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Gynecologic care for breast cancer survivors: assisting in the transition to wellness

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Abstract

Currently, there are >2 million survivors of breast cancer in the United States. Two years after cancer treatment, patients may transition to primary care providers and/or gynecologists. Many of these survivors may have difficulties with menopausal symptoms. If they do not know already, some of these women may want or need risk assessment for hereditary-or treatment-induced second cancers. At least 20% will also have significant psychologic, sexual, and/or relationship difficulties that require attention. All of the women will need assistance to learn and follow recommendations for surveillance, detecting recurrence, and promoting wellness. Thus, gynecologists play a critical role in helping these patients in their health care transitions. To assist the gynecologists, we have reviewed the evaluation and management of common sequelae of breast cancer diagnoses and treatments.

Keywords

breast cancer; depression; menopause; sexuality

More than 200,000 women in the United States are diagnosed with breast cancer annually, which ranks it the most common noncutaneous cancer in women.¹ Although the incidence of breast cancer climbed from 1994–1999, rates have declined approximately 2% annually from 1999–2006. Hypotheses for the decline have centered on the 2002 publication of the Women's Health Initiative data that showed a link between the increased risk for coronary heart disease and breast cancer and the use of estrogen plus progestin hormonal replacement therapy.² Currently, the 5-year relative survival rates for breast cancer are 98% for stage I disease and 84% for regional disease.³ As a result, survivors of breast cancer account for 23% of all cancer survivors and 40% of the 5.8 million female survivors alive today.⁴ Many survivors will continue to receive care from oncologists, although this will become more difficult as the oncology workforce shrinks and the survivor population grows.^{5,6} Therefore, care for many survivors will transition to the primary care setting; for many women, that care will come from the obstetrician-gynecologist. However, providers may believe that they are unprepared to address the concerns of patients with cancer and patients with breast cancer in particular.^{7,8}

One proposal to ease this transition has been the suggestion that oncologists should provide patients with an individualized cancer treatment summary (a synopsis of all treatments received, dates, and dosages) and a care plan (disease-specific screening and follow-up

interval recommendations, information on possible late effects/symptoms, health behavior recommendations, and any psychologic and social concerns) that the patient can then share with other providers.⁹ Thus far, implementation has been modest, with studies showing that <20% of patients receive this information.¹⁰ In this context, we highlight salient issues in comprehensive gynecologic care for the survivor of breast cancer.

Genetic testing and surveillance

Although hereditary cases account for only a small proportion of breast cancer cases (up to 10%), the identification of women with a family history of breast cancer is critical because of the significantly heightened risk for secondary cancers and premature death for themselves and, potentially, their relatives.¹¹ Unfortunately, personal and family histories may not have been obtained, and the gynecologist may need to record a history on the patient's return for care. If a patient is deemed high risk, she may benefit from genetic counseling and evaluation.¹² Table 1 provides a list of factors that should be assessed for familial risks, which should evaluate both maternal and paternal lineages.¹²

The most common genetic mutations are attributed to the BRCA1 and BRCA2 genes. These mutations place patients at increased risk for not only breast cancer but also ovarian and fallopian tube cancers. In high-risk patients, surveillance recommendations include semiannual breast examinations, annual mammograms, and annual magnetic resonance imaging, typically beginning at age 25 years.¹³ Coordination of care with medical oncologists and breast surgeons may also provide risk-reducing strategies such as the use of selective estrogen receptor modulators or prophylactic mastectomy.¹⁴

Because these patients are at increased risk for the development of ovarian and fallopian tube cancers, the gynecologist must be aware of the options that are available to decrease morbidity and mortality rates in these patients.¹⁵ Depending on patient age and preference, this may range from screening evaluation to medical or surgical intervention.

General recommendations for screening for ovarian cancer in BRCA carriers include the evaluation of CA-125 levels and transvaginal ultrasound beginning between ages 30–35 years or 5–10 years before the earliest age of diagnosis. However, patients should be aware of limitations for ovarian cancer screening, including failure to reduce mortality rates.^{15–17}

Medical intervention includes the use of oral contraceptives; however, their use in patients with a history of breast cancer is controversial.¹⁷ Because the risk of ovarian cancer increases after the age of 40 years, patients who are BRCA mutation carriers should be offered risk-reducing salpingo-oophorectomy after the completion of childbearing or when the patient reaches 35 years of age. This procedure is associated with a risk reduction of 85–96% for gynecologic cancers, because there is a continued risk of primary peritoneal cancer and a 40–70% risk reduction of breast cancer.^{18,19} The added removal of the uterus should be an individualized decision. Patients should be counseled on the benefits of the removal of the fallopian tube, a simplified hormone replacement plan, and the elimination of the risk of uterine cancer (particularly in women receiving tamoxifen therapy). Risks for the additional surgery include the possibility of increased surgical morbidity, a longer operative time, and an inpatient stay.²⁰

Menstrual function and fertility

Alterations in menstrual function and fertility may occur in women who receive chemotherapy for breast cancer. Typically, women <35 years old will resume menses 2 years after treatment, with outcomes more variable for the women 35 years old.²¹ Women who receive selective estrogen receptor modulators may experience menstrual dysfunction

and hot flashes. However, these agents do not affect fertility (and may even enhance it) and are contraindicated in pregnancy.²¹ Therefore, during and after cancer treatment, reproductive-age women should consider the use of nonhormonal contraception such as barrier methods, an intrauterine device, or sterilization (if desired).

Although safety data of these approaches are limited in survivors of breast cancer, if a patient desires continued fertility, options to be considered before the start of cancer therapy include assisted reproductive technology, embryo fertilization, and ova harvesting.²² Data show that survivors of breast cancer who become pregnant within 6 months of treatment have a poor prognosis; however, the 5-year survival rate is 54%, compared with 78% for those who became pregnant between 6 months to 2 years.²¹ Therefore, general recommendations are for survivors to wait at least until the 2-year disease-free point before attempting pregnancy.²¹

Management of menopausal symptoms

Early studies reported that hormone therapy was acceptable for use in survivors of breast cancer.^{23–25} However, in a randomized controlled trial (Hormone replacement therapy after breast cancer—is it safe?), an increase in breast cancer events was found in the hormone replacement group (hazard ratio, 3.3; 95% confidence interval, 1.5–7.4).²⁶ Another trial with women with early-stage breast cancer found the 5-year cumulative incidence of breast cancer of 22.2% in the hormone replacement arm far exceeded the 8.0% risk in the control arm.^{27,28} Studies have also shown that megestrol acetate significantly decreased the incidence of hot flashes, compared with placebo (85% vs 21%, respectively).²⁹ However, because of a potential association between progestational agents and breast cancer risk, their use has fallen out of favor. Thus, routine use of hormone therapy is not recommended in women with a history of breast cancer, and alternative therapies should be considered.³⁰

With these findings, attention has turned to nonhormonal therapies. Selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors have also been used for the amelioration of hot flashes. Favorable results have been demonstrated with paroxetine, fluoxetine, citalopram, and venlafaxine in the reduction of hot flashes, anxiety, and sleep disturbances.^{31,32} All practitioners should be aware that certain medications, such as fluoxetine and paroxetine, inhibit the cytochrome P450 CYP2D6 function and may interfere with the metabolism of tamoxifen, possibly increasing the risk of breast cancer recurrence.

Venlafaxine has minimal effect on CYP2D6 function and is the recommended selective serotonin reuptake inhibitor for women receiving tamoxifen therapy.^{33,34} Clonidine, a centrally acting alpha-adrenergic agonist, has been shown to reduce the incidence of tamoxifen-induced hot flashes by 15%. Another agent, gabapentin, which is structurally similar to γ -aminobutyric acid, was comparable with estrogen and superior to placebo in the reduction of hot flashes. However, the benefits of these agents are often overshadowed by their side-effects and other agents (such as the selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors) typically are preferred.^{34–36}

Physicians might also consider complementary and/or alternative therapies for vasomotor symptoms. The plant, black cohosh (*Cimicifuga racemosa*), which originally was used by Native Americans for menstrual-related disorders, has been used but failed to demonstrate superiority compared with placebo.³⁷ Soy food, which contains phytoestrogens that are structurally similar to estradiol, have also been evaluated. Thus far, the literature is inconclusive, although trials are ongoing.³⁸ Other complementary therapies that have been or are being studied include red clover, flaxseed, vitamin E, primrose oil, dong quai, ginseng, and wild yam.³¹ Furthermore, the use of acupuncture and stress reduction methods (progressive muscle or biofeedback-assisted relaxation training, yoga, hypnosis) and

exercise have been evaluated.³¹ Small trials have shown promising results; however, larger studies and randomized trials are needed to evaluate efficacy.³¹

Complicated survivorship: psychological, social, and sexual issues

Most women who are treated and remain disease free have a quality of life trajectory much like that of women with no cancer history.^{39,40} However, 20–40% of all patients will have their survivorship complicated by poor adjustment, quality of life, or persistent morbidities from the disease or its treatment.

Mood and anxiety disorders

Mood disorders are common, disabling, and unremitting. More than 16% of people will experience a major depressive disorder (MDD) in their lifetime, with 6.6% of people will meet the criteria for depression within a 12-month period.⁴¹ It is also the case that depression and anxiety cooccur, so upward of 50% of patients with MDD will have a comorbid anxiety disorder and vice versa.^{42,43} The most common disorders (MDD and generalized anxiety) are more common for women than men, and depression is the leading cause of disease-related disability among women.⁴⁴ For patients with cancer, metaanalysis shows the point prevalence of MDD to be 12.5%, which is 4 times the rate of 3.3% in the general population (Wu SM and Andersen BL. Prevalence of mood and anxiety disorders in cancer patients: a systematic review and meta-analysis. Personal communication.). When the primary diagnostic categories are considered, the point prevalence estimates are extremely high: 23.2% for all mood disorders, 18% for all anxiety disorders, and 14.1% for all adjustment disorders. With base rates being so high, one might expect that patients with psychiatric comorbidity would be identified readily, but they are not. Health care professionals miss symptoms in two-thirds of the patients with these disorders, under estimate the severity of the disorder, and thus undertreat the disorder.^{45–49} Mood disorders are associated with lowered quality of life, a loss of work productivity, and soaring health care costs.^{50,51} In the context of cancer, the concerns are magnified, and the outcomes are worsened.^{52,53} The sequelae include more symptom distress, poorer quality of life, greater fatigue, less meaning in life, maladaptive coping, and employment absenteeism, among others.^{54–63} Clinical depression is also associated with heightened risk for premature mortality (relative risk, 1.22–1.39).^{64,65} For patients with breast cancer, both cancer death (relative risk, 1.18) and all-cause death rates (relative risk, 1.31) are elevated.^{65,66} Conversely, a decrease in depressive symptoms is associated with longer survival.⁶⁷

There are recommendations and clinical guidelines for depression screening for adults in primary care.^{68–70} Practitioner awareness of risk factors for depressive and anxiety disorders is an important first step; Table 2 provides a summary and useful first level questions that, when answered in the affirmative, can then be followed with reliable and valid self-report measures. Further, the questions are brief, understandable, readable, and face valid. If significant symptoms are identified, referral to specific resources or professionals (pharmacist, psychologist) who are trained to treat psychiatric disorders is essential. Triage and staff-assisted care support referral follow US Preventive Service Recommendations (2009) and is the only method that has been found to significantly impact subsequent levels of distress; screening alone, even with patient feedback, is insufficient.^{68,69,71}

Efficacious treatments for disorders exist. Generally, the primary options for MDD, for example, are antidepressant medication or cognitive behavior therapy.^{72,73} However, there are only 5 random controlled trials with antidepressant medications with patients with cancer, and the available data are not compelling.^{74,75} In 3 trials, mianserin and paroxetine were associated with symptom improvement compared with placebo, but the remaining 2

trials found null effects for fluoxetine and worse effects for desipramine or paroxetine.^{76–80} We note, however, that venlafaxine is at least as efficacious as any of the other widely used antidepressants and has the additional advantage of reducing the frequency and intensity of hot flashes for these patients.⁸¹ Considering psychotherapy, in studies of patients with no cancer, cognitive behavior therapy is as effective as antidepressant medication during the acute phase of MDD treatment; however, patients who undergo cognitive behavior therapy are at lower risk for relapse.⁸² Results of cognitive behavior therapy combined with cancer-specific elements to reduce stress are promising.⁸³

Sexual concerns and sexual dysfunction

There is extensive literature on the sexual morbidities after breast cancer, most of which focus on the newly diagnosed patient who is coping with mastectomy and adjuvant treatments.⁸⁴ For these women, there is an immediate reduction in sexual activity and responsiveness; for most of the women, this disruption does not resolve.⁸⁵ For example, we followed patients (n = 163) longitudinally.⁸⁶ Patients with partners reported that, before diagnosis, the frequency of intercourse was approximately once per week. The frequency dropped by one-half (1–2 times/month) when chemotherapy was initiated; during the next 5 years, there was no return to precancer levels and was little improvement overall. The same trajectory was found with data on sexual satisfaction. Thus, by the time a patient returns to her gynecologist, it is likely that sexuality has declined and stabilized at a level below that before cancer diagnosis.^{74,87} This is generally true for all, but particularly so for those women who undergo radical surgeries rather than segmental mastectomy. An even more difficult trajectory is seen for women with recurrence. In these cases, sexual activity declines once again at diagnosis and continues to do so thereafter.⁸⁸ There are individual differences among patients, with the greatest disruption for those with disseminated (distant) disease and/or those younger (<55 years).⁸⁶ For many women who are treated for breast cancer, a contributor to their sexual difficulties is the stress with body changes.⁸⁹ Significantly higher levels of traumatic stress over breast changes are found with women who have received a modified radical mastectomy vs those who received breast conservation. There is considerable variability in cosmetic outcomes for those women who undergo reconstructive surgery, and data show that it is not a panacea. In fact, the data show worse outcomes (lower levels of sexual activity and less sexual responsiveness) for patients who undergo reconstruction compared with outcomes for patients who do not.⁸⁵

There are limited interventions that the gynecologist may use that can produce significant relief.⁹⁰ First, acknowledgment to the patient that sexual problems after breast cancer are common may be of some help. In particular, the most frequent symptom is a loss of sexual desire. Fatigue can be a powerful contributor, because it remains a significant problem; full recovery takes upwards of 2 years after all cancer treatments to end.⁹¹ Patients are unaware that recovery time is this lengthy. Also, useful sexual educational materials are available (the American Cancer Society's *Sexuality and Cancer* booklet). Second, managing menopausal symptoms relevant to vaginal health should be addressed for all patients. The most common symptom is vaginal dryness, which can be reduced with instructions to use vaginal moisturizers or vaginal lubricants.⁹² Another consideration is the use of vaginal estrogen therapy (creams, tablets, estrogen-releasing ring), which have minimal systemic absorption and high patient satisfaction rates.^{93,94} Although studies are limited, these local therapy options have a high success rate (80%) and have been used safely in survivors of breast cancer.^{92,93} However, the use of local estrogen therapy may negate the benefit of aromatase inhibitors and should not be recommended in patients who undergo this therapy.^{95,96} Vaginal dryness may be accompanied by diminished sensation and pleasure and possibly dyspareunia with partnered activity. For pervasive sexual difficulties, referral of patients to professionals with training in behavioral sex therapies is advised.

Many women with mood or sexual difficulties may be doubly burdened if the difficulties arise in the context of a troubled partnered relationship. Mood disorders, typically depression, are a particular problem.⁹⁷ Marital distress is usually a chronic problem.^{98,99} Among patients with cancer whose marriages fail, it is not because relationships become discontented after cancer diagnosis. Divorce and breakups occur primarily among those women who report that marital difficulties predated their diagnosis.^{39,100} For patients who remain partnered, marital distress is associated with continued stress and slowed post-treatment recovery. All patients have stress when diagnosed with cancer, but stress declines more slowly and can remain elevated for years for the maritally distressed.¹⁰¹ Also, maritally distressed patients have more symptoms/signs of illness and treatment side-effects. Thus, referral of patients for psychologic assistance is made all the more important when mood and/or sexual difficulties are accompanied by marital distress.

Surveillance and late onset morbidities

The appropriate follow-up examinations and tests must be conducted to minimize morbidity and death. The first 5 years after cancer treatment is the period of highest risk for recurrence. The National Comprehensive Cancer Network guidelines suggest surveillance should consist of a physical examination every 4–6 months for 5 years and an annual mammography.²¹ Additional tests, such as bone scans and chest radiographs, should be ordered only if disease recurrence is suspected.²¹ Patients should be counseled on signs and symptoms, including bone pain and shortness of breath, that may be signs of metastatic disease that requires further evaluation. Therefore, gynecologists should be comfortable with performing a comprehensive breast examination, following surveillance guidelines, and evaluating for recurrent disease. Table 3 provides a list of recommendations for follow-up care for survivors of breast cancer.

Lymphedema

One of the most common surgical complications for patients with breast cancer is lymphedema, which has been reported in upwards of 60% of cases.¹⁰² Patients should be counseled that the risk of lymphedema could be reduced by performing arm exercises, wearing a compression sleeve, and minimizing trauma (intravenous medications, blood pressure) in the affected arm. If lymphedema develops, early intervention with compression sleeves and physical therapy may reduce its severity. As recent data have shown, regarding the comparable survival for patients who are treated with sentinel lymph node dissection (when compared with patients who are treated with standard axillary lymph node dissection), the incidence of this chronic morbidity, hopefully, will decline.¹⁰³

Osteoporosis

Patients who undergo premature menopause are at high risk for osteoporosis. Additionally, the use of tamoxifen, which may be used in the prevention and treatment of receptor positive breast cancer, has been shown to promote osteoporosis in premenopausal women.¹⁰⁴ More recently, aromatase inhibitors (letrozole and arimidex), which are also used in the adjuvant treatment of breast cancer, are associated with an increased risk of osteoporosis.¹⁰⁴ Patients who are at increased risk should be advised to use calcium (1200–1500 mg daily) and vitamin D (400–800 international units) and should be monitored with bone density testing. If the development of osteoporosis occurs, patients may be candidates for bisphosphonate therapy or raloxifene, which unlike tamoxifen, has been shown to reduce the osteoporosis risk.^{105,106}

Uterine cancer

Because of estrogenic effects on the endometrium, tamoxifen is associated with a 2- to 3-fold increased risk of uterine cancer in women 50 years old.¹⁰⁴ Thus, the gynecologist plays a critical role in counseling and assessing patients with abnormal uterine/vaginal bleeding with tamoxifen therapy. Gynecologists should be aware of the limited role of ultrasound scans in tamoxifen users because of development of endometrial polyps and increased endometrial thickness.¹⁰⁷ Screening with ultrasonography and endometrial biopsy have been shown to be low yield. However, if a patient experiences bleeding, the gynecologist readily should perform an evaluation with endometrial sampling.¹⁰⁸ Although endometrial cancers are often diagnosed in the early stages, reports of aggressive histologic subtypes, which include sarcomas, have been reported.

Summary

As the number of cancer survivors grows, more patients with breast cancer will be transitioning (and doing so more rapidly) to primary care for all their needs, including gynecologic. In preface, we note the importance of identifying the risk for breast cancer for all gynecology patients. For patients who are returning after completing cancer therapies, gynecologists have a multifaceted role in their care.

First, the gynecologist should obtain personal and family histories to identify the patients who are at high risk for hereditary breast cancer if that has not already been done. This will insure timely interventions, if needed, to reduce cancer risk. Second, management of menopausal symptoms is needed commonly, but assessment for uterine bleeding with tamoxifen use may be necessary as well. Gynecologists may need to be alert to psychologic, social, and sexual difficulties, which are likely for at least 20% of returning patients. Last, continued surveillance for breast cancer, routine health maintenance, and promotion of wellness are integral to comprehensive care for the survivor of breast cancer.

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TABLE 1

High-risk factors for genetic predisposition

History	Factor
Personal	Breast cancer
	Ovarian cancer ^a
	Close relative with ovarian cancer or premenopausal breast cancer
	Ashkenazi Jewish Ancestry
	Early age (<40 y) onset breast cancer
	2 breast primaries
Family	2 breast primaries or breast and ovarian cancer in close relatives of the same parental lineage
	Family member with known Mutation
	Male breast cancer

^aOvarian, fallopian tube, or primary peritoneal cancer.

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TABLE 2

Characteristics of risk and screening for significant emotional distress

Factor	Assessment strategies
Risk	Other psychiatric disorders (eg, substance use)
	Familial psychiatric history (1st degree relative)
	2 chronic illnesses (including chronic pain)
	Obesity
	Social isolation (eg, no spouse or partner)
	Recent (<6 mo) major stressor (eg, child loss, divorce, death of close family member)
	Lower socioeconomic status, unemployment, and/or financial strain
	Older or elderly age
Assessment	
Depressed mood	First level
	“Do you often feel sad or depressed?”
	“In the past 2 years, have you been bothered by depressed mood most of the day, on more days than not?”
	Second level
	Beck Depression Inventory or Geriatric Depression Scale
Anxiety	First level
	“Do you feel tense, anxious, or nervous on most days?”
	“Do you worry all the time?”
	Second level
	General: Beck Anxiety Inventory
	Generalized anxiety disorder: Pennsylvania State Worry Questionnaire

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TABLE 3

Surveillance and screening recommendations for survivors of breast cancer

Variable	Screening	Examination	Additional considerations
Breast cancer	Annual mammography	Every 4–6 mo for 5 y	Consider magnetic resonance imaging and genetic testing
Gynecologic care	Cervical cytologic tests	Annual examination	Assess for menopausal symptoms
Uterine cancer evaluation	Assess for abnormal bleeding, particularly in tamoxifen users	Endometrial sampling if bleeding present	
BRCA carriers: ovarian cancer evaluation	Ultrasound and CA-125 yearly	Semiannual examination	Risk-reducing surgery and genetic Testing
Colorectal cancer screening	Colonoscopy every 5–10 y, beginning at age 50 y	Hemoccult testing annually	
Osteoporosis: postmenopausal women	Dual energy x-ray absorptiometry scan every 2 y		Prevention with calcium/vitamin D and bisphosphonates

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