Adverse Effects of Breast Cancer Treatment

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As breast cancer outcomes improve and more people with breast cancer survive longer following diagnosis, many survivors must deal with the effects of treatment. Some adverse effects last a short time and have little influence on breast cancer patients' quality of life, yet others can cause long-term complications and add to increased morbidity and mortality among survivors. This article reviews the adverse effects of breast cancer treatments and how they affect the health and quality of life of those receiving treatment. The article also explains how adverse effects can interrupt treatment and how physicians and survivors can manage adverse effects of breast cancer treatment.

After completing this article, the reader should be able to:
- Identify adverse effects associated with specific breast cancer treatments.
- List common treatment-related adverse effects of breast cancer.
- Explain treatment-related complications that can interrupt treatment.
- Discuss how treatment-related adverse effects affect breast cancer survivors' quality of life.
- Describe management strategies for treatment-related adverse effects.
- Understand the role of the radiologic technologist in caring for breast cancer patients or survivors with treatment-related adverse effects.

Modern therapies to treat breast cancer have contributed to improved survival rates and excellent prognoses for cure among patients with early-stage disease. As many as 1 million cases of breast cancer are diagnosed each year around the world and approximately 275,000 cases are diagnosed each year in the United States. More than 2 million breast cancer survivors live in the United States. As men and women with breast cancer live longer following diagnosis, they also are more likely to experience a number of adverse effects from their treatment.

Adverse effects from breast cancer treatment vary by treatment type and often vary according to a patient's age, cancer type or stage, and other factors. Still, as many as 90% of breast cancer patients experience treatment-related adverse effects. Some adverse effects are minor, and others are debilitating. When adverse effects are particularly persistent or difficult to bear, patients might not comply with treatment, which can affect their prognosis.

Over the past few decades, breast cancer treatments have been targeted more specifically to individual patients. As a result, each patient and survivor has experienced a unique range of treatment-related adverse effects. Adverse effects of treatment should be of concern to cancer patients, survivors, and those who care for them. In particular, treatment-related adverse effects are of concern when they affect a patient's long-term health, quality of life, or adherence to treatment.

Breast Cancer Management Overview

Management of breast cancer depends on the type and stage of breast cancer at the time of diagnosis. Physicians consider tumor size, metastatic spread, and hormonal involvement when designing management...
plans, along with a patient’s age and other conditions affecting the patient’s overall health. Physicians also might consider the patient’s lifestyle and potential adverse effects of treatments.4,4

**Surgery**

Most women with early-stage breast cancer undergo breast-conserving surgery or a modified radical mastectomy. One form of breast-conserving surgery, a lumpectomy, excises only the tumor and a small amount of the tumor margin, or normal surrounding tissue.4,9 Lumpectomy often is followed by radiation therapy and is the recommended management choice for women with ductal carcinoma in situ.10 Another form of breast-conserving surgery is the partial or segmental mastectomy, which removes the tumor, along with a margin of tissue that surrounds the tumor, from the breast in which the malignancy was found. This surrounding tissue includes both tumor margin and normal tissue.4,9

Mastectomy might be the only surgical option for some women, even those with early-stage disease. If the breast cancer is widespread or there are several areas of suspicious calcifications, breast-conserving surgery is not possible. Sometimes resection of the primary tumor offers poorer cosmetic results than a mastectomy might offer, or mastectomy is required because breast-conserving surgery fails to remove the entire tumor margin adequately.4,9

Today, radical mastectomies are performed only on women who have locally advanced tumors and who are not good candidates for preoperative chemotherapy. Some women have a double mastectomy or oophorectomy (surgical removal of the ovaries) as a prophylactic measure to prevent breast cancer when high risk factors for genetic forms of the disease are present.4

In addition to surgical options to remove cancerous lesions and margins, breast cancer patients might have surgical biopsies of the breast or lymph nodes. In about one-fourth of patients, breast cancer has spread to the lymph nodes by the time of diagnosis.11 A physician might remove positive lymph nodes, particularly in the axillary area.

Finally, women with breast cancer might undergo breast reconstruction surgery to improve cosmesis immediately (at the same time as mastectomy) or following completion of cancer treatment. Breast reconstruction following lumpectomy depends on a preoperative evaluation and the patient’s satisfaction with the cosmetic outcome of the surgery.6,9,11

**Radiation Therapy**

The use of breast-conserving surgery followed by breast irradiation first was investigated in the 1920s and has led to reduced use of radical mastectomies.7 More than 40% of all women in the United States who receive a breast cancer diagnosis each year receive radiation therapy as part of their treatment.11 Radiation therapy often is used after surgery to destroy any remaining cancer cells. This local control is essential for reducing the risk of recurrence or metastatic spread.4 Adjuvant radiation therapy reduces recurrence risk 70% and mortality risk 9% to 12%.14

Breast cancer patients who have breast-conserving surgery can receive whole-breast radiation therapy followed by a series of treatments to the surgical cavity to prevent local recurrence. Whole-breast therapy generally involves a dose of 1.8 to 2.0 Gy delivered daily over 5 to 7 weeks,15 and partial-breast irradiation is a short course of radiation delivered over approximately 5 days to the surgical cavity and a small margin of normal surrounding tissue.4

Partial-breast radiation has become a viable alternative to whole-breast irradiation.4,16 Accelerated partial-breast radiation therapy can be delivered with external-beam radiation, through intraoperative radiation therapy, or with brachytherapy. The purpose of accelerated partial-breast radiation therapy is to deliver the radiation locally to the breast tissue in which recurrence of the cancer is most likely.16 With brachytherapy, the radiation is delivered to the tumor bed directly, typically using a balloon catheter or multiple interstitial catheters to place tiny seeds or implants in the intracavitary space.4,9,16

**Chemotherapy**

Nearly all breast cancer patients with locally advanced disease receive chemotherapy, surgery, and radiation therapy. The value of adjuvant chemotherapy for early-stage disease is less well-demonstrated, however.4

Patients with operable breast cancer should receive preoperative (ie, neoadjuvant) chemotherapy to manage systemic, metastatic spread of the disease.17
Preoperative chemotherapy can reduce the size of breast tumors that otherwise would require excisions resulting in poor cosmesis. National Comprehensive Cancer Network guidelines recommend preoperative chemotherapy for invasive breast cancers. Systemic chemotherapy generally is administered orally, intravenously, or intramuscularly.

Breast cancer patients who have hormone-receptor–positive and ERBB2 (formerly HER2 or HER2/neu)-positive disease might receive adjuvant chemotherapy with trastuzumab before receiving endocrine therapy. Adjuvant chemotherapy with trastuzumab also is considered a systemic treatment for patients who have small tumors (< 1 cm) and hormone-receptor–negative disease that is positive for ERBB2. Patients who have tumors greater than 1 cm or positive lymph nodes generally receive trastuzumab therapy. Trastuzumab is a monoclonal antibody that works against ERBB2 and generally is incorporated with anthracycline and cyclophosphamide combination therapy. Doxorubicin is the preferred anthracycline agent.

Improved ability to identify the genes responsible for some forms of breast cancer has led to targeted therapeutic approaches for some patients. For example, patients who have ERBB2-positive cancer can benefit from adjuvant therapy targeted specifically at ERBB2 receptors. Trastuzumab is an example of a successful targeted therapy, and newer agents such as lapatinib have been approved by the U.S. Food and Drug Administration for targeting ERBB2-positive breast cancers. Pertuzumab is another monoclonal antibody that helps block ERBB2 receptors. It is part of a combination first-line therapy for patients with ERBB2-positive disease, along with trastuzumab and docetaxel or paclitaxel.

Some therapies specifically target angiogenesis, which is the formation of new blood vessels that promote growth of local and metastatic cancers. Clinical trials are underway to investigate a number of targeted therapies aimed at ERBB2 and epidermal growth factor receptor, along with other breast cancer markers.

In general, the benefits of adjuvant chemotherapy depend on a number of factors, such as lymph node status, patient age and health status, and type and length of therapy. In view of its adverse effects, the decision to use adjuvant systemic therapy is highly individual and a topic of continued research, particularly into targeted therapies.

**Endocrine Therapy**

Hormone receptor status is an important consideration in breast cancer treatment. Breast cancer patients who have hormone-receptor–positive and ERBB2-positive disease generally receive adjuvant endocrine therapy. The therapy usually immediately follows chemotherapy, and studies show that use of endocrine therapy along with radiation therapy is safe. Use of pharmacologic endocrine therapies such as tamoxifen, aromatase inhibitors, or pure antiestrogens can help reduce risk of disease recurrence. Endocrine agents might be used singly or in combination for 2 to 5 years for long-term therapy. Researchers still are determining the safety and effectiveness of endocrine therapy use for more than 5 years.

Endocrine therapy also can be achieved by suppressing ovarian function with surgery. Women who are premenopausal and have hormone-receptor–positive breast cancer might be treated with oophorectomy or ovarian irradiation for ovarian ablation or suppression. Women who are postmenopausal receive adjuvant endocrine therapy with an aromatase inhibitor alone or following tamoxifen therapy.

**Adverse Effects of Treatment**

Because therapy planning, surgical techniques, and other methods for managing breast cancer have improved over time, adverse effects of breast cancer treatment are no longer as severe. Still, many breast cancer patients and survivors experience adverse effects during and after treatment. Serious adverse reactions to medications or other breast cancer treatments can be difficult to detect or study because of the time that often elapses between treatment and the appearance of adverse effects. In addition, clinicians must distinguish between a breast cancer patient’s underlying cancer, comorbidities, and the potential treatment toxicity when determining the cause of signs or symptoms of a therapy’s adverse effect.

Acute adverse effects occur soon after treatment and last for a short time. Other complications of therapy can arise later and usually are called late adverse effects or late sequelae. Some adverse effects are chronic, lasting for months or years.

**Surgery**

Many women who have breast surgery experience pain and numbness in the chest wall, breast, and axilla.
Aching muscles and weight gain are reported symptoms for women who have mastectomies. As many as 5% to 20% of patients who have breast-conserving surgery or mastectomy report arm edema, most likely from the axillary procedure. In fact, axillary lymph node dissections once were made through level III (below the collarbone), but today dissection mainly involves the first 2 levels that receive lymph fluid: level I is the bottom level at the lower edge of the pectoralis minor, and level II is under the pectoralis minor. As a result, incidence of lymphedema has declined but remains an incurable adverse effect of breast cancer treatment.

Lymphedema is swelling caused by poor lymphatic drainage. In breast cancer patients and survivors, the poor drainage results from complications related to surgery or radiation therapy. Generally, a change of 200 mL or more in arm volume or a 2-cm change in arm circumference not related to changes attributed to surgery determines lymphedema. Early lymphedema might not be indicated as easily by objective measurements, however, and clinicians should consider patient-reported symptoms such as swelling, a sensation of heaviness, or restricted motion to help prevent the progression of edema. From 12% to 26% of patients have lymphedema 12 months after axillary lymph node dissection. Swelling and heaviness from lymphedema are strongly associated with pain.

The literature reports that 25% to 60% of breast cancer patients who receive surgery experience pain following their procedures. Whether pain is persistent can depend on several factors, including the type of surgery, psychosocial factors, and how investigators and patients define persistent pain. Risk factors for pain following breast surgery include young age, obesity, and preoperative breast pain. Patients often report pain and problems with mobility and range of motion in the upper axilla following breast surgery, as well.

Concerns about body image following surgery can affect breast cancer patients and survivors regardless of age. In particular, patients who prefer to receive breast-conserving surgery but instead must have a mastectomy often have the poorest body image. A conservative mastectomy preserves the skin and areola. The surgeon creates a flap with skin and enough subcutaneous tissue to provide a vascular supply to the nipple-areola complex. Following the surgery, patients typically experience transient nipple ischemia, but the ischemia is reversible. In about 1% to 30% of cases, the necrosis fails to reverse and the patient must have the affected nipple excised. Women who smoke and are young are more likely to have complications related to nipple vascularization; the type of incision also affects nipple necrosis.

Cosmesis is a major concern to patients who have breast-conserving surgery, and surgeons must balance the cosmetic effects of lesion removal with the need to adequately excise the entire tumor margin. A study published in England in 2012 revealed that as many as 20% of women who had breast-conserving surgery required a second operation to remove additional tissue with malignant cells not removed in the original procedure.

When given a choice, women who have mastectomies and are candidates for breast reconstruction tend to choose autologous tissue, particularly abdominal flaps. Many cosmetic surgeons prefer to use expanders to reconstruct patients’ breasts. Breast reconstruction surgery also can present complications such as seroma formation, infection, rippling, and malposition.

Use of acellular dermal matrices has helped eliminate some complications from breast cancer surgery. An acellular dermal matrix is a soft tissue graft. A decellularization process on donated tissue leaves the extracellular matrix intact to provide a scaffold that the patient’s own cells repopulate and revascularize. However, the grafts do not eliminate all complications related to breast augmentation. Long-term data on high-risk patients could help further determine possible complications related to the soft-tissue replacement system. Although breast reconstruction can increase complications following breast cancer surgery, the effects often are acceptable and complications vs benefits are weighed on an individual patient basis.

Radiation Therapy

Improvements in treatment planning and delivery techniques have eliminated many complications associated with radiation therapy that women experienced approximately 20 years ago. Symptoms severe enough to require a break in treatment can affect radiation therapy’s effectiveness and treatment outcome.

Skin reactions from radiation therapy affect up to 90% of cancer patients. As many as 85% of those who have skin reactions have moderate to severe effects such as swelling, a sensation of heaviness, or restricted motion. The literature reports that 25% to 60% of breast cancer patients who receive surgery experience pain following their procedures. However, the pain can be persistent and can affect patients regardless of age.
as edema, erythema, fibrosis, ulceration, or changes in pigmentation. Radiation-related skin reactions are likely caused by a decrease in functional stem cells and by changes that radiation causes to the endothelial cells of the skin. In addition, inflammation and skin cell necrosis cause reactions. Patients might have itching, dryness, pain, warmth, or burning of the skin. Skin reactions usually appear within 1 to 4 weeks after radiation therapy initiation and can persist through treatment and for several weeks following completion of the radiation therapy treatment plan. 

Moist desquamation, a condition in which the skin blisters and peels to expose the dermis underneath, is a fairly common acute adverse effect of radiation therapy for breast cancer. About 30% to 50% of women who receive radiation therapy to the breast experience moist desquamation. Research has shown that patients who have moist desquamation have much higher risk of developing a late effect called telangiectasia, which is abnormal dilation of superficial capillaries just below the skin’s surface.

Radiation therapy alone or in combination with surgery also can cause lymphedema. Gärtner et al reported that although lymphedema occurred in women who had radiation therapy, lymphedema from radiation was not associated with functional impairment for patients.

Rib fractures can occur in up to 5% of women following radiation therapy, but the fractures usually are asymptomatic. However, the possibility of this adverse effect should be considered when women who have received radiation therapy have nuclear bone scans for rib or chest tenderness.

By reducing dose slightly to part of the breast, radiation oncologists can escalate dose to the tumor bed. Boost volumes to the tumor bed have been associated with increased rates of moderate to severe breast fibrosis 10 years after treatment. Fibrosis is formation of fibrous, or scar, tissue.

Nausea or vomiting can occur as a result of radiation therapy treatment. Patients who receive upper abdominal radiation therapy are the most likely to experience this adverse effect, but the potential for nausea and vomiting exists for any patient who receives large daily fractionated doses or large total doses.

Late cardiac toxicity is possible but rare following radiation therapy, most often for women who receive radiation to the chest wall following a mastectomy. Investigators also have studied late cardiac effects related to dose per fraction. In general, when dose exceeds 2 Gy per fraction, there is increased potential for late toxicities and poorer cosmesis.

The advent of partial-breast irradiation made radiation therapy following breast-conserving surgery accessible to more women and offered similar outcomes. Partial-breast irradiation potentially involves smaller treatment volumes and therefore lower radiation doses to critical structures. Likewise, hypofractionated therapy delivers higher doses in fewer treatment fractions, improving access to therapy for many patients. Studies found, however, that both partial-breast irradiation and hypofractionated radiation therapy of the whole breast were associated with some unexpected adverse effects.

There have been reports of pneumonitis associated with partial-breast irradiation, most likely because of escalated dose to the ipsilateral lung (20 Gy or higher). Treatment plan modification can prevent pneumonitis associated with partial-breast irradiation. Additional complications related to partial-breast irradiation with brachytherapy have been reported. With brachytherapy, additional steps are required to implant the radioactive seeds accurately; these steps introduce opportunities for adverse effects. For example, inserting needles extends surgical time and can add risks for hematoma, infection, or abscess.

Cosmesis-related issues from partial-breast irradiation include volume loss, retraction, contour defect, and telangiectasia. The late development of a soft-tissue sarcoma within the radiation therapy portal is a rare adverse effect of radiation therapy for breast cancer (0.1% incidence).

Patients who smoke and are receiving external-beam radiation therapy have significantly more skin toxicity from radiation therapy than former smokers or non-smokers. Women who smoke and who received breast-conserving therapy and radiation therapy might be at higher risk of developing ipsilateral lung cancer.

Boost techniques used in radiation therapy and breast-conserving surgery have helped with local tumor control, but clinical research on the effects of various boost volume techniques is difficult to compare because of varied data points and the influence of patient and treatment-related factors on outcomes. Clinical trials
following women for 10 years suggest that whole-breast irradiation with a hypofractionated technique is tolerated well.39

Regardless of adverse effects from radiation therapy, studies have yet to identify subsets of female populations who have better outcomes following breast-conserving therapy without radiation therapy than those who have breast-conserving surgery and radiation therapy. Elderly women who have several comorbidities might be the only group best served by opting out of radiation therapy.4

Chemotherapy

Acute, life-threatening events rarely occur as a result of today’s chemotherapy combinations for breast cancer. Although mostly tolerated well by patients, chemotherapy agents can cause breast cancer patients to experience alopecia (hair loss), gastrointestinal complications, and infections as short-term effects. In addition, patients undergoing chemotherapy experience myelosuppression, or short-term suppression of blood cell and platelet production by bone marrow. Patients often experience anemia along with peripheral neuropathy and muscle or joint pain.4

Nausea and vomiting have been known for some time to be associated with chemotherapy, and they are the most frequently reported adverse effects. A study on the effects of chemotherapy-induced nausea and vomiting on daily life reported that 36% of patients receiving chemotherapy experienced vomiting and 60% had nausea. Other reports have found that clinicians often can predict acute nausea and vomiting but underestimate how often delayed effects occur.40 Fatigue and weight gain also are common complaints following chemotherapy.4

Over the years, various treatment regimens have been identified to ease adverse effects of chemotherapy. For example, clinicians are aware that diarrhea, nausea, and vomiting occur more often with a lapatinib and capecitabine combination than with ado-trastuzumab emtansine.41 Still, both acute and delayed nausea can affect breast cancer patients’ quality of life.38,42 Nausea and vomiting in a patient receiving cancer treatment can cause metabolic imbalances, nutrient depletion, anorexia, cognitive decline, and withdrawal from treatment.38

Premature menopause is a complication of chemotherapy for young women, depending on the type of adjuvant chemotherapy. The cessation of menses can be temporary or permanent. As a result of ovarian suppression, some women experience menopausal symptoms such as hot flashes and vaginal dryness, in addition to infertility. In more severe cases, women might have rapid bone loss or osteoporotic complications.4

Cardiovascular disease now competes with breast cancer as the cause of death in women who have early-stage breast cancer. Studies show an overall increased risk of cardiovascular disease among female breast cancer patients compared with their age-matched peers who do not have breast cancer.43 Clinical trials have shown an approximate 2% increase in risk of heart failure or cardiomyopathy among patients who have anthracycline therapy. The risk increases to 4% with the addition of trastuzumab. Risk increases for both agents the longer patients delay beginning chemotherapy and the more comorbidities patients have at the time of treatment. The highest risk is among women who use both anthracycline and trastuzumab.18

Toxicity from anthracycline correlates to cumulative dose, and older women are at much higher risk of heart failure from the agent’s use. Specifically, anthracycline can cause irreversible cardiomyopathy that can lead to severe left ventricular systolic dysfunction and heart failure in its most severe form. Most cardiac toxicity from anthracycline appears months or years following exposure. Acute cardiac toxicities of anthracycline administration include elevated troponin levels, electrocardiogram changes, and dysrhythmia. Most adjuvant therapy regimens now limit cumulative dose of doxorubicin to a total of 300 mg/m² because of anthracycline’s cumulative effect.5 Systemic therapy with trastuzumab is associated with several known toxicities, most notably cardiac toxicity.11 The effects do not appear to be related to cumulative dose, and although problems with cardiotoxicity from use of trastuzumab alone are rare, it appears that trastuzumab adds to the concurrent effects of anthracycline on the heart. Trastuzumab also has been associated with adverse gastrointestinal effects.44 Clinicians have focused for several years on developing agents to magnify the positive effects of trastuzumab but lessen its toxic effects.19 The adverse cardiac effects of trastuzumab and anthracyclines might be underestimated because clinical trials investigating the agents’ effects include only select patient populations.2
Bevacizumab is a chemotherapy agent used in combination with paclitaxel. Bevacizumab also can lead to a decline in left ventricular function. The cause of the ventricular decline most likely is related to hypertension instead of myocardial toxicity. Bevacizumab is associated with higher risk of arterial thromboembolism as well.

Early trials have demonstrated lower cardiac toxicity from lapatinib than from anthracycline or trastuzumab, but longer follow-up might be required to determine potential for long-term cardiotoxicity. Initial results show no symptomatic left ventricular effects or significant cardiac events.

As early as 30 years ago, patients reported neurotoxicity that affected cognitive abilities. Controlled trials more recently confirmed patients’ reports that breast cancer patients who receive chemotherapy experience slight cognitive impairment, particularly in verbal processing and ability. Studies show that older patients appear to be more susceptible to the cognitive effects of chemotherapy, at least as measured by processing speed.

The benefit of targeted therapies is that they reduce toxicities by focusing action on malignant cells and therefore are less toxic to healthy cells. Still, some targeted therapies can cause toxicities, and investigators have been trying to determine the exact mechanism for trastuzumab’s cardiotoxicity. Evidence shows that trastuzumab’s cardiotoxicity is reduced when more time elapses between anthracycline therapy and administration of trastuzumab.

The antiangiogenic agents now used in oncology, including bevacizumab, also are associated with cardiac complications. Several emerging targeted therapies in development, such as receptor tyrosine kinases, are involved in cancer cell proliferation and survival. Investigators also are researching the potential for these targeted therapies to cause off-target effects such as cardiotoxicity.

**Endocrine Therapy**

Tamoxifen and aromatase inhibitors have been shown to cause musculoskeletal pain, and the joint pain from aromatase inhibitors has been severe enough to interfere with treatment in some patients. Reports demonstrate that up to 25% of aromatase inhibitor users discontinue therapy and that arthralgia, or joint pain, is the No. 1 reason. The adverse effects of these drugs differ. Aromatase inhibitors are associated with an increased risk of developing cardiovascular disease or osteoporosis and bone fractures. Tamoxifen has been associated with blood clotting complications and increased risk of venous thromboembolism or stroke.

The bone-related complications of aromatase inhibitors are contributing to a higher number of hip fractures among breast cancer patients. The drugs block estrogen production, which makes them highly effective in managing estrogen-receptor–positive breast cancer, but the hormone-blocking action also affects circulation and peripheral tissue estrogen levels, causing accelerated bone loss and fracture risk. The risk is higher for women who have fractures when they begin treatment. Fractures occurred in women who had chemotherapy, aromatase inhibitors, or both across all age groups in a study by Edwards et al (see Figure 1).

Adverse effects of tamoxifen therapy are a major reason for treatment interruption. The hormonal therapy can be associated with undesirable effects in a patient’s uterus, vagina, and central nervous system, along with bone loss in postmenopausal women. Treatment interruption rates are high for adjuvant endocrine therapy. Between 19% and 33% of women reportedly halt tamoxifen therapy at 3 years, and up to 50% discontinue therapy at 5 years. The reasons vary depending on the patient’s age, stage of treatment, and other factors (see Box 1). Some women resume their treatment after interruption, but up to 40% discontinue treatment altogether after only 10.7 months of adjuvant endocrine therapy.

Clinicians continue to study the adverse effects of adjuvant endocrine therapy to attempt to minimize treatment interruption. The literature reports that 10 years of treatment with tamoxifen offers even more protection against estrogen-receptor–positive breast cancer than a 5-year course. Finding ways to minimize or manage long-term adverse effects of endocrine therapy can benefit premenopausal women in particular.

**Combined Therapies**

Some adverse effects of particular breast cancer therapies are exacerbated by other treatments. For example, radiation therapy can add to the cardiotoxic effects of systemic therapies. Women who have brachytherapy appear to have more complications following breast surgery but similar survival to women who have not had brachytherapy. Significant complications...
Adverse Effects of Breast Cancer Treatment

Pregnant Patients

Breast cancer is rare in pregnant women but is the most common cancer occurring during pregnancies, at a rate of about 13 per 100,000 live births. The incidence is increasing, partly because many women are delaying childbearing until later years. Most pregnant women with breast cancer have a modified radical mastectomy, although breast-conserving surgery is an option for some pregnant women. In general, pregnant women deserve the same typical and timely treatment based on cancer stage and other decision factors as they would if they were not pregnant. Breast surgery generally is considered safe during pregnancy. Chemotherapy administration beyond the first trimester has been reported to result in no fetal damage, but malformations to the fetus have occurred when chemotherapy was administered during the first trimester. Most chemotherapy agents have been rated in pregnancy category D, which means there is evidence of human fetal risk, but because benefits outweigh the risk in situations such as breast cancer, the drugs’ use is acceptable despite the risks. There is little clinical information on the long-term effects of chemotherapy delivered to fetuses during treatment of maternal cancers.

Likewise, a paucity of data exists on targeted agents such as trastuzumab and lapatinib. The scarce data on administration of trastuzumab during pregnancy is mixed, and only 1 report on the use of lapatinib exists to date. Tamoxifen use is not recommended during pregnancy because of reported birth defects. Up

include mastitis, abscess, delayed wound healing, and hematoma. Radiation therapy can increase complication risk and affect the aesthetic outcome of reconstructed breasts. Some reports have shown that skin toxicity from radiation therapy is made worse if patients are taking aromatase inhibitors. No difference in skin toxicity has been found when combining radiation therapy and tamoxifen, however.

Preclinical findings raised concerns that endocrine therapy with aromatase inhibitors would increase adverse effects of radiation therapy, but Chargari et al found that aromatase inhibitors could be used concurrently with hypofractionated radiation therapy without leading to severe cosmetic effects or disruption in treatment. Some women treated with radiation therapy and endocrine therapy have experienced weight loss, most likely associated with nausea or eating problems.

Treatment Complications in Specific Populations

Each patient with breast cancer is unique, and part of the challenge for clinicians is determining how to treat breast cancer optimally while minimizing the adverse effects of treatment modalities. Certain populations of breast cancer patients deserve special mention regarding treatment-related adverse effects.


Box 1

Reasons Patients Discontinue Endocrine Therapy

- Adverse events complicated by surgery and radiation therapy.
- Clinical intolerance.
- Financial difficulties.
- Joint pain.
- Thromboembolic event.
- Weight gain, sexual dysfunction/loss of libido in men.
- Hot flashes, menopausal symptoms in younger women.
Male Breast Cancer

Male breast cancer occurs rarely and makes up less than 1% of all breast cancers diagnosed around the world. When men have breast cancer, it is even more likely to be hormone-receptor–positive than breast cancer in women. Most male breast cancer treatment follows the typical treatment regimen for female patients, and men commonly receive tamoxifen as endocrine therapy.

Because so few men have breast cancer, studying endocrine therapy’s effects has been difficult. The few studies conducted have reported discontinuation rates of endocrine therapy of approximately 21% to 24%, and clinicians have yet to define the most effective strategies for treating male breast cancer.

Prognosis for many men with breast cancer can be worse than the general population of women with breast cancer because many male breast cancer diagnoses are delayed.

Men tend to report many adverse effects from tamoxifen, some of which are serious. Over a 10-year period, Pemmaraju et al evaluated 64 male breast cancer patients who had been treated with tamoxifen therapy. The authors found a 20% discontinuance rate related to toxicity, including thromboemboli, loss of libido, bone pain, and neurocognitive deficits. The most common adverse effects reported by men in the study were loss of libido, weight gain, hot flashes, mood alteration, and depression. The authors encouraged further study into the mechanisms leading to discontinuation, particularly in understanding tamoxifen’s effects on testosterone levels and subsequent sexual dysfunction.

Xu et al studied tamoxifen therapy adherence among 116 men diagnosed with breast cancer between 1987 and 2012. The authors found that 64.6% of patients who had a 5-year prescription for tamoxifen were still taking the medication one year after receiving the prescription. In the Xu et al study, nearly 64% of patients reported adverse effects from tamoxifen, including sweating, sleep disruption, anxiety, weight gain, fatigue, and decreased libido. The authors also found that low adherence to therapy was associated with low social support.

Quality of Life

More breast cancer patients receive diagnoses today in early stages of the disease, which means more of them...
can be effectively cured or survive for many years. In fact, most women diagnosed with early-stage breast cancer die of unrelated causes.3,21 The 5-year survival rate for women who have hormone-receptor–positive cancer is 88%.21

Improved survival underscores the necessity to minimize or manage long-term adverse effects from cancer treatments.3,21 Adverse effects of treatment can negatively affect a patient’s quality of life and his or her ability to perform daily activities. Short-term adverse effects can lead to discontinued treatment, and long-term adverse effects that are detrimental to a patient’s health-related quality of life can affect outcome or prognosis.6

Although patients often choose aggressive treatments with reduced recurrence and mortality risk regardless of potential late toxicity, they might be faced with chronic disease or psychosocial issues as a result of breast cancer therapies.4,21 One such issue is osteoporosis, a chronic problem in many older women. Women who are diagnosed with breast cancer and receive aromatase inhibitor therapy face decreased bone health and quality of life and increased risk of mortality from fractures.21

Younger premenopausal women face lifelong effects of breast cancer therapy’s induction of premature menopause. Aside from symptoms such as hot flashes and weight gain, treatment can affect a woman’s sexuality by causing vaginal dryness, decreased sexual desire, and infertility.4,57

Menopausal symptoms cause significant morbidity, discomfort, and quality-of-life issues in breast cancer patients, affecting their body image, sexual functioning, and psychological well-being.24 In a survey of more than 600 young breast cancer survivors (mean age at breast cancer diagnosis was 32.9 years), 57% expressed significant concerns about the effect of breast cancer treatment on their future ability to reproduce, and 72% said they had expressed concerns about fertility with their physicians.5,59

Effects of cancer treatments on a woman’s body image, along with fear of recurrence, can add to sexual problems and overall depression or anxiety.25,37 A review by Cesnik et al found that even patients who had intense and fulfilling sex lives before breast cancer diagnoses often had altered sexual functioning following disease treatment. Treatment affected the women’s body image, added to stress, caused pain and fatigue, and lowered their self-esteem.60 Concerns about body image factor into quality of life, regardless of a breast cancer survivor’s age.27

Cancer-related fatigue disrupts patients’ routines and upsets quality of life more than pain, according to some reports. Fatigue is experienced often by cancer survivors, regardless of the type of treatment they receive, and can continue long after tumor control.61

Health-related quality of life also is an important measure during treatment and to the continuation of treatment. The stress, fatigue, breast pain, and skin irritation that accompany radiation therapy for breast cancer can affect quality of life. In addition, attending daily appointments over a 6-week course of treatment affects women’s personal and professional lives.14

Härtl et al investigated changes in quality of life over time in 236 breast cancer survivors who completed questionnaires at 6 months and 12 months postsurgery. The authors found that one year after surgery, breast cancer diagnosis and treatment still affected the survivors’ quality of life. In particular, the survivors studied were anxious about cancer recurrence and body image issues. The authors also stated that social effects from breast cancer diagnoses and treatments might be felt more by younger survivors because of family and work demands, which also can lead to financial difficulties if work is missed for treatment time.62

Breast cancer is the most common malignancy in women of working age. Women who are away from work for prolonged periods for cancer treatment can experience financial hardship and feelings of social isolation. Returning to work as soon as possible improves survivors’ quality of life.63,64

Finally, adverse effects of breast cancer treatment are worsened by stress and anxiety, which are common in people with breast cancer. Stress or anxiety can add to how frequently a patient experiences certain adverse effects or how intensely they are felt.65

Managing Adverse Effects

As people treated for breast cancer live longer, clinicians must coordinate care to improve long-term effects of breast cancer treatment, along with surveillance and monitoring for cancer recurrence. During and following treatment, breast cancer patients and survivors often turn to primary care physicians for management of adverse effects; therefore, these physicians must be aware of the potential adverse effects associated with cancer therapies.4
Follow-up of treatment effects is challenging for clinicians because the effects vary among survivors and because treatments constantly are revised and updated; toxicity profiles on chemotherapy agents also change. There is limited information regarding exact incidence and prevalence of many late effects of treatment among cancer survivors, and although many adverse effects occur at the same time, they often have distinct causes.

The health care system is not prepared to care for breast cancer survivors. In a system that is specialty-focused, breast cancer patients are released from the care of oncologists and radiation oncologists and back to the care of primary care physicians. Using pain as an example, patients receive attention for pain management while under the active care of physicians for their primary cancers, but often pain management is neglected once a patient transitions to survivor status even though pain continues in some cases.

To help clinicians better manage care of long-term effects of cancer treatment and to help with surveillance for disease recurrence or serious adverse events as a result of treatment, survivor care plans were developed. The care plans provide detailed summaries of cancer patients’ treatments; these details can help primary care physicians better monitor and manage potential breast cancer treatment toxicities or late effects. In addition, the care plans help survivors take more responsibility for posttreatment care.

Pain

Managing chronic pain is essential because of the 20% to 50% of breast cancer patients who develop chronic neuropathic pain in the breast, axilla, or arm and because of the effect persistent pain has on breast cancer survivors’ quality of life. Andreada et al investigated the use of local anesthetics and regional anesthesia vs conventional analgesia in preventing pain 6 to 12 months following surgery. The authors theorized that using local or regional anesthesia during or soon after surgery could reduce chronic pain in women who had breast cancer surgery. They found that a paravertebral block, in which a local anesthetic is injected close to the nerves, could reduce risk of chronic pain from breast cancer surgery for 6 months following surgery in about one-fourth of those studied.

Patients who report chronic neuropathic pain often need pharmacological interventions such as opioid analgesics, antidepressants, or antiepileptic medications. The literature on the management of persistent pain from breast cancer treatment is scarce, and even the few small studies included might not offer conclusive evidence for physicians because patient experiences, medical histories, and reports of pain differ widely. Some studies have indicated that high doses of vitamin D supplements can significantly reduce the joint pain associated with aromatase inhibitors.

Osteoporosis

Women aged older than 65 years and men aged older than 70 years are at risk for bone loss and should have bone densitometry before breast cancer treatment decisions are made. Other patients at high risk for osteoporosis are those who have had previous fragility fractures and anyone taking a medication or having a medical condition associated with accelerated bone loss or low bone mass.

People who have osteoporosis can reduce fracture risk by 30% to 70% by taking bisphosphonates. Calcium and vitamin D supplements often are given to patients receiving aromatase inhibitors. Vitamin D supplementation has been shown to improve patients’ bone metabolism, increase bone mineral density, and even decrease the number of fractures. Although the optimal dose for patients with chemotherapy-related bone loss is unknown, improvements in bone metabolism biomarkers and bone mineral density have been observed when patients had daily doses of between 500 and 1200 IU of vitamin D.

Physicians should closely monitor patients’ bone density measurements during and after therapy. Patients who have T scores of less than -1.5, a body mass index below 20 kg/m², family history of hip fracture, or a previous fragility fracture, along with other osteoporosis risk factors such as smoking, should receive bisphosphonate therapy. The medication can be taken orally or administered intravenously to prevent bone loss associated with use of aromatase inhibitors to treat breast cancer.

Nausea

Nausea and vomiting severity depend on the specific therapy regimen, dose, schedule, and route, along with
other factors. Patient characteristics such as age, sex, or history of alcohol use also can be factors. Significant advancements were made in preventing chemotherapy-induced nausea and vomiting when 5-HT3 agonists (antiemetics) were introduced in the early 1990s. Incidence of vomiting can be as high as 90% with highly emetogenic chemotherapy but reduced to about 30% when prophylactic antiemetic regimens are used. Nausea is more difficult to control, however.

Physicians select antiemetics for patients based on the associated emetic risk for the type of chemotherapy or radiation therapy administered along with patient characteristics and previous experience with the drugs. When a patient receives chemotherapy and radiation therapy, the antiemesis treatment is based on the chemotherapy regimen. Breast cancer patients should be treated for nausea and vomiting throughout the full period of risk, which can continue for 2 to 3 days following treatment cessation. Prophylactic antiemetics should be administered before chemotherapy begins. Patients can receive many 5-HT3 antagonists orally or intravenously.

Hilarius et al found that monitoring of nausea and vomiting throughout treatment can help prevent adverse effects and allows physicians to adjust antiemetic dosage for subsequent cycles. Pregnant women can safely receive antiemetics to help control nausea caused by chemotherapy.

**Cardiotoxicity**

A number of breast cancer therapies and modalities can cause cardiovascular problems (see Table 1). Breast cancer patients who receive combination therapies with anthracyclines are at higher risk for cardiotoxicity than others. Some patients are at more risk than others because of existing diseases or medical conditions at the time they receive therapy. For example, patients who have hypertension or cardiac disease are more vulnerable to the effects of anthracyclines.

Key to helping reduce cardiotoxicity among breast cancer patients is detecting potential cardiac conditions before or during therapy. Physicians cannot predict all signs of cardiotoxicity, but a patient’s medical history, clinical examination that includes assessing left ventricular function and potential hypertension, and serial monitoring of cardiac function during therapy can help prevent serious adverse events.

Clinicians can identify patients at risk for cardiac adverse effects from anthracycline administration immediately following therapy by identifying certain biomarkers. For example, elevated troponin I or natriuretic peptide indicates a patient might be at risk for cardiotoxicity and requires further evaluation of cardiac function. Troponin I is a marker of cell death that can indicate potential alterations in left ventricular function. Certain natriuretic peptides indicate changes such as volume overload or signal cumulative exposure of anthracycline that leads to late-term effects in survivors.

Cancer patients with cardiac stress from existing conditions can receive anthracyclines under certain carefully managed conditions. For example, the anthracycline dose might be lowered in the therapy regimen, or the patient might receive continuous infusion to reduce peak plasma levels of anthracycline. Introducing an agent called dexrazoxane can lessen the cardiotoxic effects of the anthracycline. Physicians also will consider not using an anthracycline-based chemotherapy combination on patients who have cardiac stress when evidence exists that the alternative agents would work as well as or better than the anthracycline-based therapy.

Breast cancer patients who receive trastuzumab should be monitored every 3 months while in treatment and every 6 months for at least 2 years following treatment to assess left ventricular function. If signs of cardiotoxicity or the potential for cardiac effects is noted, clinicians design a strategy to prevent or treat the problem based on the degree of risk or extent of disease. Standard regimens such as angiotensin converting enzyme (ACE) inhibitors, beta-blockers, or statins can help prevent cardiac effects of breast cancer treatment.

When patients who receive trastuzumab or other targeted therapy have decreased left ventricular function during treatment, their physicians should discontinue the medications at least temporarily. Physicians should measure function again after 4 to 6 weeks and resume trastuzumab therapy if left ventricular function improves or returns to normal levels.

Few studies specific to treating cardiotoxicity in the oncology setting are available. Generally, physicians should provide the patient with antihypertensive medications (particularly ACE inhibitors) until the left ventricle’s function returns to normal. Managing chemotherapy-induced cardiomyopathy requires
would reduce or exclude anthracyclines but offer the same survival benefits to breast cancer patients.²

**Lymphedema**

Little has been written on how to prevent lymphedema following breast cancer treatment. Devoogdt et al reported on a method of exercise therapy and manual lymph drainage therapy consisting of 40 brief sessions over a 6-month period.²⁴ Not all participants presented for all 40 sessions; most absences were attributed to adverse effects or illness related to chemotherapy and radiation therapy. The authors did not find a medium or significant effect on lymphedema from the manual drainage but recommended a study aimed at determining the small effects of manual lymph drainage on lymphedema.²⁴

**Anxiety and Depression**

Stress and anxiety can worsen adverse effects of breast cancer treatment, and both are common at the time of diagnosis and throughout treatment. Stress and anxiety can lead to increased frequency of many adverse effect symptoms or the intensity of adverse effects.⁶⁵ Psychological effects in people undergoing breast cancer treatment often go unrecognized and untreated. These symptoms could be identified and treated by primary care physicians if the physicians are properly prepared to watch for them.⁷³

Selective serotonin reuptake inhibitors (SSRIs) usually help treat anxiety and depression related to breast cancer and its treatment. Examples of SSRIs used in patients receiving chemotherapy are paroxetine and amitriptyline.⁷ Breast cancer patients who have anxiety and depression related to diagnosis or treatment also can receive help from complementary and alternative therapies such as acupuncture and mind-body medicine.⁷⁴,⁷⁵

**Fatigue**

Unfortunately, some of the medications used to manage adverse effects of breast cancer treatments also add to the fatigue already experienced by patients. In addition, many patients undergoing treatment have problems sleeping or experience mood disturbances, which exacerbate fatigue.⁶¹

National Comprehensive Cancer Network guidelines recommend that cancer patients be screened for cooperation from oncology and cardiology clinicians.⁷² In addition to ACE inhibitors, patients might receive diuretics or dietary sodium restrictions or other control of hypertension risk factors as typical management of chemotherapy-related cardiotoxicity.² If breast cancer patients or survivors develop heart failure, clinicians should prescribe treatments similar to those prescribed for patients who have heart failure from other causes.²⁰ This might include the use of ACE inhibitors or angiotensin receptor blockers and beta-blockers with diuretics. A small study investigated using enalapril or ramipril in women who developed heart failure after anthracycline therapy. Enalapril in particular showed positive results when implemented within 6 months of detecting dysfunction in the left ventricle.⁴¹

Some breast cancer patients at higher risk for cardiac complications might need an alternative to trastuzumab as part of their therapy.²⁶ Clinical trials in the United States and Europe are investigating regimens that

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cardiovascular Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Left ventricular dysfunction</td>
</tr>
<tr>
<td>Radiation therapy short-term</td>
<td>Angina</td>
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<tr>
<td>effects</td>
<td>Dyspnea</td>
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<td>Heart failure</td>
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<td>Pericardial effusion</td>
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<td>Sudden death</td>
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<tr>
<td>Radiation therapy long-term</td>
<td>Coronary artery disease</td>
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<tr>
<td>effects</td>
<td>Pericardial constriction</td>
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<td>Atherosclerosis</td>
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<td>Mediastinal fibrosis</td>
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<td>Valvular heart disease</td>
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<tr>
<td>Monoclonal antibodies (trastuzumab)</td>
<td>Left ventricular dysfunction</td>
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<td></td>
<td>Cardiomyopathy</td>
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<tr>
<td>Monoclonal antibodies (bevacizumab)</td>
<td>Arterial thromboembolism</td>
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<td>Endocrine therapy (tamoxifen)</td>
<td>Venous thromboembolism</td>
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<td></td>
<td>Stroke</td>
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<tr>
<td>Antimetabolites (fluorouracil,</td>
<td>Ventricular ectopy</td>
</tr>
<tr>
<td>capecitabine, methotrexate)</td>
<td>Myocardial ischemia/infarction</td>
</tr>
</tbody>
</table>

Table 1: Cardiovascular Effects of Breast Cancer Treatment⁴³,⁴⁴,⁷²
Fatigue regularly. Counseling and education on recognizing and managing fatigue can help breast cancer patients and their families better cope with the adverse effect. Physical activity, whether home-based or supervised, is a nonpharmacologic approach to managing fatigue.\(^a\)

Studies have found that methylphenidate, a dopamine enhancer, might help alleviate fatigue related to cancer treatment. Methylphenidate normally is used to treat attention deficit disorder. Other stimulants are under investigation with less promising results. Modafinil, normally used to treat sleep disorders, has been shown to reduce severe fatigue among patients receiving chemotherapy, but the drug had no effect on patients with mild or moderate fatigue.\(^5\) Patients with fatigue can benefit from exercise, yoga, and complementary and integrative medicine approaches.\(^6,56,74\)

**Cognitive Functioning**

Because of adjuvant chemotherapy’s long-term effects on cognitive function, many women with estrogen-receptor–positive disease can receive more benefit from additional years of ovarian function suppression than from chemotherapy.\(^4\) Modafinil has proved effective in helping alleviate cognitive difficulties related to cancer treatment in breast cancer survivors.\(^4\) No clinical trials have proved positive effects on cognitive function from vitamin D supplementation, but some observational studies report improved cognition from increased vitamin D levels.\(^6\)

**Skin Toxicity**

Optimal localization of the tumor bed helps avoid delivering unnecessary radiation to normal breast tissue. Image-guidance techniques also have helped reduce toxicity to skin and other surrounding organs.\(^37\) Many factors contribute to skin erythema in breast cancer patients who receive radiation therapy. For example, women with large breasts have higher skin toxicity, most likely because of larger breast volumes leading to dose inhomogeneities. Patients with allergies, who smoke, or who are receiving endocrine therapy have higher risk of skin toxicity.\(^41\) Patients can help reduce skin toxicity by quitting smoking.\(^37\)

There is little evidence to support the use of various topical agents to minimize skin toxicity related to radiation therapy. Salvo et al performed a review of the literature in 2010 and found insufficient evidence to support the use of any particular agent to prevent or manage acute skin reactions from radiation therapy.\(^36\)

Radiation oncology department practices for treating skin toxicity vary, but most clinicians agree that moisturizing the irradiated area helps reduce skin reactions. Corticosteroid creams, aloe vera, and other moisturizing products that do not contain lanolin have been recommended.\(^36\) At times, patients may require treatment such as amifostine, oral hydrolytic enzymes, pentoxifylline, or zinc supplement.\(^35\)

When dry desquamation occurs, clinicians should educate patients about keeping affected areas moisturized. Areas of moist desquamation should be treated with hydrocolloid dressings to prevent infection.

Patients should be cautioned to avoid use of topical products with metallic bases (such as zinc oxide) on or near the breasts during radiation therapy; these products increase skin surface dose. They also should keep the irradiated breast dry and clean, avoid extreme temperatures, and wear loose-fitting clothing over irradiated breasts to prevent friction that might further irritate the skin.\(^36\)

**Sexual and Reproductive Effects**

Klaeson et al conducted focus groups on the effects of breast cancer treatments on sexuality. The authors found that having love, support, and confirmation helped women cope with the adverse sexual side effects of treatment. Support groups helped women think about their own needs and receive nurturing from others. The authors also suggested that nurses help coordinate how members of the breast cancer treatment team talk about and confirm breast cancer patients’ feelings about sexuality.\(^57\)

Duitjs et al found that cognitive behavioral therapy and physical exercise could help alleviate some of the symptoms related to treatment-induced menopause from breast cancer therapy. The 2 therapies particularly helped alleviate endocrine-related symptoms such as hot flashes. To a lesser degree, cognitive behavioral therapy and physical exercise reduced symptom severity of adverse sexual side effects.\(^58\)

Guidelines from the American Society of Clinical Oncology and the American College of Obstetricians
and Gynecologists suggest that physicians refer breast cancer patients to fertility specialists before they begin treatment with aromatase inhibitors. Most patients who wish to preserve fertility opt for embryo cryopreservation. The preservation of embryos typically occurs in a 6-week window between surgery and initiation of chemotherapy. Reddy and Oktay reported on a method to stimulate the ovaries with the use of aromatase inhibitors and gonadotropins, concluding that the method is safe and offers additional options to breast cancer patients.1

Role of Integrative Medicine

An estimated 40% of cancer survivors use some type of complementary and alternative medicine (CAM) approach at some stage in their therapy or survivorship, and as many as 75% of breast cancer patients use CAM,6 although its use is mostly not reported. One reason might be that patients often choose their CAM techniques or providers without their conventional medicine practitioner’s input and without telling their oncologists that they are receiving alternative treatments.

Many patients turn to CAM to help avoid or manage treatment-related adverse effects.1,6,74 Others choose CAM practitioners because their oncologists are intimidating, cold, or adversarial when the patient questions treatment decisions. Most women diagnosed with breast cancer who chose CAM methods and were interviewed by Citrin et al said they were treated with impersonal attitudes by conventional medicine practitioners and did not believe their physicians were working in their best interests.1

Citrin et al also reported that some patients view chemotherapy as poison because of its many adverse effects. Although patients often have misinformation about treatment protocols and adverse effects of conventional treatment approaches, they often are seeking some power in decision making. Physicians must explain treatment recommendations and potential adverse effects without taking authoritative and impersonal approaches in their communications.1

The most frequently cited CAM use among cancer survivors is taking herbal supplements, vitamins, and minerals. Many of these CAM methods lack clinical evidence to support their efficacy, but they appeal to patients who want to regain control and enhance their quality of life.6,75 Examples of CAM methods used by breast cancer patients are listed in Box 2.

The potential for harm in using CAM comes from not coordinating patient-chosen CAM methods with conventional treatments being directed by oncologists and other members of the breast cancer patient’s treatment team.6-75 Integrated medicine takes a holistic approach to cancer care by supporting collaboration among the patient and caregivers from conventional and CAM disciplines. With integrated care, patients can have access to complementary therapies that support their care or alleviate symptoms from conventional treatments with full disclosure to their oncologists.

Integrated medicine helps minimize interference of CAM with conventional treatments, which can happen when patients use certain supplements without their physicians’ knowledge.74,75 For example, antioxidants often are recommended to help lower risk of cancer or fight the disease’s effects. Although eating a diet rich in healthful foods with high antioxidant levels might be recommended, antioxidant supplements suggested by CAM providers have been thought to interfere with cancer treatment. Others contend that there is not enough evidence supporting the use of the supplements to outweigh their interference with conventional therapies.74

Because antioxidants neutralize free radicals, supplements can interfere with radiation and some forms of chemotherapy, which generate free radicals to destroy malignant cells.76 For example, the use of green tea can enhance the effects of some chemotherapy agents and inhibit the use of others.77 One systematic review determined that antioxidants and other supplements do not interfere with conventional treatments for cancer,78 yet another concluded that findings are inadequate to confidently develop guidelines for integrating antioxidants into conventional cancer therapy regimens.79 Ultimately, communication between patient and provider is crucial, along with using integrative strategies when possible.77

Examples of integrative care in oncology can be found in the Middle East, Germany, and increasingly in cancer centers in the United States. The focus of each integrated care program varies slightly, but most are patient-centered, offer at least some behavioral and CAM methods, and provide cooperative, cross-disciplinary care.6,76

One of the nonpharmacologic methods that breast cancer patients choose is mind-body medicine. Following a breast cancer diagnosis, as many as 64% of patients use mind-body techniques to enable the
Adverse Effects of Breast Cancer Treatment

Box 2

Complementary and Alternative Medicine Methods Used by Breast Cancer Patients

- Acupuncture for 8 weeks to help relieve fatigue and symptoms that add to fatigue.
- Acupuncture for chemotherapy-induced nausea, which is endorsed by the National Institutes of Health.
- Acupuncture for 8 weeks to relieve pain.
- Ginger (500 to 1000 mg of ginger root extract every 4 to 6 hours) to help reduce nausea.
- Massage to relieve stress and anxiety during chemotherapy.
- Relaxation, meditation, and yoga to promote sleep.
- Cannabinoids for neuropathic pain.
- Calendula cream to reduce dermatitis severity.
- Hypnosis to relieve fatigue.

Mind to affect body functions. Examples of mind-body techniques are meditation and yoga.\(^6\) Harder et al performed a systematic review of investigations into the effectiveness of yoga interventions.\(^6\) The authors found reports of moderate to good evidence for yoga’s role in helping women recover from breast cancer treatments. In particular, yoga was found to be effective in alleviating fatigue and nausea from chemotherapy and in reducing adverse effects of endocrine therapy.\(^6\)

Patient Strategies for Managing Adverse Effects

The integrated medicine approach to breast cancer care takes a more holistic path and involves the patient more than conventional practice. Even in traditional care settings, however, patients can take many steps to manage treatment-related adverse effects under physician guidance. Many of these interventions are lifestyle-based and aimed at preventing or relieving adverse effects. Others might be behaviorally based. Clinicians can help educate patients about possible adverse effects, the importance of continuing regimens such as endocrine therapies, and evidence that a healthy lifestyle leads to better breast cancer outcomes.\(^1\)

Breast cancer patients and survivors often want to make informed decisions about their care and feel they have some control over their treatment, its effects, and quality of life.\(^7\) Involving patients helps physicians tailor interventions to individual patient needs and situations, often helping to improve management results. Exercise is an excellent example of a patient activity that can improve several treatment-related adverse effects such as cardiotoxicity, impaired immune function, fatigue, bone loss, anxiety, and depression.\(^6\)

Regular walking has been shown to reduce pain in breast cancer patients undergoing chemotherapy and radiation therapy; any form of aerobic exercise has been shown to be helpful during and after treatment.\(^6,7\) Studies have found exercise improves anxiety levels of patients during treatment, and one study found that patients participating in aerobic exercise could tolerate higher relative doses of chemotherapy. Resistance exercise can improve bone mineral density in patients affected by endocrine therapy, and breast cancer survivors who combine aerobic and resistance exercise had better sleep quality and improved muscular strength.\(^6\)

Physicians often have excluded patients who have lymphedema from participating in exercise programs to relieve treatment-related adverse effects because of concerns that exercise will make the condition worse. However, several studies showed no adverse effects from resistance or aerobic exercise among breast cancer survivors with lymphedema. Finally, research appears to show that breast cancer patients who exercise regularly are more likely to complete their course of chemotherapy.\(^7\)

Patients often receive education about adverse effects such as those that indicate lymphedema. For example, patients who have had axillary lymph node dissections should be told to avoid lifting heavy objects and using the affected arm for repetitive movements.\(^2\)

Oncology centers often provide nutrition and diet advice for patients to help alleviate adverse effects such as nausea. These might include eating small and frequent meals, consuming room-temperature foods, and avoiding foods that make the patient feel nauseated.\(^3\)

Behavioral activities such as support groups and attention to spiritual and emotional issues are patient-specific, but they can empower patients and survivors to better cope with treatment-related complications.\(^7\) As with any treatment, clinicians can recommend mind-body medicine techniques, but it is up to patients to use recommended techniques regularly to relieve stress or depression and to attend support groups or psychotherapy sessions.
Patient strategies to manage adverse effects from breast cancer treatment might involve lifestyle changes that are difficult at an already stressful time but critical to decreasing the negative symptoms associated with therapy. A crucial behavior change is smoking. Peppone et al investigated symptom burden for 947 cancer patients over a 6-month treatment period to determine smoking’s effect on treatment-related adverse effects.80 The authors found that smokers had significantly higher symptom burdens at 6 months posttreatment based on 12 common complaints (see Box 3). The authors said that smokers were much more likely to report severe fatigue, hair loss, concentration problems, hot flashes, skin problems, sleep problems, and depression. Overall, they found that smokers have more adverse effect symptoms than nonsmokers at the end of treatment and 6 months posttreatment.80

Role of the Radiologic Technologist

Radiologic technologists should be aware of the adverse effects of breast cancer treatment in preparation for potential encounters with patients. Technologists must consider patient comfort when performing mammograms or other imaging studies, along with possible artifacts that could be caused by treatment.

Mammography is the only imaging examination routinely recommended for breast cancer survivors, but breast cancer patients and survivors might require other imaging to investigate adverse treatment effects.4,46,81 The American Society for Clinical Oncology updated its breast cancer surveillance guidelines in 2012 and reiterated that women treated with breast-conserving therapy should not have their first mammogram until at least 6 months after completing radiation therapy (see Figure 2).82 These women should continue having mammograms every 6 to 12 months. Once no abnormalities are found and all local-regional therapy is completed, they should have a mammogram annually.82

American Society for Clinical Oncology guidelines mention that chest radiographs, bone scans, ultrasound of the liver, computed tomography (CT) scans, positron emission tomography scans, and magnetic resonance (MR) imaging scans are not recommended for routine breast cancer surveillance.42

Box 3

<table>
<thead>
<tr>
<th>Common Complaints After Breast Cancer Treatment</th>
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<tbody>
<tr>
<td>Fatigue.</td>
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<tr>
<td>Hair loss.</td>
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<tr>
<td>Memory loss.</td>
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<tr>
<td>Nausea.</td>
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<tr>
<td>Depression.</td>
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<tr>
<td>Sleep problems.</td>
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<tr>
<td>Pain.</td>
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<tr>
<td>Difficulty concentrating.</td>
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<tr>
<td>Hot flashes.</td>
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<tr>
<td>Weight loss.</td>
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<tr>
<td>Skin problems.</td>
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<tr>
<td>Shortness of breath.</td>
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</tbody>
</table>

Mammography Technique for the Treated Breast

Radiologic technologists should be prepared to encounter a number of special considerations for patients who have undergone breast surgery, radiation therapy, and systemic therapy. One concern of breast cancer patients and clinicians is cumulative radiation exposure.83 Radiologic technologists should be aware of this concern and remain particularly vigilant regarding the ALARA (as low as reasonably achievable) principle. Technologists should avoid retakes of mammograms or any imaging examination that uses ionizing radiation, particularly near the chest area.

Mammographers typically can image breasts postsurgically in the craniocaudal and mediolateral or mediolateral oblique projections. Use of scar markers can help identify the surgical scar site for the interpreting radiologist, but the use of too many markers can be distracting. Mammographers should apply compression as needed, keeping in mind that a postsurgical breast might be tender.84 In addition, mastectomy and breast-conserving surgery can affect symmetry between the treated breast and the contralateral breast.85

Mammographers should be aware of the effects that radiation therapy can have on breast skin. In addition to the itching, dryness, pain, burning, and general discomfort that can persist following therapy, skin thickening and diffuse tissue or parenchymal pattern density can occur at the site of radiation.85,84
completed in the craniocaudal projection, with a spot projection of any area of concern, along with a possible axillary tail projection or mediolateral oblique projection. If a referring physician requests a mammogram of a breast augmented with implants, the mammographer can complete the examination using manual technique to produce minimal compression. Additional projections are required to show natural tissues that surround the implant, such as 90° lateral projections. Use of the Eklund technique helps displace the implant posteriorly and pulls the breast tissue over and in front of the implant to display more breast tissue. The Eklund technique adds 2 craniocaudal and mediolateral oblique projections to the standard mammogram (see Figure 3).

Imaging of Treatment-Related Adverse Effects

Imaging for axillary pain or lymphedema might involve CT or MR. Not all patients require imaging to diagnose or manage lymphedema. Radiographs can exclude other causes, such as fractures or bone abnormalities. CT can help distinguish lymphedema from a malignancy, and MR helps physicians determine whether the signs and symptoms are from surgery and radiation therapy or metastatic spread of the disease. Imaging might be required to detect and monitor cardiotoxicities from breast cancer treatment. Assessment of cardiac function often begins with an electrocardiogram, along with 2-D and 3-D echocardiography. Modern techniques include transthoracic echocardiography and multigated radionuclide angiography to assess left ventricular function in patients receiving chemotherapy. Multigated radionuclide angiography exposes breast cancer patients to additional radiation but has demonstrated accurate assessment of left ventricular systolic and diastolic function. MR imaging also can be used to provide information beyond that available from echocardiography.

Because many imaging techniques do not identify cardiotoxicity until left ventricular function has declined significantly, investigators have focused on more sensitive imaging methods that could detect cardiotoxicity earlier, when there is still time to alter the disease process. Echocardiographic techniques with tissue Doppler and myocardial stain imaging could provide sensitive early detection of left ventricular cardiotoxicity.
Conclusion

Breast cancer treatment continues to offer patients longer progression-free survival. Adverse effects from breast cancer therapy can cause dose reductions or cessation of treatment. Complications and adverse effects of treatment also can affect breast cancer survivors for years, causing significant morbidity or quality-of-life issues. Oncologists and other members of the treatment team must weigh the potentially detrimental effects of a particular therapy on a patient’s quality of life with its expected benefits.

Radiologic technologists should be aware of the physical and psychological adverse effects of breast cancer treatments on patients and consider them when imaging breast cancer patients and survivors. Breast cancer patients need to understand the advancing science behind conventional treatment protocols and the careful attention researchers and clinicians pay to potential adverse effects in clinical trials. Patients need time to assimilate their diagnosis and the abrupt and long-term changes to their bodies and quality of life, and they need help minimizing the adverse effects of treatment.

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Adverse Effects of Breast Cancer Treatment

1. The recommended management choice for women who have ductal carcinoma in situ is:
   a. radiation therapy only.
   b. mastectomy followed by radiation therapy.
   c. lumpectomy followed by radiation therapy.
   d. endocrine therapy only.

2. More than ______ % of all U.S. women diagnosed with breast cancer each year receive radiation therapy as part of their treatment.
   a. 20
   b. 30
   c. 40
   d. 50

3. ______ is a short course of radiation delivered over approximately 5 days to the surgical cavity and a small margin of normal surrounding tissue.
   a. Whole-breast irradiation
   b. Partial-breast irradiation
   c. Endocrine therapy
   d. Systemic chemotherapy

4. Systemic chemotherapy generally is administered:
   1. orally.
   2. intravenously.
   3. intramuscularly.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

5. A monoclonal antibody that works against ERBB2 is:
   a. trastuzumab.
   b. anthracycline.
   c. cyclophosphamide.
   d. doxorubicin.

*Your answer sheet for this Directed Reading must be received in the ASRT office on or before this date.

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continued on next page
6. Endocrine agents might be used for breast cancer treatment for 2 to 5:
   a. days.
   b. weeks.
   c. months.
   d. years.

7. As many as 5% to 20% of patients who have breast-conserving surgery or mastectomy report:
   a. infection.
   b. arm edema.
   c. fatigue.
   d. weight gain.

8. Which of the following statements regarding radiation therapy adverse effects is false?
   a. Up to 90% of cancer patients have skin reactions from radiation therapy.
   b. Skin reactions usually appear 1 to 4 months following radiation therapy.
   c. Patients might have itching, dryness, pain, warmth, or burning of the skin.
   d. A decrease in functional stem cells can cause radiation therapy reactions.

9. Lymphedema from radiation is associated with significant functional impairment for patients.
   a. true
   b. false

10. Reports of pneumonitis associated with partial-breast irradiation most likely occur because of:
    a. the total volume of radiation dose delivered.
    b. novelty of the procedure and lack of established treatment planning protocols.
    c. escalated dose to the ipsilateral lung.
    d. patient inactivity during surgery and radiation therapy recovery.

11. Patients who ______ and are receiving external-beam radiation therapy have significantly more skin toxicity from radiation therapy than those who do not.
    a. smoke
    b. exercise
    c. eat fatty foods
    d. drink alcohol

12. The only group who might be best served by opting out of radiation therapy is:
    a. young women with estrogen-receptor–positive tumors.
    b. young women planning to have children in the next 2 years.
    c. older women with estrogen-receptor–positive tumors.
    d. older women who have several comorbidities.

13. Toxicity from anthracycline:
    a. occurs only in people with preexisting cardiac conditions.
    b. occurs in everyone who uses the agent.
    c. only happens with a single dose over threshold.
    d. correlates to cumulative dose.

14. Evidence shows that trastuzumab’s cardiotoxicity is reduced when:
    a. the agent is administered along with bevacizumab.
    b. administered along with statin therapy.
    c. more time elapses between anthracycline therapy and administration of trastuzumab.
    d. less time elapses between anthracycline therapy and administration of trastuzumab.

continued on next page
15. Up to ______ % of aromatase inhibitor users discontinue therapy.
   a. 5
   b. 15
   c. 25
   d. 35

16. Tamoxifen has been associated with:
   1. blood clotting complications.
   2. increased risk of stroke.
   3. increased fracture risk.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

17. Some women treated with radiation therapy and endocrine therapy have experienced weight loss.
   a. true
   b. false

18. Which of the following statements is true regarding breast cancer and pregnant women?
   a. Breast cancer is the second most common cancer occurring during pregnancies.
   b. Most pregnant women with breast cancer have mastectomies.
   c. Breast surgery is generally considered safe during pregnancy.
   d. Radiation therapy is considered safe during the first trimester.

19. Up to 20% of exposed neonates have had malformations linked to exposure to:
   a. radiation therapy.
   b. aromatase inhibitors.
   c. lapatinib.
   d. tamoxifen.

20. Which of the following statements is true regarding male breast cancer?
   a. Men commonly receive tamoxifen as endocrine therapy.
   b. Prognosis generally is better for men with breast cancer than for women.
   c. The most common adverse effect of treatment men report is pain.
   d. Men tend to report few adverse effects from tamoxifen.

21. Andreae et al found that ______ could reduce risk of chronic pain from breast cancer surgery for 6 months following surgery in one-fourth of patients studied.
   a. general anesthesia
   b. elimination of radiation therapy from the treatment regimen
   c. use of opioid analgesics
   d. a paravertebral block

22. People who have osteoporosis can reduce fracture risk by 30% to 70% by taking:
   a. vitamin D.
   b. calcium.
   c. bisphosphonates.
   d. multivitamins.

23. Prophylactic antiemetics should be administered:
   a. before chemotherapy begins.
   b. after nausea symptoms appear.
   c. only intravenously.
   d. to any patient except a pregnant woman.

24. ______ is a marker of cell death that can indicate potential alterations in left ventricular function.
   a. Natriuretic peptide
   b. Troponin I
   c. Dexrazoxane
   d. Angiotensin converting enzyme
   a. enalapril
   b. ramipril
   c. methylphenidate
   d. paroxetine

26. Areas of moist desquamation from radiation therapy should be treated with ______ to prevent infection.
   a. aloe vera
   b. any over-the-counter oil
   c. hydrocolloid dressings
   d. debridement

27. The most frequently cited complementary and alternative medicine used among cancer survivors is:
   a. acupuncture.
   b. meditation.
   c. taking herbal supplements, vitamins, and minerals.
   d. taking yoga classes.

28. Research shows that breast cancer patients who exercise regularly are more likely to complete their course of chemotherapy.
   a. true
   b. false

29. American Society for Clinical Oncology guidelines recommend that women treated with breast-conserving therapy should not have their first mammogram until at least ______ after completing radiation therapy.
   a. 1 month
   b. 3 months
   c. 6 months
   d. 1 year

30. A postmastectomy mammogram usually is conducted in the ______ projection.
   a. mediolateral oblique
   b. craniocaudal
   c. lateral
   d. none of the above; women should not have mammograms after mastectomies