Overview of long-term complications of therapy in breast cancer survivors and patterns of relapse

AUTHOR: Steven E Come, MD
SECTION EDITORS: Patricia A Ganz, MD, Lori J Pierce, MD, Gary J Whitman, MD
DEPUTY EDITOR: Sadhna R Vora, MD

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide. In the United States, breast cancer is second to lung cancer as the most common cause of cancer death in women [1]. However, there has been a decline in breast cancer mortality rates in the United States and elsewhere in the Western world, attributable to the increased use of screening mammography and advances in adjuvant therapies. As a result of improved survival and the aging of the population, there are over three million women living with a history of breast cancer in the United States alone, accounting for 41 percent of all female cancer survivors [2]. Breast cancer survivors are the largest constituent of all cancer survivors (excluding skin cancers), representing 3.6 percent of the United States population [3,4].

The majority of breast cancer recurrences occur within the first five years of diagnosis, particularly with hormone receptor-negative or human epidermal growth factor receptor 2 (HER2)-positive disease. However, some recurrences occur much later, particularly in the setting of hormone receptor-positive, HER2-negative tumors, which tend to behave more indolently.

Long-term complications of therapy for in situ and invasive breast cancer in women who have completed their therapy and patterns of relapse will be reviewed here.

Acute complications of chemotherapy as well as recommendations for surveillance strategies in breast cancer survivors, an overview of the approach to breast cancer survivors, and data regarding late recurrences of hormone receptor-positive breast cancers are discussed separately. (See "Approach to the patient following treatment for breast cancer" and "Overview of side effects of chemotherapy for early-stage breast cancer" and "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Duration of endocrine treatment'.)

APPROACH TO THE BREAST CANCER SURVIVOR

Patients with a history of breast cancer should undergo regular follow-up including medical history, physical examination, surveillance mammography, and evaluation and management of treatment-related late effects, including assessment of psychosocial distress. Breast magnetic resonance imaging for surveillance should not be performed routinely except in specific patient groups, including those with breast cancer susceptibility gene 1 or 2 (*BRCA1* or *BRCA2*) mutations, those who received therapeutic chest radiation therapy, and those with more than a 20 to 25 percent lifetime risk for breast cancer. (See "MRI of the breast and emerging technologies", section on 'Screening high-risk women'.)

Breast cancer survivors should also receive ongoing age-appropriate screening studies and preventive care, consistent with recommendations for the general population, for conditions other than those related to breast cancer and its treatment. An extensive discussion on the follow-up of long-term breast cancer survivors is covered separately. (See "Approach to the patient following treatment for breast cancer".)

Additionally, oncologic consultation is indicated if there is suspicion or evidence of disease recurrence, or if questions arise regarding the safety of certain interventions (eg, vaginal estrogen in a patient who has severe atrophic vaginitis despite nonhormonal remedies). (See "Genitourinary syndrome of menopause (vulvovaginal atrophy): Treatment", section on 'Patients with breast cancer'.)

LONG-TERM ADVERSE EFFECTS OF PRIMARY THERAPY

Most breast cancer survivors report good quality of life, but some patients may have chronic difficulties associated with physical, cognitive, and social functioning [5-7]. The various long-term physical and psychological sequelae due to specific breast cancer treatments are summarized in the table (table 1).

Given meaningful improvements in breast cancer outcomes including survival, management strategies are increasingly addressing the "de-escalation" of therapies in an effort to minimize the short- and long-term consequences of treatment. Examples of this include the possible elimination of breast radiation for patients ≥65 with small estrogen receptor (ER)-positive cancer, a reduction in the frequency and extent of axillary node surgery, a substantial decrease in the proportion of women with ER-positive tumors who receive chemotherapy in addition to antiestrogens, and the use of neoadjuvant chemotherapy with adaptive management based on pathology at surgery to reduce the extent of systemic therapy in women with human epidermal growth factor receptor 2-positive and triple-negative cancers.

Chest wall and breast complications — Breast surgery, breast reconstruction, and radiation therapy (RT) may result in long-term complications in the breast and chest wall. These include formation of seromas, fat necrosis, chronic pain, and recurrent skin infections (cellulitis). (See "Complications of reconstructive and aesthetic breast surgery" and "Clinical manifestations and diagnosis of postmastectomy pain syndrome" and "Postmastectomy pain syndrome: Risk reduction and management".)

In addition to surgical complications, RT may result in long-term issues, including skin and soft tissue fibrosis or necrosis and poor cosmesis when implants are radiated. Radiation-induced fibrosis of the skin and subcutaneous tissue is seen most commonly in breast cancer patients in areas with overlapping treatment fields following breast-conserving surgery with postoperative RT or after mastectomy and RT, particularly in patients with implants. The risk of radiation fibrosis after conventional RT for breast cancer is low, particularly with the use of modern skin-sparing megavoltage equipment. (See "Clinical manifestations, prevention, and treatment of radiation-induced fibrosis", section on 'Skin and subcutaneous tissue'.)

Soft tissue necrosis in long-term survivors is exceedingly rare, with an estimated incidence of 0.2 percent of patients undergoing RT for early-stage breast cancer in one series [8].

Musculoskeletal complications

Pain and mobility issues — Breast and axillary surgery also can result in musculoskeletal issues including reduced arm mobility, with some data suggesting improvement with early physical therapy [9]. RT may compound surgery-related pain and motor restriction, both in the short and long term [10]. One small prospective study found that breast cancer patients undergoing axillary dissection and nodal RT did not experience increased shoulder morbidity relative to those treated with RT to the breast alone and sentinel node biopsy, but the pectoralis major was stiffer [11], suggesting compensatory mechanisms.

Rib fractures from RT are uncommon. In one report, the incidence of a rib fracture was less than 3 percent, and the median time to develop a fracture was about one year [8]. The incidence appears to be higher with RT doses that exceed 50 Gy.

Women treated with an aromatase inhibitor (AI) frequently experience muscle and joint pains, resulting in treatment discontinuation in up to 20 percent of patients. In addition to these complaints, treatment with an AI increases the risk for osteoporosis and subsequent fractures. This is discussed in detail elsewhere. (See "Evaluation and management of aromatase inhibitor-induced bone loss" and "Managing the side effects of tamoxifen and aromatase inhibitors", section on 'Musculoskeletal pains and stiffness'.)

Lymphedema — Both breast surgery and RT can lead to the development of early- or delayed-onset lymphedema, which can involve the breast, chest, and the ipsilateral extremity. Rates of lymphedema are highest in women who undergo breast-conserving surgery or mastectomy with axillary lymph node dissection followed by breast/chest wall and comprehensive nodal RT including the full axilla. Patients in long-term follow-up who present with new-onset lymphedema should be evaluated for alternate causes of new swelling including tumor recurrence, infection, and thrombosis. (See "Clinical features and diagnosis of peripheral lymphedema", section on 'Cancer and cancer treatment'.)

Pulmonary morbidity — RT to the breast can result in pneumonitis, which typically presents as a persistent dry cough or shortness of breath [8]. Fortunately, with modern RT techniques, pneumonitis is a rare event [12] (see "Radiation-induced lung injury"). Overlapping exposure to taxanes may increase the risk of acute pneumonitis.

Neurologic morbidity — Breast cancer treatment can cause several types of neurologic adverse effects.

Nerve injury — Breast surgery can cause nerve injury, which may result in long-term symptoms of paresthesias and/or persistent pain in the chest wall. In addition, RT can result in a brachial plexopathy, manifesting as paresthesia or weakness in the arm or hand [8]. Permanent brachial plexopathy occurs in less than 1 percent of women receiving ≤50 Gy in 2 Gy fractions administered to a supraclavicular and axillary apex field. The incidence of plexopathy is significantly higher with an axillary dose greater than 50 Gy, concomitant chemotherapy administration [8], and daily RT fractions in excess of 2 Gy [13,14]. (See "Brachial plexus syndromes", section on 'Neoplastic and radiation-induced brachial plexopathy'.)

Peripheral neuropathy — Neurotoxicity is also a well-recognized side effect of adjuvant chemotherapy, particularly with taxanes. The peripheral neuropathy that develops during and after taxanes is generally limited to distal paresthesias and is usually at least partially reversible

after treatment discontinuation. However, in a meta-analysis, neuropathic symptoms persisted in 11 to >80 percent at one to three years following treatment [15]. As an example of available data, in one study, approximately 40 percent of patients receiving anthracycline- and taxane-based chemotherapy experienced peripheral neuropathy two years after treatment initiation [16]. In some instances, the neuropathy is permanent. Neuropathy may be painful and interfere with activities of daily living. Symptomatic improvement may be seen with the antidepressant duloxetine. (See "Overview of neurologic complications of conventional non-platinum cancer chemotherapy", section on 'Taxanes'.)

Cognitive dysfunction — The extent of disability associated with cancer or treatment-related cognitive impairment (eg, impaired memory and decreased ability to concentrate, also known as "chemo-brain") is not well characterized. Data suggest that cognitive dysfunction related to chemotherapy and/or endocrine therapy may be an issue for breast cancer survivors. In addition, symptoms appear to stabilize with the passage of time. Patients considering chemotherapy may be counseled that the acute effect of treatment on cognitive functioning stabilizes six months following completion of treatment. However, patients may be aware of minor cognitive dysfunction affecting verbal and visuospatial abilities. Data, evaluation, prevention, and treatment are discussed elsewhere. (See "Cognitive function after cancer and cancer treatment", section on 'Breast cancer'.)

Cardiovascular morbidity — Cardiovascular disease may be a complication of breast RT and specific systemic agents used in the treatment of breast cancer. Symptoms of early congestive heart failure should prompt a cardiac evaluation.

Radiation therapy — At present, there does not appear to be a minimum radiation dose that is entirely safe; however, studies are ongoing to better quantify low radiation doses and the effects on the heart. It appears clear that the effects of radiation on the heart increase with increasing doses of radiation. The increased risk can be seen within the first five years and remains elevated for at least 20 years. Women with significant risk factors for an acute coronary event may be at a particularly increased risk. In addition, RT that involves the internal mammary nodes may be associated with treatment-related cardiovascular toxicity if by treating the nodes, a portion of the heart is placed in the radiation field. (See "Cardiotoxicity of radiation therapy for breast cancer and other malignancies", section on 'Breast cancer'.)

Systemic treatment — Exposure to chemotherapeutic and biologic agents, such as anthracyclines and trastuzumab, can result in cardiac morbidity. The incidence of cardiomyopathy and heart failure secondary to doxorubicin is dose dependent, typically occurring at higher doses than those administered in the adjuvant setting. In contrast to cardiotoxicity from anthracyclines, trastuzumab-related cardiotoxicity does not appear to be

related to cumulative dose. (See "Cardiotoxicity of trastuzumab and other HER2-targeted agents" and "Risk and prevention of anthracycline cardiotoxicity" and "Clinical manifestations, diagnosis, and treatment of anthracycline-induced cardiotoxicity".)

Endocrine therapy — The AIs, used in the treatment of hormone-positive postmenopausal breast cancers, may increase the risk of cardiovascular adverse events compared with tamoxifen, although the overall risk appears to be low and remains not fully characterized. As tamoxifen has been associated with a cardioprotective effect in some long-term studies, it is unknown whether AIs are associated with increased cardiac risk relative to placebo, or only relative to tamoxifen. (See "Managing the side effects of tamoxifen and aromatase inhibitors".)

Second cancers — Although difficult to quantify, there is an increased risk for second cancers associated with breast cancer treatment, whether RT, chemotherapy, or tamoxifen. Second cancers that have been associated with breast cancer treatment include esophageal, lung, and uterine cancers, as well as melanoma, soft tissue sarcoma (notably angiosarcoma), acute myeloid leukemia (AML), and myelodysplastic syndromes (MDS) [17].

The development of second malignancies is dependent upon treatment factors (type of treatment, including dose and duration of exposure), lifestyle factors (including a history of smoking or alcohol use), and genetic susceptibility. (See "Overview of cancer survivorship care for primary care and oncology providers", section on 'Risk of subsequent primary cancer'.)

Risks associated with radiation therapy — While patients treated with adjuvant RT are at risk for radiation-induced solid tumors and myeloid neoplasms, these are rare late complications [18-21].

A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group including over 40,000 women randomly assigned to radiation or not reported that radiation was associated with an increase in overall second cancer incidence (relative risk [RR] 1.23, 95% CI 1.12-1.36), and increased rates, specifically of [22]:

- Contralateral breast cancer (881 versus 673 cases; RR 1.20, 95% CI 1.08-1.33),
- Esophageal cancer (RR 2.42, 95% CI 1.19-4.92), mainly in trials including irradiation of the internal mammary chain nodes and supraclavicular fossa where the esophagus was not shielded from the radiation field,
- Leukemia (RR 1.71, 95% CI 1.05-2.79), and
- Lung cancer incidence in the second decade following RT (RR 2.10, 95% CI 1.48-2.98). The risk was increased primarily in women who smoked prior to and after their diagnosis of

breast cancer.

However, the absolute risk of developing a secondary malignancy because of radiation is small. In a cohort study of 58,000 patients treated for invasive breast cancer, although the 10-year risk of a second nonbreast primary cancer relative to the general population was elevated (RR 1.22, 95% CI 1.17-1.27), this translated into approximately 13 cancers per 1000 women [20].

The risk of a secondary malignancy after RT varies on the time that has elapsed since treatment was completed. As an example, secondary leukemias (usually myeloid) tend to occur within five to seven years; solid tumors, including esophageal cancer, usually present at least 10 years after radiation [23-25]. However, radiation-induced angiosarcoma typically presents with a latency period of five to eight years. These issues are discussed in detail elsewhere. (See "Breast sarcoma: Epidemiology, risk factors, clinical presentation, diagnosis, and staging".)

Women with germline mutations in *p53* are at high risk for second malignancies as a result of radiation exposure and should not be treated with this modality. (See "Li-Fraumeni syndrome", section on 'Breast cancer'.)

Risks associated with chemotherapy — The cumulative incidence of developing treatment-related AML and MDS is generally less than 1 percent, but corresponds to a twofold increased risk of AML/MDS for patients treated with adjuvant therapy as compared with controls (five excess cases per 10,000 treated patients at 10 years) [20,25-39]. Two-thirds of these patients are first recognized by evidence of myelodysplasia (usually trilineage dysplasia), marrow failure, and pancytopenia. In general, treatment-related leukemias are more refractory to conventional antileukemic therapy, and they have a very poor prognosis. (See "Therapy-related myeloid neoplasms: Epidemiology, causes, evaluation, and diagnosis".)

Menopausal symptoms — Menopausal symptoms such as hot flashes and vaginal dryness and atrophy may result from aging, chemotherapy (in premenopausal women), and hormonal therapy (regardless of menopausal status). There may also be an impact on sexual function as well as fertility. These issues are discussed below.

Hot flashes — Management of hot flashes in breast cancer survivors is similar to that of patients not being treated for breast cancer (particularly in its reliance on nonhormonal treatments for this symptom) and is discussed in further detail elsewhere. (See "Menopausal hot flashes", section on 'Women with breast cancer'.)

While systemic estrogens and progestins are sometimes utilized to treat hot flashes in women without history of breast cancer, we avoid such treatments in women with a history of breast cancer given a potentially heightened risk of recurrence associated with these treatments.

Women with hot flashes related to prior cancer treatments may benefit from nonhormonal pharmacotherapy such as gabapentin or selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs). Available data regarding interactions between tamoxifen and SSRI/SNRIs are discussed elsewhere. Use of these agents in patients treated for cancer is discussed in detail elsewhere. (See "Mechanisms of action of selective estrogen receptor modulators and down-regulators", section on 'Patients taking SSRIs' and "Management of psychiatric disorders in patients with cancer", section on 'Depression'.)

Sexual dysfunction — Sexual activity may become less enjoyable and even painful after treatments for breast cancer. The psychological sequelae of a breast cancer diagnosis can include strains on relationships and changes in body image, both of which can be detrimental to sexual functioning [40,41]. Sexual dysfunction is associated with depression in breast cancer survivors [42]. It is important for clinicians to routinely ask breast cancer survivors about their sexual functioning. Referral to a sexual health and/or mental health expert may be helpful.

Details on the approach to vulvovaginal atrophy in patients who have had breast cancer are found elsewhere. (See "Genitourinary syndrome of menopause (vulvovaginal atrophy): Treatment", section on 'Patients with breast cancer'.)

Briefly, nonhormonal treatments, specifically water or silicone-based lubricants and vaginal moisturizers, are used as first-line therapy for vaginal dryness and dyspareunia in breast cancer survivors [43,44]. Lubricants are used at the time of sexual activity. Vaginal moisturizers, involving bases such as polycarbophil, hyaluronic acid, gums, or gelatins, may be used on a regular basis for hydrating tissue. For women with dyspareunia that appears to be isolated to tenderness at the vulvar vestibule with penetration, topical lidocaine may provide relief [45,46]. (See "Vulvar pain of unknown cause (vulvodynia): Treatment", section on 'Topical lidocaine ointment'.)

Fatigue — A sense of fatigue may persist in survivors for years after cessation of treatment. In one study, for example, approximately 30 percent of breast cancer survivors had moderate to severe fatigue more than two years after treatment [47-49]. Before assuming that fatigue is related to prior treatment for breast cancer, treatable reasons for low energy should be ruled out, including anemia, thyroid dysfunction, pain, depression, and lack of sleep [49]. (See "Cancer-related fatigue: Prevalence, screening, and clinical assessment", section on 'Prevalence and time course' and "Cancer-related fatigue: Prevalence, screening, and clinical assessment", section on 'Main contributory factors'.)

Psychological effects — Women may experience heightened anxiety and depression after the completion of therapy. This can be attributed to worry about the risk of recurrence. Dealing

with this uncertainty is often the most difficult part of the recovery, and fear of recurrence may extend well past the initial five years of cancer survivorship. (See "Overview of psychosocial issues in the adult cancer survivor".)

RELAPSE PATTERNS

Genomic subtype and timing and pattern of relapse — While the outcome of breast cancer treatment is increasingly favorable, women treated for invasive breast cancer remain at risk of both a locoregional recurrence and the evolution of metastatic disease [50]. Breast cancer is no longer recognized as a homogeneous entity, but rather a family of malignancies that can be distinguished by gene expression profiling as intrinsic subtypes.

Clinical patterns of recurrence are associated with these genomic subtypes:

- In general, luminal A and B cancers exhibit a tendency to recur that is continuous over a long period of time (20 years or more), with the majority of these events identified beyond five years from diagnosis. Skeletal involvement is common. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Rationale for extended treatment in some patients'.)

- Human epidermal growth factor receptor 2 (HER2)-enriched and basal subtypes are most often associated with early recurrence events (most within five years from diagnosis), a higher incidence of visceral involvement, a predilection for central nervous system (CNS) metastases, and a lower likelihood of skeletal metastases. The risk of recurrence of these cancers after the first five years is low [51].

- Patients with a late recurrence likely have a more favorable prognosis than patients with early recurrence. As an example, in one study including over 3500 patients with breast cancer recurrence, those with a late versus early recurrence (≥10 years versus <10 years from primary diagnosis) experienced a lower risk of breast cancer-associated death (hazard ratio 0.72) [52].

Locoregional recurrence — The incidence of and time to local recurrence, and the pattern of recurrence, differ after breast-conserving therapy (BCT) versus mastectomy. This is discussed in detail elsewhere. (See "Clinical manifestations and evaluation of locoregional recurrences of breast cancer", section on 'Epidemiology'.)

Distinguishing new cancers from true recurrences is important, as it may influence the treatment approach. (See "Clinical manifestations and evaluation of locoregional recurrences of

breast cancer", section on 'Distinguishing a new primary from a recurrence'.)

The surgical approach to recurrent disease depends on the initial surgical approach, and whether (and what kind of) radiation was used:

- In general, for women who were previously treated with lumpectomy/radiation and experience an isolated operable locoregional recurrence, a mastectomy should be performed because further radiation treatment is not generally an option to reduce the risk of another local recurrence. However, there is interest in offering select patients a second BCT, as discussed elsewhere. (See "Surgery and radiation for locoregional recurrences of breast cancer", section on 'Select patients with prior radiation'.)

  For women who did not previously receive radiation therapy (RT) and for those treated with partial breast irradiation, re-excision may be appropriate because the women may be candidates for RT. (See "Surgery and radiation for locoregional recurrences of breast cancer", section on 'For those with no prior RT'.)

- By contrast, a local recurrence following mastectomy is usually manifest as a mass in the chest wall, regional nodal basins (ie, infraclavicular, supraclavicular, or axillary regions), or overlying skin. Treatment generally involves excision of the recurrence (if surgically resectable), as well as possibly RT (if not previously administered), and systemic therapy. (See "Clinical manifestations and evaluation of locoregional recurrences of breast cancer", section on 'Postmastectomy recurrence'.)

Management of locoregional recurrence, including indications for surgery, RT, and systemic therapy (including chemotherapy and endocrine therapy), is discussed elsewhere. (See "Surgery and radiation for locoregional recurrences of breast cancer" and "Systemic therapy for locoregionally recurrent breast cancer".)

Metastatic disease — Although a substantial minority of recurrences involve the chest wall and axillary or supraclavicular lymph nodes only, breast cancer has the potential to metastasize to almost every organ in the body (table 2).

The most common sites of metastases are bone, liver, and lung. Approximately 50 to 75 percent of patients who relapse distantly do so in a single organ; the remainder will develop diffuse metastatic disease [53]. Less than 5 percent of patients overall will manifest CNS involvement as the first site of metastatic disease, but the frequency is significantly higher in HER2-enriched and basal intrinsic subtypes. Management of brain metastases in breast cancer is discussed elsewhere. (See "Brain metastases in breast cancer".)

The treatment approach to women presenting with metastatic breast cancer is discussed separately. (See "Overview of the approach to metastatic breast cancer" and "Epidemiology, clinical manifestations, and diagnosis of brain metastases" and "The role of local therapies in metastatic breast cancer".)

Second primary breast tumors — A personal history of either invasive or in situ breast cancer increases the risk of developing an invasive breast cancer in the contralateral breast, although this risk is decreasing with more effective adjuvant systemic treatments that reduce both recurrences and new breast cancers [54].

As an example, in one observational study including almost 420,000 women who were ≥1 year from their primary diagnosis of unilateral invasive breast cancer, breast cancer patients had approximately twice the risk of developing cancer in the contralateral breast when compared with that expected in the general population (standard incidence rate of 2.2) [54]. The five-year cumulative incidence of contralateral breast cancer (CBC) ranged from 1.0 percent in younger women (age <50 years) with a first estrogen receptor (ER)-positive tumor to 1.9 percent in younger women with a first ER-negative tumor.

In a separate study, risks of CBC among those with hormone receptor-positive breast cancer were approximately 0.2 percent per year for the first five years after diagnosis (during adjuvant endocrine therapy), 0.5 percent per year for the subsequent five years (after endocrine treatment), and somewhere between these estimates for the following 5 to 10 years [55].

In the setting of a personal history of breast cancer, a family history of breast cancer further increases CBC risk. For example, in a case-control study of women with CBC matched with women with unilateral breast cancer as controls, having a first-degree relative with breast cancer increased risk of CBC by almost twofold [56,57]. Risks were further increased if the relative was diagnosed at age <40 years.

For women with a known genetic predisposition, the risk is much higher. The lifetime risk of second primary breast cancers may be as high as 65 percent for breast cancer susceptibility gene 1 (*BRCA1*) mutation carriers and 50 percent for breast cancer susceptibility gene 2 (*BRCA2*) carriers [58]. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes" and "Overview of hereditary breast and ovarian cancer syndromes".)

A substantial number of second primary breast cancers occur after five years, necessitating long-term surveillance for all women with a history of breast cancer. This is especially true for hormone receptor-positive breast cancers, which can recur twenty years or even more beyond primary diagnosis. (See "Approach to the patient following treatment for breast cancer", section

on 'Breast imaging' and "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Rationale for extended treatment in some patients'.)

Limited data suggest a slight excess of CBCs following breast or chest wall RT compared with nonirradiated patients [59-61], but data are conflicting [62]. As an example, in data from an Early Breast Cancer Trialists' Collaborative Group meta-analysis, the annual odds ratio (OR) for CBC for irradiated compared with nonirradiated women was 1.18 [59]. This result was statistically significant for women 50 years of age and older (OR 1.25), but not for younger women (OR 1.09). A more contemporary study also found an association between radiation for breast cancer and development of subsequent contralateral breast cancer, with a risk ratio of 1.20 [22].

By contrast, other data suggest that the risk may be higher with younger age at treatment [60,61,63,64]. A nested case-control study including patients with known *BRCA1/BRCA2* mutations did not find an increase in CBCs in carriers irradiated for breast cancer (irrespective of age) [62]. Clearly, data are conflicting and further study is needed.

SUMMARY

Approach to the breast cancer survivor – Patients with a history of breast cancer should undergo regular surveillance mammography and evaluation of treatment-related late effects. Breast magnetic resonance imaging for surveillance should not be performed routinely, except for select high-risk subgroups. (See 'Approach to the breast cancer survivor' above.)

Adverse effects of primary therapy

- **Chest wall and breast complications** – Breast surgery, breast reconstruction, and radiation therapy (RT) may result in long-term complications in the breast and chest wall. These include formation of seromas, recurrent skin infections, and rarely, soft tissue necrosis. (See 'Chest wall and breast complications' above.)

- **Musculoskeletal complications**

  - From radiation and surgery - Both breast surgery and radiation can lead to pain and reduced arm mobility, and lymphedema of the breast, chest, arm, and hand. Rates of lymphedema are highest in women who undergo a full axillary lymph node dissection plus breast/chest wall and comprehensive nodal RT. Radiation can increase fracture risks. (See 'Lymphedema' above and 'Musculoskeletal complications' above.)

- From systemic therapy – Aromatase inhibitors can cause muscle and joint pains, as well as bone thinning. (See 'Pain and mobility issues' above.)

- **Neurologic morbidity**

  - Nerve injury and peripheral neuropathy – Breast surgery, RT, and chemotherapy can be associated with nerve injury, which can cause long-term symptoms of paresthesias, weakness, and/or persistent pain. (See 'Nerve injury' above and 'Peripheral neuropathy' above.)

  - Cognitive dysfunction – The extent of cognitive dysfunction appears small, and typically stabilizes approximately six months following completion of chemotherapy, but may be ongoing during the long duration of antiestrogen treatment in some patients. Patients may be at risk for minor issues related to verbal and visuospatial abilities. (See 'Cognitive dysfunction' above.)

- **Cardiovascular disease** – Cardiovascular disease may be a complication of breast RT if a portion of the heart is in-field. Anthracyclines and human epidermal growth factor 2-directed agents also increase the risk. (See 'Cardiovascular morbidity' above.)

- **Second cancers** – There is an increased risk for second cancers associated with breast cancer treatment, whether related to breast irradiation, chemotherapy, or tamoxifen. (See 'Second cancers' above.)

- **Menopausal symptoms** – Menopausal symptoms are frequent with breast cancer treatment, including hot flashes and sexual dysfunction. (See 'Menopausal symptoms' above.)

- **Psychological effects** – Patients may experience heightened anxiety, particularly worry about the risk of recurrence, which can persist for years. (See 'Psychological effects' above.)

- **Fatigue** – Fatigue may persist in survivors for years after cessation of treatment. Before assuming that fatigue is related to prior treatment for breast cancer, treatable reasons for low energy should be ruled out, including anemia, thyroid dysfunction, pain, depression, and lack of sleep. (See 'Fatigue' above.)

Relapse patterns

- **Impact of radiation on local recurrences** – While the outcome of breast cancer treatment is increasingly favorable, women treated for invasive breast cancer remain at

risk of both locoregional and metastatic recurrence. Patterns of recurrence depend both on genomic subtype and prior treatment. (See 'Locoregional recurrence' above.)

- **Site of metastases** – The most common sites of metastases are bone, liver, and lung. Approximately 50 to 75 percent of patients who relapse distantly do so in a single organ; the remainder will go on to develop diffuse metastatic disease. (See 'Second primary breast tumors' above and 'Metastatic disease' above.)

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021; 71:7.
2. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 2014; 64:252.
3. Hewitt M, Greenfield S, Stovall E, et al. From cancer patient to cancer survivor: Lost in transition. National Academies Press, Washington DC, 2006. https://canceradvocacy.org/wp-content/uploads/2013/01/From-Cancer-Patient-to-Cancer-Survivor-Lost-in-Transition-Summary-.pdf (Accessed on June 02, 2021).
4. Stat bite: Cancer survivors in the United States. J Natl Cancer Inst 2008; 100:236.
5. Arndt V, Merx H, Stegmaier C, et al. Persistence of restrictions in quality of life from the first to the third year after diagnosis in women with breast cancer. J Clin Oncol 2005; 23:4945.
6. Ganz PA, Kwan L, Stanton AL, et al. Physical and psychosocial recovery in the year after primary treatment of breast cancer. J Clin Oncol 2011; 29:1101.
7. Ganz PA, Land SR, Geyer CE Jr, et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. J Clin Oncol 2011; 29:1110.
8. Pierce SM, Recht A, Lingos TI, et al. Long-term radiation complications following conservative surgery (CS) and radiation therapy (RT) in patients with early stage breast cancer. Int J Radiat Oncol Biol Phys 1992; 23:915.

9. Klein I, Kalichman L, Chen N, Susmallian S. A pilot study evaluating the effect of early physical therapy on pain and disabilities after breast cancer surgery: Prospective randomized control trail. Breast 2021; 59:286.
10. Kaelin, C, Coltrera, et al. The Breast Cancer Survivor's Fitness, McGraw-Hill, New York 2007.
11. Lipps DB, Leonardis JM, Dess RT, et al. Mechanical properties of the shoulder and pectoralis major in breast cancer patients undergoing breast-conserving surgery with axillary surgery and radiotherapy. Sci Rep 2019; 9:17737.
12. Blom Goldman U, Wennberg B, Svane G, et al. Reduction of radiation pneumonitis by V20-constraints in breast cancer. Radiat Oncol 2010; 5:99.
13. Olsen NK, Pfeiffer P, Johannsen L, et al. Radiation-induced brachial plexopathy: neurological follow-up in 161 recurrence-free breast cancer patients. Int J Radiat Oncol Biol Phys 1993; 26:43.
14. Powell S, Cooke J, Parsons C. Radiation-induced brachial plexus injury: follow-up of two different fractionation schedules. Radiother Oncol 1990; 18:213.
15. Rivera DR, Ganz PA, Weyrich MS, et al. Chemotherapy-Associated Peripheral Neuropathy in Patients With Early-Stage Breast Cancer: A Systematic Review. J Natl Cancer Inst 2018; 110.
16. Bandos H, Melnikow J, Rivera DR, et al. Long-term Peripheral Neuropathy in Breast Cancer Patients Treated With Adjuvant Chemotherapy: NRG Oncology/NSABP B-30. J Natl Cancer Inst 2018; 110.
17. Sung H, Hyun N, Leach CR, et al. Association of First Primary Cancer With Risk of Subsequent Primary Cancer Among Survivors of Adult-Onset Cancers in the United States. JAMA 2020; 324:2521.
18. Galper S, Gelman R, Recht A, et al. Second nonbreast malignancies after conservative surgery and radiation therapy for early-stage breast cancer. Int J Radiat Oncol Biol Phys 2002; 52:406.
19. Brown LM, Chen BE, Pfeiffer RM, et al. Risk of second non-hematological malignancies among 376,825 breast cancer survivors. Breast Cancer Res Treat 2007; 106:439.
20. Schaapveld M, Visser O, Louwman MJ, et al. Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. J Clin Oncol 2008; 26:1239.
21. Berrington de Gonzalez A, Curtis RE, Gilbert E, et al. Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. Br J Cancer 2010; 102:220.
22. Taylor C, Correa C, Duane FK, et al. Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. J Clin Oncol 2017; :JCO2016720722.

23. Roychoudhuri R, Evans H, Robinson D, Møller H. Radiation-induced malignancies following radiotherapy for breast cancer. Br J Cancer 2004; 91:868.

24. Morton LM, Gilbert ES, Hall P, et al. Risk of treatment-related esophageal cancer among breast cancer survivors. Ann Oncol 2012; 23:3081.

25. Wolff AC, Blackford AL, Visvanathan K, et al. Risk of marrow neoplasms after adjuvant breast cancer therapy: the national comprehensive cancer network experience. J Clin Oncol 2015; 33:340.

26. Matesich SM, Shapiro CL. Second cancers after breast cancer treatment. Semin Oncol 2003; 30:740.

27. Rubagotti A, Perrotta A, Casella C, Boccardo F. Risk of new primaries after chemotherapy and/or tamoxifen treatment for early breast cancer. Ann Oncol 1996; 7:239.

28. Smith RE, Bryant J, DeCillis A, et al. Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: the National Surgical Adjuvant Breast and Bowel Project Experience. J Clin Oncol 2003; 21:1195.

29. Le Beau MM, Albain KS, Larson RA, et al. Clinical and cytogenetic correlations in 63 patients with therapy-related myelodysplastic syndromes and acute nonlymphocytic leukemia: further evidence for characteristic abnormalities of chromosomes no. 5 and 7. J Clin Oncol 1986; 4:325.

30. Linassier C, Barin C, Calais G, et al. Early secondary acute myelogenous leukemia in breast cancer patients after treatment with mitoxantrone, cyclophosphamide, fluorouracil and radiation therapy. Ann Oncol 2000; 11:1289.

31. Le Deley MC, Suzan F, Cutuli B, et al. Anthracyclines, mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer. J Clin Oncol 2007; 25:292.

32. Fisher B, Rockette H, Fisher ER, et al. Leukemia in breast cancer patients following adjuvant chemotherapy or postoperative radiation: the NSABP experience. J Clin Oncol 1985; 3:1640.

33. Kaplan HG, Malmgren JA, Atwood M. Leukemia incidence following primary breast carcinoma treatment. Cancer 2004; 101:1529.

34. Howard RA, Gilbert ES, Chen BE, et al. Leukemia following breast cancer: an international population-based study of 376,825 women. Breast Cancer Res Treat 2007; 105:359.

35. Praga C, Bergh J, Bliss J, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. J Clin Oncol 2005; 23:4179.

36. Wilking N, Lidbrink E, Wiklund T, et al. Long-term follow-up of the SBG 9401 study comparing tailored FEC-based therapy versus marrow-supported high-dose therapy. Ann Oncol 2007; 18:694.
37. Hershman D, Neugut AI, Jacobson JS, et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. J Natl Cancer Inst 2007; 99:196.
38. Beadle G, Baade P, Fritschi L. Acute myeloid leukemia after breast cancer: a population-based comparison with hematological malignancies and other cancers. Ann Oncol 2009; 20:103.
39. Kaplan HG, Calip GS, Malmgren JA. Maximizing Breast Cancer Therapy with Awareness of Potential Treatment-Related Blood Disorders. Oncologist 2020; 25:391.
40. Avis NE, Crawford S, Manuel J. Psychosocial problems among younger women with breast cancer. Psychooncology 2004; 13:295.
41. Carter J, Lacchetti C, Andersen BL, et al. Interventions to Address Sexual Problems in People With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Adaptation of Cancer Care Ontario Guideline. J Clin Oncol 2018; 36:492.
42. Speer JJ, Hillenberg B, Sugrue DP, et al. Study of sexual functioning determinants in breast cancer survivors. Breast J 2005; 11:440.
43. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol 2016; 34:611.
44. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause 2013; 20:888.
45. Goetsch MF, Lim JY, Caughey AB. A Practical Solution for Dyspareunia in Breast Cancer Survivors: A Randomized Controlled Trial. J Clin Oncol 2015; 33:3394.
46. Goetsch MF, Lim JY, Caughey AB. Locating pain in breast cancer survivors experiencing dyspareunia: a randomized controlled trial. Obstet Gynecol 2014; 123:1231.
47. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 2000; 18:743.
48. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. Cancer 2006; 106:751.
49. Bower JE, Bak K, Berger A, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical Oncology clinical practice guideline adaptation. J Clin Oncol 2014; 32:1840.

50. Colzani E, Johansson AL, Liljegren A, et al. Time-dependent risk of developing distant metastasis in breast cancer patients according to treatment, age and tumour characteristics. Br J Cancer 2014; 110:1378.
51. Chumsri S, Li Z, Serie DJ, et al. Incidence of Late Relapses in Patients With HER2-Positive Breast Cancer Receiving Adjuvant Trastuzumab: Combined Analysis of NCCTG N9831 (Alliance) and NRG Oncology/NSABP B-31. J Clin Oncol 2019; 37:3425.
52. Pedersen RN, Mellemkjær L, Ejlertsen B, et al. Mortality After Late Breast Cancer Recurrence in Denmark. J Clin Oncol 2022; 40:1450.
53. Emens LA, Davidson NE. The follow-up of breast cancer. Semin Oncol 2003; 30:338.
54. Ramin C, Withrow DR, Davis Lynn BC, et al. Risk of contralateral breast cancer according to first breast cancer characteristics among women in the USA, 1992-2016. Breast Cancer Res 2021; 23:24.
55. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med 2017; 377:1836.
56. Varkas G, Van den Bosch F. NSAIDs in axial spondyloarthritis: to be continued...? Ann Rheum Dis 2016; 75:1423.
57. Reiner AS, Sisti J, John EM, et al. Breast Cancer Family History and Contralateral Breast Cancer Risk in Young Women: An Update From the Women's Environmental Cancer and Radiation Epidemiology Study. J Clin Oncol 2018; 36:1513.
58. Graeser MK, Engel C, Rhiem K, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2009; 27:5887.
59. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366:2087.
60. Boice JD Jr, Harvey EB, Blettner M, et al. Cancer in the contralateral breast after radiotherapy for breast cancer. N Engl J Med 1992; 326:781.
61. Hooning MJ, Aleman BM, Hauptmann M, et al. Roles of radiotherapy and chemotherapy in the development of contralateral breast cancer. J Clin Oncol 2008; 26:5561.
62. Bernstein JL, Thomas DC, Shore RE, et al. Contralateral breast cancer after radiotherapy among BRCA1 and BRCA2 mutation carriers: a WECARE study report. Eur J Cancer 2013; 49:2979.
63. Stovall M, Smith SA, Langholz BM, et al. Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study. Int J Radiat Oncol Biol Phys 2008; 72:1021.

64. Pierce LJ, Phillips KA, Griffith KA, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. Breast Cancer Res Treat 2010; 121:389.

Topic 754 Version 57.0

GRAPHICS

Common long-term and late effects of breast cancer treatment[1]

Effect	Management options
Surgical	
Cosmetic effects	Plastic surgery
Functional disability of arm or chest wall, pain	Physical therapy
Scarring/adhesions	Plastic surgery
Lymphedema	Physical therapy, avoid trauma to involved arm*
Radiation	
Second malignancies	Image masses arising near radiation field
Pneumonitis, pulmonary fibrosis	Symptomatic management
Cardiac damage	Lifestyle risk-reduction (diet, exercise, tobacco avoidance)¶
Lymphedema	As above
Systemic therapy	
Second malignancies (myelodysplasia and leukemia)	Check CBC if symptoms of leukemia arise
Ototoxicity (eg, cisplatin)	Symptomatic management
Cardiomyopathy (eg, anthracyclines)	Symptomatic management
Renal toxicity (eg, cisplatin)	Symptomatic management
Premature menopause and infertility (eg, alkylating agents)	Referral to infertility specialist
Menopausal symptoms	Gabapentin, SNRI (eg, venlafaxine), SSRI
Sexual dysfunction	Counseling, lubricants
Osteoporosis (eg, hormonal therapy, chemotherapy)	Calcium, vitamin D, exercise, bisphosphonate
Neuropathy (eg, taxanes and platinums)	Symptomatic management (eg, antidepressants, antiseizure medications for painful neuropathy)
Cognitive dysfunction	Cognitive therapy
Weight gain	Exercise and diet
Fatigue	Exercise, rule out other causes

CBC: complete blood count; SNRI: serotonin-norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TSH: thyroid stimulating hormone.

* Surgical approaches are also available for management of lymphedema.

¶ Referral to a cardiologist is appropriate.

Reference:

1. Hayes DF. Clinical practice. Follow-up of patients with early breast cancer. N Engl J Med 2007; 356:2505.

Graphic 81721 Version 5.0

Signs and symptoms consistent with breast cancer relapse

Locoregional recurrence
Mass in the ipsilateral breast following breast conserving therapy
Mass in the chest wall after mastectomy
Nipple discharge in the treated breast following breast conserving therapy
Rash localized to the treated breast or chest wall
Axillary, supraclavicular, infraclavicular, or cervical lymph node enlargement
Systemic recurrence
Skeletal relapse: localized, progressive bone pain or tenderness
Pulmonary metastasis: pleuritic chest pain, cough, dyspnea
Liver relapse: right upper quadrant discomfort, fullness, or pain; weight loss; anorexia
CNS metastasis: persistent headache, mental status changes, new onset seizure, focal motor or sensory loss, bladder or bowel dysfunction

CNS: central nervous system.

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Graphic 80826 Version 2.0

Contributor Disclosures

Steven E Come, MD No relevant financial relationship(s) with ineligible companies to disclose. **Patricia A Ganz, MD** Consultant/Advisory Boards: Blue Note Therapeutics [Delivery of cognitive behavioral stress management to newly diagnosed breast and lung cancer patients]; Grail [Multi-cancer detection blood test]; InformedDNA [Cancer genetic testing]; Roche [Advisory board for quality of life study in clinical trial]. All of the relevant financial relationships listed have been mitigated. **Lori J Pierce, MD** Patent Holder: PFS Genomics [Breast cancer]. Consultant/Advisory Boards: BCRF Scientific Advisory Board [Breast cancer]; Bristol Myers Squibb [Breast cancer]; Exact Sciences [Breast cancer]. Other Financial Interest: Damon Runyon Cancer Research Foundation [Board of Directors]; Physician's Education Resource [Meeting speaker]. All of the relevant financial relationships listed have been mitigated. **Gary J Whitman, MD** Consultant/Advisory Boards: Siemens [Digital mammography, tomosynthesis, breast cancer]. All of the relevant financial relationships listed have been mitigated. **Sadhna R Vora, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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