Management of Gynecologic Issues in Women With Breast Cancer

Breast cancer is the most common type of invasive cancer in American women, whose lifetime risk of the disease is one in eight. In 2009, there were an estimated 192,370 new cases of invasive breast cancer in the United States (1). Although rates have decreased slightly in the past few years, there are 2 million breast cancer survivors living in the United States. Improvements in prevention and screening and more effective treatment are continually occurring, and changes are relatively quickly translated into clinical practice. Breast cancer treatment is becoming more individualized and depends on both the extent of disease and individual tumor features. Treatments involve surgery, radiation therapy, chemotherapy, and hormonal therapies.

All types of breast cancer treatment have potential deleterious effects on women as well as how they view themselves. Therefore, it is important for women’s health care providers to have an understanding of breast cancer treatments and their potential gynecologic side effects. The purpose of this document is to review the effect of breast cancer treatment on common women’s health issues such as fertility, contraceptive management, menopause, sexual function, and osteoporosis, and to provide a rationale for follow-up and treatment of these gynecologic issues.

Background

**Adjuvant Therapy and Ovarian Function**

Premature ovarian failure or diminished ovarian reserve may occur as a result of breast cancer chemotherapy. Typically, a combination of agents is used that often includes the alkylating agent cyclophosphamide, which accounts for most of the observed ovarian toxicity (2, 3). Newer regimens contain taxanes, which are thought to have a less toxic effect on the ovaries (4, 5). The overall incidence of chemotherapy-induced amenorrhea ranges from 53% to 89%, and depends on the age of the patient and the chemotherapy regimen used (6). In general, women who experience chemotherapy-induced amenorrhea and are older than 40 years have a much higher likelihood of becoming menopausal, compared with women younger than 40 years, following chemotherapy for breast cancer (7). Also, the amount of time it takes for the development of chemotherapy-induced amenorrhea is shorter in older women compared with younger women. Most women who resume ovarian function after chemotherapy tend to resume menses within 1 year, although menstrual irregularities, often due to intermittent anovulation, are common (8). Even if menses returns, the long-term effect of chemotherapy often includes persistently poor ovarian reserve, infertility, and a higher risk of premature ovarian failure (9). Measuring anti-müllerian hormone levels has been proposed as a way to monitor ovarian reserve during and after chemotherapy (10, 11). A low anti-müllerian hormone
level may indicate reduced fertility, but pregnancy may still be achievable, unless it has been determined that a patient is menopausal.

Ovarian suppression with the use of gonadotropin-releasing hormone (GnRH) agonist or GnRH antagonist therapy, or the removal of the ovaries (eg, risk-reducing salpingo-oophorectomy) also can be used as part of breast cancer treatment in premenopausal women with hormone-receptor–positive (estrogen-receptor or progesterone-receptor) breast cancer and decreases the risk of recurrence (12). In addition, premenopausal women undergoing treatment for estrogen-sensitive breast cancer with aromatase inhibitors—which block the synthesis of estrogen from ovarian and adrenal androgens—need concurrent suppression of ovarian function in order for the medication to be effective (13).

**Gynecologic Surgery**

Some high-risk women undergoing breast cancer surgery may need, or choose, to have associated gynecologic surgery, including bilateral salpingo-oophorectomy or hysterectomy or both, to decrease their risk of other types of cancer. Carriers of the BRCA gene have a hereditary predisposition for not only breast cancer, but also ovarian cancer. Because of the lack of effective screening methods for ovarian cancer, risk-reducing salpingo-oophorectomy is typically recommended by age 40 years or when childbearing is complete (13).

Recent studies have shown that BRCA carriers who have not developed breast cancer and who undergo risk-reducing salpingo-oophorectomy decrease their risk of primary breast cancer as well as their overall mortality from this disease (14, 15). Women who are not BRCA carriers from families with a known BRCA mutation are at the same risk of breast cancer or ovarian cancer as the general population. Similar to the general population, a strong family history of breast cancer, ovarian cancer, or both places either woman at similarly elevated risk of the development of malignancy (16–19).

The primary disadvantage of salpingo-oophorectomy is loss of natural ovarian hormone secretion. The reproductive hormone profile observed with surgical menopause in a premenopausal woman is quite similar to that of a postmenopausal woman, with mean reductions in serum testosterone and estradiol concentrations of 50% and 80%, respectively (20). Systemic hormone therapy, based on studies to date, is not generally recommended in breast cancer survivors. Management of menopausal symptoms can be accomplished through nonhormonal options. Selective serotonin reuptake inhibitors (SSRIs) (eg, citalopram or fluoxetine) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, venlafaxine) have both been shown to be safe and to reduce the severity of hot flushes in patients with breast cancer, although caution must be used when these agents are used in conjunction with tamoxifen (21, 22). In patients using tamoxifen, an SNRI is preferable to an SSRI secondary to less potent inhibition of the cytochrome P450 2D6 isozyme pathway required for tamoxifen metabolism. This effect on tamoxifen metabolism by SSRIs may decrease the efficacy of tamoxifen and, as a result, SNRIs are generally preferable to SSRIs in women using tamoxifen. Other options for management of vasomotor symptoms in breast cancer survivors who cannot use estrogens or progesterones include gabapentin and clonidine (23).

For atrophic vaginitis, nonhormonal options found to be effective and safe in breast cancer survivors include vaginal moisturizers and, in a recent trial, a vaginal pH-balanced gel (24). The use of vaginal estrogen in patients in whom such therapies fail may be considered. Although data regarding the safety of topical estrogen in breast cancer survivors are limited, small retrospective trials support the safety of topical estrogen products in this population (22, 25, 26). Low-dose, 10-microgram estradiol-17β vaginal tablets or the low-dose vaginal estradiol ring, compared with oral estradiol or estradiol vaginal cream, results in the lowest systemic absorption (27). For patients in whom nonhormonal treatments fail, use of these low-dose methods may best be considered in consultation with an expert in cancer treatment such as an oncologist.

**Cancer Therapy and Sexual Function**

Despite the adverse effects of breast surgery and chemotherapy on sexual function, the most consistent predictor of satisfying sexual experiences in women with breast cancer is the quality of their relationships (28, 29). Breast surgery involves either lumpectomy or mastectomy, with or without immediate or delayed reconstructive procedures. These surgical procedures have complex effects on sexual function that relate to perception of body image changes, attitudes before diagnosis of cancer, loss of sensation in breasts, sexual desire and ability to achieve orgasm, and feelings of loss of femininity and stability of a partnered relationship (30). Some studies suggest that women who have breast-conserving surgery have better sexual function than women who undergo mastectomy, but data are inconsistent regarding this issue (28).

Research has consistently shown that patients with breast cancer who undergo chemotherapy are at higher risk of sexual dysfunction (31). One report noted that among sexually active patients who did not have a recur-
Hormonal Therapies

Hormonal therapy used for the prevention of breast cancer and for the treatment of hormone-responsive breast cancer includes estrogen agonists and estrogen antagonists (formerly called selective estrogen receptor modulators) and aromatase inhibitors. Both of these classes of drugs are effective treatments for hormone-receptor–positive breast cancer.

Estrogen Agonists and Estrogen Antagonists

Estrogen agonists and estrogen antagonists are synthetic compounds that selectively stimulate or inhibit the estrogen receptors of different target tissues. Such selectivity is made possible by the fact that the estrogen receptors of different target tissues vary in chemical structure. Estrogen agonists and estrogen antagonists have been shown to be very effective treatments for hormone-receptor–positive breast cancer (33–39). Estrogen agonists and estrogen antagonists approved for use in the United States include tamoxifen, raloxifene, and toremifene.

Efficacy

Tamoxifen is approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer and the reduction of breast cancer risk in healthy women at high risk of developing the disease. Long-term data for tamoxifen, which had been the standard of care for hormone-receptor–positive breast cancer in both premenopausal and postmenopausal women, show that 5 years of treatment decreases the annual risk of breast cancer recurrence by 40% and annual mortality risk by 34%, independent of age, menopausal status, lymph node status, or chemotherapy use (32). There are ongoing trials evaluating the effects of 10 years versus 5 years of tamoxifen use, but results to date suggest little benefit for treatment beyond 5 years (40, 41).

Raloxifene is approved by the FDA for the prevention of invasive breast cancer in postmenopausal women who are at high risk of developing the disease. Initial data from the Study of Tamoxifen and Raloxifene trial demonstrate that raloxifene was as effective as tamoxifen in preventing breast cancer in high-risk women (37). Additional data from the Study of Tamoxifen and Raloxifene trial show that after 5 years of raloxifene use, the risk of invasive breast cancer was reduced by 38% versus 49% among tamoxifen users, and the risk of noninvasive breast cancer was decreased by 39% versus 50% for the tamoxifen group (38). Raloxifene is also approved for the prevention and treatment of osteoporosis in postmenopausal women.

Toremifene is approved by the FDA for the treatment of metastatic breast cancer. Results have shown similar benefits to tamoxifen in postmenopausal women with hormone-receptor–positive breast cancer (39).

Adverse Effects and Risks

The physiologic effects of estrogen agonists and estrogen antagonists are not uniform and vary depending on the type of estrogen agonist or estrogen antagonist. Because estrogen agonists and estrogen antagonists selectively stimulate or inhibit the estrogen receptors of different target tissues, their effects in some tissues can have a deleterious physiologic effect, including an increased risk of thromboembolic events, endometrial and vulvovaginal abnormalities, and vasomotor problems.

Thromboembolic Events. The relative risks of deep vein thrombosis or pulmonary embolism associated with the use of estrogen agonists or estrogen antagonists increase with age and vary depending on the type of estrogen agonist or estrogen antagonist (35, 42). In an update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene P-2 Trial, raloxifene caused less toxicity compared with tamoxifen, including reduced thromboembolic events (relative risk [RR], 0.75; 95% confidence interval [CI], 0.60–0.93) following nearly 7 years of follow-up (38).

Endometrial and Uterine Effects. The risks to the uterus vary depending on the type of estrogen agonist or estrogen antagonist used and a woman’s menopausal status. Premenopausal women taking tamoxifen often have menstrual irregularities (43) and there have been reports of ovarian cysts (44–46), endometrial polyps, and increased leiomyoma growth (47–49). Postmenopausal women taking tamoxifen have been reported to develop endometrial pathology, including endometrial proliferation, polyps (50, 51), hyperplasia, and carcinoma, which typically presents as abnormal vaginal bleeding (34, 52). Among postmenopausal women, there is also a slightly increased risk of benign ovarian cysts and uterine leiomyomas (53, 54). Uterine cancer, especially endometrial cancer, is a rare but serious adverse effect of tamoxifen. In a systematic review of seven randomized controlled trials and one head-to-head study, tamoxifen was associated with an increased risk of endometrial cancer (RR, 2.13; 95% CI, 1.36–3.32) compared with placebo.
(42) and a slightly increased risk of uterine sarcoma (34, 35). The incidence of endometrial cancer is reported to be approximately 2 per 1,000 women taking tamoxifen (35, 37).

In contrast, raloxifene is not believed to have as significant an estrogenic effect on the uterus and has not been associated with an increased risk of endometrial cancer compared with placebo (RR, 1.14; 95% CI, 0.65–1.98) (42). In the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene P-2 Trial, raloxifene was significantly less likely to be associated with endometrial hyperplasia (RR, 0.10; 95% CI, 0.12–0.29) and endometrial cancer (RR, 0.55; 95% CI, 0.36–0.83) (38). In the Multiple Outcomes of Raloxifene randomized trial, after 40 months of follow-up, raloxifene did not increase the risk of endometrial cancer (RR, 0.8; 95% CI, 0.2–2.7) compared with controls (36). The uterine effects of toremifene are not as well studied as those of tamoxifen; however, in comparison, the endometrial risks of toremifene are thought to be similar or slightly less than tamoxifen (55).

**Vasomotor Symptoms.** Menopausal symptoms are common among patients with breast cancer, either as a result of temporary or permanent anovulation, ovarian suppression from chemotherapy, or as an adverse effect from hormonal therapies such as tamoxifen. One of the most bothersome adverse effects is hot flushes, occurring in one half of women taking tamoxifen (56). These adverse effects tend to be worse in women who previously experienced significant vasomotor symptoms with menopause and in women who previously used menopausal hormone therapy (HT), and these symptoms tend to decrease with time. Hot flushes also have been associated with the use of raloxifene (57, 58) and toremifene (59). The symptoms of menopause are often more severe in premenopausal patients with breast cancer because of the acute onset of chemotherapy-induced amenorrhea in women with previously normal ovarian function (60, 61). Also, some patients with breast cancer may have oophorectomies as part of their breast cancer treatment, or for prophylaxis, which causes immediate surgical menopause.

**Aromatase Inhibitors**

Aromatase inhibitors are used in the treatment of hormone-sensitive breast cancer alone, in combination with other drugs, or when tamoxifen is contraindicated. Aromatase inhibitors can help block the growth of estrogen-sensitive tumors by lowering the amount of estrogen in the body. Aromatase inhibitors prevent conversion of androstenedione and testosterone into estrogen and decrease peripheral circulating estrogen.

Currently, three aromatase inhibitors are approved for use by the FDA: 1) anastrozole, 2) exemestane, and 3) letrozole. Anastrozole and letrozole are approved as first-line therapy in postmenopausal women with early-stage breast cancer. Exemestane is approved for adjuvant treatment (after tamoxifen use) in postmenopausal women with advanced breast cancer, as well as for the prevention of recurrent cancer (62, 63). The optimum treatment duration with aromatase inhibitors is not known.

Aromatase inhibitors are not useful as a breast cancer treatment drug in premenopausal women with functioning ovaries because blocking aromatase in the ovaries results in lower estradiol levels, which reduces negative feedback and increases pituitary gonadotropin output, thereby increasing ovarian function. In premenopausal women taking aromatase inhibitors for breast cancer treatment, concurrent ovarian suppression is required in order for the drugs to be effective. In premenopausal women who become amenorrheic during chemotherapy, aromatase inhibitors may stimulate residual ovarian function, and this off-label use should be prescribed with caution (64, 65). Monitoring serum estradiol levels in these women is important in recognizing ovarian stimulation and identifying the possible need for ovarian suppression or ablation (64).

**Efficacy**

All three aromatase inhibitors appear to have similar clinical efficacy (66). In recent breast cancer trials that evaluated aromatase inhibitors as adjuvant hormonal therapy in postmenopausal women, aromatase inhibitors have demonstrated greater effectiveness than tamoxifen for treatment of early-stage hormone-receptor–positive breast cancer (67–72). A Cochrane review reported a statistically significant survival benefit among users of aromatase inhibitors compared with tamoxifen users (hazard ratio, 0.89; 95% CI, 0.82–0.96) (73). Aromatase inhibitors also have been found to reduce the occurrence of contralateral breast cancer in several studies, which suggests their role as a breast cancer prevention drug (74).

**Adverse Effects and Risks**

The short-term and long-term adverse effects of aromatase inhibitors in postmenopausal women are related to a lack of estrogen action at aromatase-targeted tissue sites. These adverse effects include decreased bone mineral density (BMD), an increased bone fracture rate, arthralgias, vasomotor symptoms, vaginal dryness (68), and a possible increased risk of cardiovascular effects. In contrast to tamoxifen, aromatase inhibitors are associ-
ated with no significant increased risk of thrombosis (62) and endometrial cancer (72) and a reduction in vaginal bleeding.

Musculoskeletal Effects. Because aromatase inhibitors decrease peripheral estrogen, they are associated with increased bone loss and fracture (75–77). In the most recent 120-month follow-up of the largest prospective trial, the Arimidex, Tamoxifen, Alone or in Combination trial, comparing the 5-year use of anastrozole with tamoxifen for the adjuvant treatment of early-stage breast cancer, the anastrozole group had significantly more fractures during the treatment period (451 versus 351; odds ratio [OR], 1.33; 95% CI, 1.15–1.55), but fractures were similar to the tamoxifen group in the posttreatment follow-up period (110 versus 112; OR, 0.98; 95% CI, 0.74–1.30) (78). In addition to fractures, women taking aromatase inhibitors reported more musculoskeletal problems. Up to 45% of women reported joint pain and 10–20% of women discontinued drug treatment for this reason (79, 80).

Vasomotor and Gynecologic Effects. In general, the gynecologic adverse effects caused by aromatase inhibitors are less than those caused by tamoxifen. In the Arimidex, Tamoxifen, Alone or in Combination trial, there was less vaginal discharge (3.0% versus 12.2%; P<0.001) and vaginal bleeding (4.8% versus 8.7%, P<0.001) in the anastrozole group compared with the tamoxifen group (81). There was also a statistically significant decreased risk of endometrial cancer in the anastrozole group (OR, 0.25; 95% CI, 0.08–0.63) which suggests that these drugs may prevent endometrial cancer (78). Vasomotor symptoms were less frequent compared with the tamoxifen group, occurring in 36% versus 41% (P<0.0001) of women. Overall, there were significantly fewer adverse gynecologic events in those women taking anastrozole (20.5% versus 34.2%, P<0.0001) (82, 83).

The one gynecologic adverse effect that is more commonly reported among aromatase inhibitor users compared with women taking tamoxifen is vaginal dryness. A number of trials have shown more vaginal dryness and dyspareunia in women taking aromatase inhibitors compared with those taking tamoxifen (84, 85).

Cardiovascular Disease. There are conflicting data on the effects of aromatase inhibitors on cardiovascular disease. A small, but significant, increased risk of cardiovascular disease has been noted in trials that compared aromatase inhibitors with tamoxifen, but not in studies that compared aromatase inhibitors with placebo (86–88). The cardiovascular risks associated with aromatase inhibitors are thought to be greater in women with preexisting heart disease. These effects are likely related to marked hypoestrogenism having a negative effect on serum lipid levels.

Clinical Considerations and Recommendations

How should the risk of osteoporosis be evaluated in breast cancer survivors, and what treatments are useful for those found to be at increased risk?

Osteoporosis risk assessment in patients with breast cancer should include an assessment of clinical risk factors and BMD testing and monitoring (89). First-line pharmacologic options approved by the FDA for the prevention and treatment of osteoporosis include the bisphosphonates and raloxifene. Women also should be counseled about lifestyle changes to reduce the risk of bone loss and osteoporotic fractures.

Osteoporosis presents a challenge in the long-term management of breast cancer survivors. Bone health is adversely affected by many of the cancer treatment modalities, including chemotherapy, ovarian suppression, and aromatase inhibitors, which all result in lower estrogen levels, more bone loss, and increased risk of fracture (7, 90–92). In patients with breast cancer, most discussions related to osteoporosis relate to management of women taking aromatase inhibitors. Bone loss is most rapid in premenopausal women undergoing ovarian suppression and taking aromatase inhibitors. In addition, in a large population-based study, hip fractures and falls were increased after a diagnosis of breast cancer, which suggests a disease and non–treatment-related risk of fracture.

The American Society of Clinical Oncology recommends BMD monitoring by dual energy X-ray absorptiometry to assess and manage bone loss in patients with breast cancer at high risk of osteoporosis (93). Because almost 80% of fractures occur in women with normal BMD or osteopenia, it is important to assess clinical risk factors of fracture such as advanced age, estrogen deficiency, postmenopausal use of aromatase inhibitors, history of fracture, family history of osteoporosis, chronic corticosteroid use, low body mass index, inadequate physical activity, cigarette smoking, and excessive alcohol consumption (93–95). The World Health Organization has devised a multivariate model that uses BMD or osteopenia, it is important to assess clinical risk factors of fracture such as advanced age, estrogen deficiency, postmenopausal use of aromatase inhibitors, history of fracture, family history of osteoporosis, chronic corticosteroid use, low body mass index, inadequate physical activity, cigarette smoking, and excessive alcohol consumption (93–95). The World Health Organization has devised a multivariate model that uses BMD and risk factors of fracture to calculate a 10-year probability of any major osteoporotic fracture and is available on-line (www.sheffield.ac.uk/FRAX/).

Pharmacologic options for the prevention and treatment of bone loss include bisphosphonates and raloxifene. There are several randomized controlled trials with data showing that bisphosphonates, which inhibit osteoclasts and prevent bone reabsorption, can prevent
or reduce bone loss for women taking aromatase inhibitors (96). To reduce the risk of osteoporosis in high-risk patients, bisphosphonates may be administered to patients during long-term treatment with aromatase inhibitors.

The 2009 National Comprehensive Cancer Network Task Force report recommends that pharmacologic therapy should be considered for women with breast cancer who have T scores between -1.5 and -2.0 (89). The task force suggested that health care providers strongly consider initiation of pharmacologic treatment in women with T scores less than -2.0 or with a 10-year fracture risk greater than 20% for a major fracture or 10-year hip fracture risk greater than 3%. Monitoring should annually occur for patients with cancer whose bone loss risks significantly change or who undertake a major therapeutic intervention; otherwise, patients with cancer with elevated fracture risks should be monitored every 2 years (97).

There is clinical and preclinical evidence that the bisphosphonates may have antitumor activity in addition to protecting and treating bone loss. Although the mechanism is not clearly known, the bisphosphonate most frequently used in patients with breast cancer, zoledronic acid, is thought to affect angiogenesis, induce tumor apoptosis, affect tumor migration, disrupt bone deregulation, and possibly reduce disseminated tumor cells in the bone marrow (98). Very rare adverse effects associated with the long-term use of these drugs have been suggested but not yet confirmed, including atypical femur fractures and osteonecrosis of the jaw (99, 100).

Raloxifene has been shown to have estrogen-like activity in the prevention of bone loss and is approved by the FDA for the prevention and treatment of osteoporosis. In the Multiple Outcomes of Raloxifene Evaluation trial, it was shown to significantly reduce the risk of vertebral fracture relative to placebo (101). Although generally well tolerated, the adverse effects of raloxifene include vasomotor symptoms (hot flushes and night sweats) and an increased risk of thromboembolic events (36, 102).

Women with or at risk of osteoporosis should be counseled about lifestyle changes to reduce the risk of bone loss and osteoporotic fractures, such as weight-bearing and muscle-strengthening exercises to reduce the risk of fractures and falls, increasing vitamin D and calcium intake, cessation of smoking, reducing alcohol intake, and fall-prevention strategies (103). Because vitamin D is an important cellular regulator and many women are deficient, 25-hydroxyvitamin D levels should be assessed in all patients with breast cancer.

What therapies are useful in the treatment of vasomotor symptoms in breast cancer survivors?

Treatments for vasomotor symptoms include lifestyle alterations, alternative and complementary therapy, and pharmacologic agents. A variety of low-dose antidepressants or gabapentin can be used to manage vasomotor symptoms. The use of hormonal therapy is generally contraindicated in patients with breast cancer. Safety and efficacy data on herbal treatments are unclear, and more data are needed on the efficacy of lifestyle changes and alternative therapies.

The safety of estrogen or estrogen and progesteron HT for the treatment of vasomotor symptoms in breast cancer survivors is unknown, and randomized controlled trials initiated in the 1990s were terminated early when findings indicated increases in breast cancer recurrence (104). This is still a controversial area because a large quantitative review of published data that evaluated the use of menopausal HT in women with a history of breast cancer showed that HT was not associated with an increased risk of cancer recurrence, cancer-related mortality, or total mortality. Women using HT had a decreased chance of recurrence (OR, 0.5; 95% CI, 0.2–0.7) and cancer-related mortality (OR, 0.3; 95% CI, 0.0–0.6) compared with nonusers (105). Given the controversial reports, the use of HT is generally contraindicated in patients with hormone-positive breast cancer, and the need for safe and effective nonhormonal treatments for vasomotor symptoms in patients with breast cancer has accelerated research in this area (106, 107).

Nonhormonal pharmacologic treatments that have been investigated for the treatment of vasomotor symptoms include SSRIs, SNRIs, and gamma-aminobutyric acid analogs. Overall, most of these treatments are not as effective as HT, but they do offer some relief for symptomatic hot flushes (108). In trials evaluating the efficacy of the SNRI venlafaxine for the treatment of hot flushes, the most effective dose has been much lower than the typical treatment dose for depression (109, 110). In a number of randomized controlled trials, significant reduction in hot flushes among breast cancer survivors using venlafaxine was seen. The optimal balance between effectiveness and adverse effects (most commonly, dry mouth, nausea, constipation, and poor appetite) appears to be a dose of 75 mg, with larger doses associated with an increased likelihood of adverse effects with no further clinical benefit (111).

Other trials have evaluated low doses of the SNRI desvenlafaxine and the SSRIs paroxetine, fluoxetine, and citalopram, which have all showed a benefit in reducing vasomotor symptoms compared with placebo (22).
However, there is some significant concern that the use of pure SSRIs, in women taking tamoxifen may interfere with tamoxifen metabolism and thus block the drug’s therapeutic benefit. This interference with tamoxifen appears to be less severe or nonexistent for SNRIs such as venlafaxine (89, 112).

Gabapentin, a gamma-aminobutyric acid analog used as an anticonvulsant and in managing neuropathic pain in patients with breast cancer, has shown a benefit for the management of vasomotor symptoms at low doses. In a meta-analysis of four trials, gabapentin users had a significantly greater reduction in hot flushes (weighted mean difference=23.72 [95% CI, 16.46–30.97]; \( P < 0.001 \)), although adverse effects like dizziness were common (113). It also has been shown to improve sleep quality, which is a problem for many patients with breast cancer (114). Pregabalin, a newer compound that works similarly to gabapentin, also has demonstrated effectiveness in treatment for hot flushes in randomized controlled trials (115). It is important to note that none of these drugs has FDA approval for the treatment of vasomotor symptoms.

Investigations of many herbal products have been contradictory, and there is little information regarding the long-term effect of these products for women with a history of breast cancer (108, 116, 117). Of the herbal products, probably the best studied is black cohosh, which has shown mixed results. Although older, lower-quality studies suggested a benefit for the treatment of vasomotor symptoms, recent randomized controlled trials in menopausal women have not shown a benefit compared with placebo (118, 119). There are less data regarding the use of black cohosh specifically in women with breast cancer. However, a recent prospective observational trial of patients with breast cancer who were taking tamoxifen did find a statistically significant improvement in hot flushes with black cohosh (120). Trials that have evaluated the efficacy and safety of soy products in the treatment of vasomotor symptoms in patients with breast cancer have found that soy, purported to have estrogen-like activity, is not beneficial for the treatment of vasomotor symptoms (121), which is also the case for women experiencing natural menopause (117, 122). Because safety data are also lacking, many oncologists advise breast cancer survivors to avoid the use of soy products.

Lifestyle and behavioral changes to reduce vasomotor symptoms include paced-breathing, relaxation techniques, environmental modifications, and dietary changes (123). Many patients with breast cancer also look to complementary modalities, such as acupuncture. In a 2009 review, five of six randomized controlled trials found no benefit for acupuncture compared with sham or placebo acupuncture in postmenopausal women (124). Another review that analyzed the use of acupuncture in patients with breast cancer also did not show an overall benefit for reducing vasomotor symptoms compared with placebo (125). A recent 12-week randomized controlled trial found acupuncture and venlaxafine equally effective for the treatment of vasomotor symptoms; however, adverse effects were more common in the venlaxafine group (126).

In a Cochrane review that evaluated nonpharmacologic therapies, including homeopathy, acupuncture, and relaxation therapy, for the treatment of vasomotor symptoms, only relaxation therapy seemed to show a benefit (127). A Cochrane review of exercise for menopausal vasomotor symptoms found insufficient evidence to determine the effectiveness of exercise for the treatment of vasomotor symptoms, or whether it is any more effective than HT or yoga (123). Many other complementary modalities are being evaluated for the treatment of vasomotor symptoms in patients with breast cancer and postmenopausal women in general, including stellate ganglion blocks, yoga, and hypnosis. Efficacy data currently are limited, but research into these and other complementary therapies is growing.

What therapies are useful for treating vaginal atrophy in breast cancer survivors?

Vaginal dryness and atrophy are common gynecologic issues in patients with breast cancer. It is estimated that 20–40% of patients with breast cancer have severe vaginal dryness that affects libido (32, 128). Vaginal dryness is a particular problem in young patients with breast cancer and one of the biggest predictors of sexual function (129, 130). Given the increasing use of aromatase inhibitors, which suppress all peripheral estrogen, reports of vaginal dryness and sexual dysfunction are even more common (84). Tamoxifen use also has been associated with vaginal dryness and decreased sexual satisfaction (131).

Treatment options for vaginal dryness and atrophy have been limited because there are little data on the safety and efficacy of the traditional topical hormonal therapies in patients with breast cancer. However, many women have found nonhormonal vaginal lubricants and moisturizers to be effective in managing vaginal dryness (132, 133), and small studies of vaginal moisturizer compared with placebo in patients with breast cancer have shown a benefit (134).

There are many studies that have demonstrated the success of local hormonal therapies for vaginal dryness in postmenopausal women, but the variable rates of estrogen absorption raise safety concerns for patients.
with breast cancer. This has led to the use of local hormonal therapies for which rates of systemic absorption are thought to be quite low. The estradiol vaginal ring, a silastic vaginal ring that slowly releases estradiol-17β without significant systemic absorption (135), is frequently used in patients with breast cancer; however, there are no randomized controlled trial data assessing its safety. A recent small study evaluated the use of vaginal estriol cream and found improvement in symptoms for women taking aromatase inhibitors (136). In postmenopausal women, estradiol-17β vaginal suppositories have been associated with improvement in vaginal dryness comparable with the use of conjugated equine estrogen vaginal cream (137). However, a small study showed that the use of estradiol tablets in women taking aromatase inhibitors was associated with increases in circulating estradiol after 2 weeks of use, leading the authors to conclude that estrogen suppositories might interfere with the estrogen-suppression efficacy of aromatase inhibitors, and thus, their use should be avoided in this population (22, 138).

Given the lack of data to determine whether transient increases in estradiol are clinically significant, and whether the effects of long-term exposure pose increased risk, nonhormonal methods should be considered first-line treatment for vaginal atrophy in women with a history of hormone-sensitive breast cancer (139). Short-term use of hormonal methods may be considered for women with severe or refractory symptoms in whom other options have failed, following appropriate counseling with their oncologists about the potential risks.

There are a lack of safety data evaluating testosterone supplementation for the treatment of vaginal dryness and sexual function in patients with breast cancer, and most studies that have evaluated testosterone have also included the use of estrogen, which typically is contraindicated in this population. A placebo-controlled trial of transdermal testosterone alone in patients with breast cancer did not show an improvement in sexual function (140). A small Phase I/II study that evaluated the use of either 150-microgram testosterone cream or 300-microgram testosterone cream found an improvement in dryness for women taking aromatase inhibitors without an increase in systemic estradiol or testosterone levels (141). However, the largest randomized trial of testosterone versus placebo showed a nonstatistically significant increased risk of breast cancer in the testosterone group (142). Overall, the relationship between testosterone supplementation and general breast cancer risk is not clear, and the FDA has yet to approve testosterone supplementation to treat sexual dysfunction in women, in part, due to a lack of breast safety data.

**When is uterine evaluation useful in breast cancer survivors, and how is it best accomplished?**

Because uterine abnormalities associated with tamoxifen use present as abnormal vaginal bleeding, routine endometrial biopsy and uterine ultrasonography are not recommended for postmenopausal women taking tamoxifen without bleeding (89, 143, 144). For postmenopausal women taking tamoxifen who experience vaginal bleeding, endometrial evaluation, including biopsy and follow-up investigation of possible uterine structural anomalies, is essential (89). Although premenopausal women taking tamoxifen are not at an increased risk of endometrial cancer, any irregular bleeding should be investigated. Hysteroscopy or hysterasonography may be useful in the initial evaluation because polyps are common. A lower threshold for biopsy should, however, be considered if the bleeding remains unexplained.

Ultrasound surveillance has been associated with a significant false-positive rate because tamoxifen induces enlargement of the subendometrial glands, resulting in increased endometrial thickness, irregular echoes, and cystic changes; but, these findings do not correlate with malignant histology (145, 146). In general, endometrial thickness alone should not be used as an indicator for intervention because it will lead to unnecessary invasive diagnostic procedures (147).

**What contraceptive options are safe and effective in breast cancer survivors?**

Contraceptive options for patients with breast cancer include barrier methods, such as condoms and diaphragms, the copper intrauterine device, and sterilization. The U.S. Medical Eligibility Criteria for Contraception Use (U.S. MEC) published by the Centers for Disease Control and Prevention provides guidance on the safety of contraceptive method use for women with specific characteristics and medical conditions. For women who currently have breast cancer, all hormonal methods of contraception have a U.S. MEC Category 4 rating and are contraindicated. For women with a history of breast cancer who have not had disease recurrence for 5 or more years, hormonal contraceptive methods have a U.S. MEC Category 3 rating, indicating that “the theoretical or proven risks usually outweigh the advantages.” For women treated or with a history of breast cancer, the copper intrauterine device has a U.S. MEC Category 1 rating (148).

Almost two thirds of breast cancer diagnoses are hormone-receptor–positive breast cancer. Premenopausal women with this type of cancer are typically treated with
tamoxifen for 5 years, which is chemically similar to the fertility drug, clomiphene citrate, and can induce ovulation. Hormonal contraception in any form is not recommended in women taking tamoxifen.

Breast cancer that is hormone-receptor–negative is biologically different and it is not thought to be stimulated by estrogen or progesterin. However, it is relatively contraindicated to use hormonal contraceptive options in these patients (U.S. MEC Category 4), although there is a lack of data that demonstrates harm (149). Typical contraceptive recommendations include barrier methods and the copper intrauterine device.

One emerging area of interest is whether the levonorgestrel-releasing intrauterine system is a safe option in patients with breast cancer, given its minimal rate of systemic absorption of levonorgestrel. A recent retrospective case–control study that used cancer registries in Finland and Germany did not find an increased risk of primary breast cancer associated with use of the levonorgestrel-releasing intrauterine system (150). But there have been conflicting reports as to whether these devices increase breast cancer recurrence (151). Larger and longer follow-up studies are needed to assess whether the levonorgestrel-releasing intrauterine system is associated with any increased risk of breast cancer recurrence. Use of the levonorgestrel-releasing intrauterine system should balance this unknown risk with its potential benefit on a case-by-case basis. Consultation with the patient’s medical oncologist can be useful in these cases.

How should patients be counseled about the effects of breast cancer treatment on future fertility?

When breast cancer is diagnosed in a premenopausal woman, it is important to discuss her fertility concerns (152). Pregnancy after breast cancer is not thought to increase breast cancer recurrence. If future pregnancy is desired, appropriate consultation with fertility specialists should be offered to ascertain whether immediate assisted reproductive strategies are possible to preserve fertility. Certainly, the extent of the disease and prognosis may affect decision making.

Given that more and more women delay childbearing, the issue of pregnancy after breast cancer is not uncommon. The main safety concerns are whether the hormonal environment of pregnancy could affect tumor regrowth or stimulate preexisting micrometastases. There are a number of published series in which pregnancy after breast cancer has been studied, and subsequent pregnancy has not been found to affect breast cancer recurrence or prognosis (153). There have been concerns that this may reflect a healthy mother effect (mothers who are healthier may be more likely to get pregnant), but a 2010 meta-analysis of pregnancy and breast cancer survival studies and a review of breast cancer survival data from the Surveillance, Epidemiology, and End Results database found no significant increase in the risk of breast cancer recurrence or mortality associated with subsequent pregnancy (154, 155).

Breast cancer treatments affect fertility primarily by the negative effect of chemotherapy on ovarian function. Typically, chemotherapy involves a combination of agents, including the alkylating agent cyclophosphamide, which likely accounts for most of the ovarian toxicity. Most women who resume ovarian function experience a return of menses within 1 year of completing chemotherapy, although menstrual irregularities are common, and women are still at risk of premature menopause (8). In addition to ovarian toxicity from chemotherapy, premenopausal women with hormone-sensitive breast cancer are typically treated with tamoxifen for 5 years, which stimulates ovarian function. Depending on a woman’s age at diagnosis, a 5-year delay in fertility attempts may diminish ovarian reserve.

Ovarian suppression using GnRH agonists, sometimes used as a part of breast cancer treatment in premenopausal women, has been suggested as a method to preserve fertility. The mechanism of protection is unclear, but it is thought that GnRH agonists may place the ovary in a premenarchal state without active recruitment of follicles (156, 157). Human studies of GnRH analog cotherapy for the preservation of ovarian function during gonadotoxic chemotherapy have had mixed results (158, 159). A 2011 systematic review and meta-analysis of six randomized controlled trials to determine the potential benefit of GnRH cotreatment with chemotherapy in premenopausal women found higher rates of spontaneous resumption of menses and ovulation but no improvement in pregnancy rates in women treated with GnRH (158, 160). To date, it is unclear whether ovarian suppression does indeed preserve fertility, and most fertility programs for patients with breast cancer focus on methods such as cryopreservation of embryos.

Potential fertility preserving options include in vitro fertilization (IVF) with embryo cryopreservation, if there is a male partner or if use of a sperm donor is acceptable. One of the concerns with immediate IVF with embryo cryopreservation is whether the high levels of estrogen produced by ovarian stimulation will have adverse effects on breast cell proliferation. In the general infertility population, there are no convincing data that ovulation induction or IVF increases the risk of breast cancer (161). It is not known if the high estrogen milieu has any adverse effect on breast cancer that is already established. Some oncologists have felt that conventional ovulatory stimu-
lating agents are contraindicated; therefore, patients with breast cancer have previously been offered unstimulated or natural-cycle IVF, which has results in patients without-out cancer that may approach IVF pregnancy rates (162).

Tamoxifen, alone or in combination with follicle-stimulating hormone, has been successfully used in patients with breast cancer for ovarian stimulation for IVF (163). Other potential options for ovarian stimulation are aromatase inhibitors. These drugs cannot be used as a breast cancer treatment in premenopausal women with functioning ovaries because they lower ovarian estradiol levels, which reduces negative feedback and increases pituitary gonadotropin output. However, this mechanism of action allows them to be used as fertility agents, and they have been used successfully for ovulation induction in healthy patients with infertility (164). A prospective study using the aromatase inhibitor, letrozole, in combination with gonadotropins for controlled ovarian stimulation found no increases in cancer recurrence at 2 years of follow-up compared with controls (165). Ovarian tissue cryopreservation and oocyte cryopreservation are two additional options with the potential to preserve fertility. Although these methods are developing rapidly, their use as a means to have a child after cancer treatment must be considered investigational (166). Further research and longer-term follow-up are needed to determine the safety and efficacy of these approaches.

**Summary of Recommendations and Conclusions**

*The following recommendation and conclusion is based on good and consistent scientific evidence (Level A)*

- SSRIs and SNRIs have both been shown to be safe and to reduce the severity of hot flushes in patients with breast cancer, although caution must be used when using these agents in conjunction with tamoxifen. Gabapentin and clonidine are other options for management of hot flushes.

*The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B)*

- The 2009 National Comprehensive Cancer Network Task Force report recommends that pharmacologic therapy should be considered for women with breast cancer who have T scores between -1.5 and -2.0.

- Routine endometrial biopsy and uterine ultrasonography are not recommended for postmenopausal women taking tamoxifen without bleeding.

- Contraceptive options for patients with breast cancer include barrier methods, such as condoms and diaphragms, the copper intrauterine device, and sterilization.

- Pregnancy after breast cancer is not thought to increase breast cancer recurrence.

- If future pregnancy is desired for women in whom breast cancer has been diagnosed, appropriate consultation with fertility specialists should be offered to ascertain whether immediate assisted reproductive strategies are possible to preserve fertility.

*The following recommendation is based primarily on consensus and expert opinion (Level C)*

- Nonhormonal methods should be considered first-line treatment for vaginal atrophy in women with a history of hormone-sensitive breast cancer.

**Proposed Performance Measure**

The percentage of postmenopausal patients taking tamoxifen with vaginal bleeding who received endometrial biopsy

**References**


40. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. J Natl Cancer Inst 2001;93:684–90. (Level I) [PubMed] [Full Text]  


156. Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embryos, oocytes, or ovaries. Oncologist 2007;12:1044–54. (Level III) [PubMed] [Full Text]


The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists’ own internal resources and documents were used to conduct a literature search to locate relevant articles published between June 2010–November 2011. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.