantly lower cumulative dose of cyclophosphamide, is associated with lower rates of amenorrhea than with CMF.[8]

While treatment-related amenorrhea may be temporary in some patients, it is likely to be permanent if it is present 1 year after chemotherapy, as amenorrhea rates continue to increase over time.

Bilateral oophorectomy reduces breast cancer recurrence in premenopausal women

IS PREMATURE MENOPAUSE DESIRABLE?

One could argue that inducing menopause is desirable in this situation because it should decrease the chances that breast cancer will recur. Ovarian ablation, either by surgery or radiation therapy, clearly reduces the risk of breast cancer recurrence in premenopausal women with early-stage disease.[5] Several studies suggested that, in the same situation, chemical ovarian ablation could achieve a similar favorable effect in early-stage breast cancer.[9–12] Other studies did not confirm this observation, however.[13–15]

In one of the largest studies addressing this issue,[13] most patients received tamoxifen if they had hormone receptor-positive disease, but no benefit of treatment-related amenorrhea was observed. Most likely, when adjuvant chemotherapy is combined with appropriate hormonal therapy, inducing menopause provides little additional benefit in reducing breast cancer recurrence rates. Whether permanent ovarian ablation is better than reversible hormonal therapies for breast cancer also remains unclear.

On the negative side, premature menopause increases the number of years that a woman is postmenopausal, possibly increasing her risk of complications such as osteoporosis and coronary heart disease. In addition, hot flashes and other menopausal symptoms may be more severe when menopause occurs abruptly, as with chemotherapy, and anticancer drugs such as tamoxifen may worsen vasomotor symptoms.

SHOULD BREAST CANCER SURVIVORS RECEIVE HORMONE REPLACEMENT?

Benefits, risks in healthy women

In evaluating potential risks and benefits of estrogen replacement therapy in breast cancer patients, it is important to understand its effects in healthy women. Estrogen replacement therapy is very effective in treating the symptoms of perimenopause and in preventing and treating osteoporosis. It may also decrease mortality and coronary artery disease, although the evidence for this assertion comes from observational studies and not from definitive randomized controlled trials. On the negative side, it may increase the risk of breast cancer slightly.

Possible decrease in mortality. The Nurses' Health study,[3] although observational, was one of the largest studies of the risks and benefits of hormone replacement therapy, with approximately 121,700 women followed for 18 years. After adjusting for potentially confounding factors such as heart disease, breast cancer, body mass index, exercise, and intake of vitamin E and fat, the investigators

calculated that current users of hormone replacement therapy had a 37% lower risk of all-cause mortality compared with nonusers. The survival benefit seemed to disappear by 5 years after hormone replacement therapy was stopped.

Possible decrease in coronary artery disease. In theory, estrogen replacement should decrease the incidence of coronary artery disease, since it decreases serum levels of total cholesterol and LDL and increases HDL.[16] (On the other hand, it increases levels of triglycerides.) Moreover, observational studies[3,17,18] suggested that estrogen users had lower rates of coronary artery disease than did nonusers. And in the Nurses' Health Study,[3] the decrease in total mortality was particularly strong in women with risk factors for coronary artery disease: a 49% relative risk reduction.

However, in one of the few large *randomized controlled* trials of hormone replacement therapy, estrogen replacement therapy had no effect on coronary artery disease. The Heart and Estrogen/progestin Replacement Study (HERS)[19] randomized 2,763 postmenopausal women with established coronary artery disease to receive either estrogen and progestin or placebo. At approximately 4 years of follow-up, there was no difference between the groups in the rates of myocardial infarction or coronary death.

Possible increase in cancer risk. In the Nurses' Health Study,[3] prolonged use of hormone replacement therapy was associated with an increased risk of breast cancer and an attenuation of the survival benefit. Women who used hormone replacement therapy for more than 10 years had a 43% higher rate of breast cancer, although they still had a 20% lower rate of overall mortality.

While some epidemiologic studies found an increased risk of breast cancer with hormone replacement therapy, others found no increase. The Collaborative Group on Hormonal Factors in Breast Cancer,[4] in a meta-analysis of 51 studies, calculated the relative risk of breast cancer to be a modest 1.023 for each year of hormone replacement. Like the benefits, the risk seemed to disappear by 5 years after therapy was stopped. In addition, the breast cancers diagnosed in patients receiving hormone replacement therapy were less advanced than those in nonusers.

The randomized HERS trial[17] did not have sufficient power to detect a significant difference in the rate of breast cancer or other cancers.

Despite the modest increase in breast cancer risk in observational studies, the overall benefits of hormone replacement therapy seem to favor its use in most groups of women, and a survival benefit has been observed even in women with a family history of breast cancer.[20]

Hormone replacement in breast cancer survivors

In the general population the most common cause of death is cardiovascular disease, but for women with a history of breast cancer the number-one cause of death is breast cancer recurrence. For this reason, any calculation of benefit vs risk for hormone replacement therapy will be quite different for breast cancer patients than for women with no history of breast cancer. Furthermore, while the risk of hormone replacement therapy causing new cases of breast cancer has been extensively studied, its influence on the risk of recurrence of established breast cancer remains unknown.

Small trials showed no increased risk of breast cancer recurrence with hormone replacement

Two small trials suggest that hormone replacement therapy may be safe for some breast cancer patients, however.

In a pilot study at the M.D. Anderson Cancer Center,[21] 39 women with predominantly hormone receptor-negative breast cancer who had been disease-free for at least 2 years were given unopposed conjugated estrogen for 25 days each month. No increase in breast cancer recurrence was observed in the treated group compared with a control group of 23 women randomized to no hormone replacement therapy and an additional 257 women who met the eligibility criteria for the study but elected not to participate.

A somewhat larger retrospective cohort study of breast cancer patients also found no adverse effect from hormone replacement therapy.[22] In this study, 125 women with a history of breast cancer received hormone replacement therapy for a median of 22 months. The risk of death in this group was

actually lower than in a control population matched for age, breast cancer stage, and year of diagnosis.

Randomized controlled trials are required to determine the precise risks and benefits of hormone replacement therapy in women with breast cancer, but preliminary data do suggest that consideration of hormone replacement therapy may be reasonable in some breast cancer survivors.

Until more information is available, however, most breast cancer survivors are unlikely to accept hormone replacement therapy: in the M.D. Anderson pilot study,[21] fewer than 20% of patients approached agreed to participate. In Europe, where hormone replacement therapy is more widely accepted, a large randomized trial is currently underway and should provide important information as to the degree of risk associated with postmenopausal estrogen use in breast cancer patients.

ALTERNATIVES TO SYSTEMIC HORMONE REPLACEMENT THERAPY

Treat menopausal symptoms on an individual basis

Because even a small increase in the risk of breast cancer recurrence is unacceptable for many patients, management of menopausal consequences in breast cancer survivors largely focuses on specific symptoms or disease processes. Follow-up of these patients should include assessment of cardiovascular risk factors as well as periodic bone densitometry to test for osteoporosis. The severity of menopausal symptoms, including vasomotor and genitourinary complaints, should be assessed.

Alternatives for reducing cardiovascular risk

Strategies for reducing cardiovascular risk in breast cancer survivors are similar to those in other primary care populations. While smoking cessation, dietary modification, and exercise have not been shown to decrease the risk of breast cancer recurrence, such lifestyle modifications can clearly influence overall prognosis by improving cardiovascular health. Optimal control of associated medical conditions such as hypertension, diabetes, and hyperlipidemia is also important in reducing coronary heart disease risk.

Alternatives for preventing and treating osteoporosis

A variety of alternatives to estrogen are available for patients with osteoporosis or osteopenia.

Adequate **calcium and vitamin D** intake and **weight-bearing physical activity** are important components of osteoporosis treatment and prevention.

Bisphosphonates, such as alendronate (Fosamax), increase bone mineral density and decrease the rate of vertebral fractures.[23]

Calcitonin (Miacalcin) increases bone mineral density, but resistance to its effects may develop over time.

Raloxifene (Evista), a mixed estrogen agonist/antagonist, has been shown to increase bone density without evidence of increased rates of uterine or breast cancer and may be appropriate for some postmenopausal breast cancer patients requiring therapy for osteoporosis. It has not, however, been demonstrated to be an adequate substitute for tamoxifen as a treatment for breast cancer.

Tamoxifen (Nolvadex), like raloxifene, increases bone mineral density in postmenopausal women.

Alternatives for managing vasomotor symptoms

Management of vasomotor symptoms such as hot flashes can be difficult for breast cancer survivors.

Vitamin E may help some patients, although some of its activity may well be a placebo effect.

Antidepressants. Recent data suggest that some of the newer antidepressants (specifically, venlafaxine—Effexor[24,25]) reduce the frequency and severity of menopausal hot flashes. Other agents, including paroxetine (Paxil) and fluoxetine (Prozac) have similarly demonstrated the ability to reduce hot flashes in small studies.[26,27]

Megestrol acetate (Megace) is effective for treating hot flashes in breast cancer patients.[28] Its safety in this population is currently under evaluation.

Central-acting agents such as clonidine (Catapres) and the drug combination of belladonna, ergotamine, and phenobarbital (Bellergal) also reduce hot flashes, but have

relatively high side effect profiles and may not be preferred to placebo.[29,30]

Soy phytoestrogens showed conflicting results in trials for reducing hot flashes, and the effectiveness of soy products in this setting remains unclear.[31,32] Many herbal preparations containing phytoestrogens have been used anecdotally, but the safety and efficacy of most of them remain largely untested.

Genitourinary symptoms

Genitourinary symptoms are an important consequence of menopause in breast cancer patients. Patients may experience recurrent urinary tract infections, vaginal atrophy, pruritus, dyspareunia, or other forms of sexual dysfunction.

Over-the-counter **vaginal lubricants** or **vaginal moisturizers** may be helpful and are frequently recommended as first-line treatment for genitourinary symptoms. Unfortunately, many patients find them ineffective.

Vaginal estrogen creams tend to be systemically absorbed when given at standard doses of 0.625 or 1.25 mg, and blood estrogen levels can reach the premenopausal range.[33,34] Although lower doses appear to result in less systemic absorption, the question is frequently raised as to whether it is appropriate to give vaginal estrogens to breast cancer patients.

The vaginal estrogen ring (Estring) provides an alternative method of local estrogen delivery. It appears to be effective for treating urogenital atrophy and does not seem to lead to significant systemic absorption of estrogen.[1] Although this device is not currently approved for use in patients with a history of breast cancer, it is expected to be safer than other forms of vaginal estrogens and warrants further evaluation in this population.

FERTILITY AND BREAST CANCER

Systemic chemotherapy for breast cancer is associated with high rates of premature ovarian failure and consequent infertility. In addition, women who undergo a 5-year course of tamoxifen may need to delay childbearing for the duration of therapy, further diminishing their chances for childbearing.

Nevertheless, pregnancy after treatment for breast cancer may be reasonable for some patients. Some small studies suggested that ovarian suppression during chemotherapy, such as with gonadotropin-releasing hormone analogs, may provide some protection against ovarian toxicity, although these methods remain unproven.[35] Limiting exposure to alkylating agents improves the prospects for maintaining fertility. Younger patients have the greatest likelihood of maintaining fertility after treatment.

Most studies found no increase in the risk of recurrence in patients who became pregnant after being treated for breast cancer[36]; however, recurrence risk remains important to consider when contemplating motherhood after breast cancer.

While chemotherapy during pregnancy, particularly during the first trimester, may adversely affect the fetus, there appears to be no increased risk of birth defects or nonhereditary cancers in the offspring of women who received chemotherapy prior to conception.[37]

CONCLUSION

Pregnancy after breast cancer may be reasonable for some patients

Long-term survival following a diagnosis of breast cancer is common. Menopause in breast cancer patients is often associated with concerns regarding general health and quality of life. While the induction of premature menopause may be prevented in some patients, therapies for breast cancer frequently exacerbate menopausal symptoms. A variety of nonhormonal approaches are available for the treatment of vasomotor and other menopausal symptoms. Similarly, interventions for treating and preventing heart disease and osteoporosis are available. Physicians treating patients with a history of breast cancer need to be aware of the variety of health concerns faced by these patients. Issues regarding hormone replacement therapy frequently arise following treatment for breast cancer and must be considered on an individual basis with an understanding of the limited data currently available. Improved understanding of the role of estrogen replacement therapy in breast cancer patients including its influence on disease recurrence is needed.

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