CHAPTER

47

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Early Stage Breast Cancer

INTRODUCTION

Carcinoma of the breast is the most common cancer in women, and the second most common cause of female cancer deaths (after lung cancer) in the United States.[1] Globally, breast cancer had the highest cancer incidence rate in women, with an estimated 1.7 million cases in 2012 and 522,000 estimated deaths.[1,2] The incidence of invasive breast cancer has demonstrated an upward trend over the past several decades, despite a brief decline in the early 2000s.[3,4]

During 2002–2003, early data from the Women's Health Initiative validated the potential risk of breast cancer associated with the use of hormone replacement therapy after menopause.[5] In response to these findings, most women quit taking hormone replacement therapy and many providers changed their hormone prescribing habits.[5] Hormonal alterations were thought to be responsible for a downward trend in breast cancer incidence. Despite these changes in patterns of use for hormone replacement therapy, the incidence of breast cancer subsequently began to rise.[1,3] This upward trend continues despite the availability of effective interventions (e.g., selective estrogen receptor modulators, aromatase inhibitors) that can significantly decrease breast cancer development.[3,5,6]

Outcomes for patients with newly diagnosed breast cancers are often better when the person presents for treatment at an early stage with node-negative disease.[7] The recommendations for localized and systemic treatments depend on the type of breast cancer, extent of disease, and individual characteristics of the tumor and host.[7,8] Attention to the stage of disease, cellular characteristics of the tumor, specific markers, and oncogenes enables the multidisciplinary team to provide personalized care for each patient.[8] Localized treatment of breast cancer includes surgery with a lumpectomy or mastectomy, sentinel lymph node biopsy or axillary node dissection, and options of immediate or delayed reconstruction following a mastectomy.[7] Radiation

therapy, a treatment component of localized therapy, is recommended based on stage of disease, extent, and type of surgical procedure.[8] Systemic treatment of breast cancer includes both oral and intravenous drugs; these effective agents treat micrometastatic disease that is invisible to the human eye but believed to be present based on the history of this disease. Targeted agents may also be prescribed based on the oncogenetic characteristics of the tumor.[9] Long-term rehabilitation and surveillance are necessary to enhance survivorship, prevent or treat persistent side effects of the disease, and screen for recurrence or secondary cancers.

EPIDEMIOLOGY

Breast cancers are classified into two categories: noninvasive and invasive. Noninvasive tumors do not extend beyond their cellular wall (e.g., breast duct) and therefore, do not have the potential to develop into metastatic disease.[10] These tumors occur inside the milk ducts of the breast and are termed ductal carcinoma in situ (DCIS). Invasive breast cancers extend beyond the cellular wall (e.g., ductal, lobular) into areas rich with lymphatic channels and blood vessels.[10] Invasive cancers can penetrate these structures, grow, and shed cells that travel to other parts of the body. This mechanism enables abnormal growth of cancer in other organs, termed metastatic disease.[9]

INCIDENCE

The incidence of invasive breast cancer continues to demonstrate an upward trend despite known interventions that can decrease its occurrence.[4] This increase is in part attributable to improved and advanced imaging that can detect breast cancer in its earliest stages, for example, through mammography, magnetic resonance imaging (MRI), advanced ultrasonography, three-dimensional imaging, and computerized assessment of images.[3] An estimated 232,000 women are diagnosed with invasive breast cancer annually,[1] and this number continues to grow secondary to widespread screening and education. Another 60,000 women are diagnosed with DCIS, a noninvasive cancer.[10] State-wide tumor registries record each case of invasive cancer and each cancer-related death, but do not always report cases of noninvasive malignant cells in the breast, including DCIS.[4] Therefore the incidence of DCIS may be higher than the reported cases, as only some states collect these data. Improved screening rates and techniques are thought to be responsible for the high number of DCIS cases, along with high skill level of dedicated breast radiologists who are trained to note even subtle breast changes.

Breast cancer accounts for 29% of all newly diagnosed cancers in the United States and approximately 12% of women (1 in 8) will develop breast cancer in their lifetime.[1] Death rates from breast cancer have gradually declined. Nevertheless, despite the many advances in therapy over the past decade approximately 40,290 females die from breast cancer in the United States each year.[10] Early detection is integral to disease-free outcomes, yet even those persons diagnosed with early-stage node-negative disease can eventually die from their cancer.[11,12] This irony highlights the various interactions between the host and cancer that may positively or negatively affect outcomes regardless of type or stage of breast cancer.[11,12]

GEOGRAPHICAL DIFFERENCES

Geographical conditions may or may not account for the incidence and death rates of breast cancer. Breast cancer mortality rates among non-Hispanic white women tend to be highest in the West, Midwest, and Mid-Atlantic regions of the United States.[1] In African American women, the highest mortality rates are found in the Southern and Midwestern states, which are home to the largest groups of African American women. In addition, U.S. women of eastern European decent and Jewish faith are at increased risk of breast cancer.[1] These geographic variations in incidence and mortality may be related to patterns of screening and treatment of early breast cancers, or they may represent true geographical variations.

Men are considered to be at low risk of breast cancer and high risk of prostate cancer: Both of these diseases are hormonally-dependent cancers.[13] More than 2,300 men are diagnosed with breast cancer every year, with 440 estimated deaths occurring annually from the disease.[1] The treatment of male breast cancer is similar to the interventions recommended for female breast cancer.[13] Men who are diagnosed with breast cancer should consider genetic testing due to the cancer's variance from normalcy.[12–14] First- and second-degree relatives of men with breast cancer are at increased risk of cancer development.[12]

Breast cancer can occur at any age, but the median age at diagnosis is 61 years.[4] Seventy-nine percent of new cases of breast cancer occur in women 50 years of age and older, with a noted decrease in women older than 80 years of age. It is unknown why breast cancer diagnoses decrease in older women, although that trend may reflect lower rates of screening, slower growing cancers, and death from non-cancer-related causes.[4] Eighty-eight percent of breast cancer deaths occur in women 50 years of age and older.[1]

The highest breast cancer incidence rates in the United States are found in non-Hispanic white women, less in African American women and the lowest in Asian/Pacific Islander women.[1] The risk of death from breast cancer is highest among younger (20 to 49 years of age) African

American women due to their more frequent development of aggressive cancers[15]; the risk is increased by 41% in this population, as compared to non-Hispanic white women.

ETIOLOGY AND RISK FACTORS

The etiology of breast cancer is multifactorial, with nonmodifiable and modifiable risk factors. An estimated 5% to 10% of breast cancers have identifiable hereditary mutations that commonly affect younger women.[12] Women who have undergone breast biopsies may be at increased risk of breast cancer development due to evolutionary changes in breast tissue over time, especially with pathologic findings of atypia, lobular carcinoma in situ, or DCIS.[12,16] Other risk factors for breast cancer include increasing age, family history of breast cancer, age at menarche, and age at first birth of child.[11,12] Most breast cancers occur without known etiology, although a long list of potential causative factors has been postulated.[4,11,12]

Scientists continue to research the full etiologic complement of genetic and heterogenic cellular mutations of breast cancers that affect selected female and male hosts. Risk factors can be classified as modifiable or nonmodifiable in relation to personal risks and lifestyle habits.[1,15–20] The multiple risk factors related to breast cancer are reviewed in **Table 47-1**.[1,16–20] Approximately 5% to 10% of genetically involved breast cancers are directly related to the known genetic mutations of the breast cancer 1 and 2 genes (*BRCA1* and *BRCA2*).[19] These gene mutations have a strong relational risk to occurrence of breast cancer.[16,17,19] The remaining 90% to 95% of breast cancer cases have no known singular causative factor, although advancing age and female gender are the two most important risk factors overall.[1,17] The remaining risk factors are difficult to ascertain for each individual, as they are general risk factors for all women or men. Some persons may have multiple risk factors and never develop the disease, whereas others may have few risk factors and still develop the disease.[20]

Risk factors that are associated with the occurrence of breast cancer often are similar to factors of concern for cancer recurrence or a second breast primary.[16] Thus, providers and patients alike must be educated about risk factors and their role in potential cancer recurrence, progression, metastatic disease development, or development of additional primary cancers.[20–22] Initial approaches to improve the prevention of breast cancer in women at increased risk may focus on identifying gaps in women's breast cancer risk knowledge, gaps in knowledge about individual risk profiles, and fears about breast cancer development. It is also helpful to explore individuals' willingness to participate in known primary, secondary, and tertiary preventive interventions or clinical trials to potentially reduce their risk.

NONMODIFIABLE RISK FACTORS

Nonmodifiable risk factors (Table 47-1) are those that are inherent in a person's family or personal health history and cannot be changed.[16,22] Nonmodifiable risk factors for breast cancer are common yet relatively unknown by most women until their diagnosis. Many of the more significant nonmodifiable risk factors are not changeable in women, nor are they associated with male breast cancer, causing increased uncertainty about the origin of breast cancer in men.

Gender

Being a woman is the primary risk factor for breast cancer development. Men can develop breast cancer, but this disease is about 100 times more common among women than among men.[1] Men have far smaller quantities of the female hormones estrogen and progesterone, which promote breast cancer cell growth.[14] A woman today has a 12.3% chance of developing breast cancer in her lifetime.[1]

The risk of breast cancer in lesbians is increased as compared to heterosexual women due to hormonal differences across their lifetime.[23,24] Lesbians visit medical offices less often, and they may forego annual breast clinical examinations or mammography.[23] Some lesbian women and homosexual men may take hormones to alter their physical attributes and heterosexual libido. In male-to-female transgender persons, the endogenous hormonal status is often altered with significant amounts of exogenous estrogen.[25] There are reported cases of breast cancer in augmented breast tissue secondary to extended hormone therapy.[25,26] Annual mammography may be important in this population, especially when hereditary risks exist, and may need to be performed at an early age.[26]

Age

Age is the second most important risk factor for breast cancer with 79% of new invasive breast cancers occurring in individuals older than age 50.[4] Only one out of eight new invasive breast cancers is found in women younger than 45 years.[1] Younger women with breast cancer should be referred to a genetic counselor for genetic testing to maximize their healthcare planning. If genetically positive, women often undergo bilateral mastectomies and bilateral oophorectomy to provide protection against future hormone-related cancers.[19,22]

Genetic Profile

Genetics is a risk factor that persons cannot change, as this genetic patterning is created at conception.[16,17,19] Persons with a genetic mutation commonly develop breast cancer at an earlier age (e.g., before age 40) given that the

TABLE 47-1

Modifiable and Nonmodifiable Factors That May Increase the Risk of Breast Cancer

	Risk Factor	Relative Risk
Nonmodifiable	Gender (female greater than male)	High
	Increasing age (higher risk after age 65)	High
	Genetic profile (positive genes, *BRCA1* and *BRCA2*, combination of genes)	High
	Family history (2 or more first-degree relatives, younger than age 50 at diagnosis)	High
	Race/ethnicity (African American/non-Hispanic white)	High (for triple-negative cancer)
	Breast density (including persistent density after menopause)	High
	Abnormal breast biopsy (atypia or lobular carcinoma in situ)	High
	Geographic location (exposure to chemicals or ionizing radiation)	Moderate (depending on exposure)
	History of chest radiation	Moderate
	Personal history of breast cancer	Moderate
	Endogenous hormone levels (high level of estrogen or testosterone)	Moderate
	Diethylstilbestrol exposure (secondary to mother's use)	Low
	Personal history of other cancers (endometrium, ovary, or colon cancer)	Low
(May be modifiable)	Personal history of increased bone density (signifies increased endogenous estrogen)	Low
Modifiable	Exogenous hormone use (use of estrogen, progesterone, or testosterone)	Low
	Birth control pills (recent and long-term use)	Low
	Age at menarche (before 12 years of age)	Low
	Age at menopause (after 55 years of age)	Low
	Age at first full-term pregnancy (after 30 years of age)	Low
	Occupational exposure	Low (depending on specific chemicals)
	Lifestyle risks (alcohol, diet, weight, exercise, smoking)	Low
	Ashkenazi Eastern European Jewish descent	Low
	High socioeconomic status	Low
	Absence of breastfeeding	Low
	Absence of full-term pregnancy	Low

Source: Data from American Cancer Society[1]; National Comprehensive Cancer Network[16]; Cummings et al[17]; National Cancer Institute[18]; Moyer[19]; Hilgart et al.[20]

abnormality occurred at conception, as compared to persons who develop breast cancer based on environmental, personal, or unknown risk factors (e.g., after age 50).[16,17,19] It is recommended that women and men who are diagnosed with breast cancer talk with their oncologist and obtain a referral to a genetic counselor if they desire or need genetic testing.[6,12,16] A woman undergoing genetic testing is theoretically asymptomatic, but is generally tested if she has a family member with breast or ovarian cancer who has tested positive for a gene mutation, if she has a strong family history of breast or ovarian cancer but no members who can be tested, or if the woman herself has developed breast or ovarian cancer at a young age, or both ovarian and breast cancer at any age.[18,19]

Predictive genetic testing for predisposition of breast cancer can cause increased short- and long-term distress.[20] Genetic counselors are armed with interventions to help patients understand their potential risk, comprehend accurate information, increase knowledge of breast cancer risk, and decrease distress.[19-21] Every person has a set of the *BRCA1* and *BRCA2* genes and it is the mutation of these genes that causes the genetic defect and propensity to develop breast

cancer.[16,17,19] These genes were identified in the mid-1990s.[22] Approximately 5% to 10% of breast cancer cases are thought to be genetically related to mutations of these two genes.[12,16,19] While some persons with *BRCA1* mutations have a lifetime risk of breast cancer as high as 80%, on average this risk is in the range of 55% to 65%.[16,19] In persons with *BRCA2* mutations the risk of developing a breast cancer is approximately 45%.[16,19] Breast cancers linked to these mutations occur more often in younger women and often affect both breasts.[16,19] Women with these inherited mutations also have an increased risk for developing other cancers, specifically ovarian cancer.[16,19] In the United States, *BRCA* mutations are more common in Jewish women of Ashkenazi (Eastern Europe) origin than in women from other racial and ethnic groups, although they can occur in anyone.[1,6]

Risk management options in women or men with *BRCA1* or *BRCA2* mutations include intensive screening and surveillance, discussion of chemoprevention, and consideration of risk-reducing surgery such as bilateral mastectomies and oophorectomy.[22,27] One study noted a potential 80% reduction in the risk of ovarian, fallopian tube, or peritoneal cancer in *BRCA1*- or *BRCA2*-positive women following bilateral prophylactic oophorectomy.[22]

BRCA1 and *BRCA2* mutations negatively affect deoxyribonucleic acid (DNA) repair and therapeutic responses. Poly (ADP-ribose) polymerase (PARP) inhibitors have been studied as a means to repair or stop DNA alterations.[19] In addition, some other genes have been identified as part of the *BRCA* network.[28,29] Mutations in these genes collectively account for 25% to 30% of breast cancer heritability.[28,29] They can lead to inherited breast cancers, although these susceptibility mutations are rare and do not increase the risk of breast cancer as much as mutations of the *BRCA1* and *BRCA2* genes.[12] One of these genes, the ataxia telangiectasia mutated (*ATM*) gene, normally helps repair damaged DNA.[29,30] Inheriting one mutated copy of this gene has been linked to a higher rate of breast cancer in some families.[29,30] The tumor protein 53 (*TP53*) gene is linked to a protein called p53 that helps stop the growth of abnormal cells[28–30] and inherited mutations of this gene cause Li-Fraumeni syndrome.[28–30] Persons with Li-Fraumeni syndrome have an increased risk of developing breast cancer (although such cases remain rare) as well as several other cancers such as leukemia, brain tumors, and sarcomas.[28–30] Li-Fraumeni syndrome can also be caused by inherited mutations in the checkpoint kinase 2 (*CHEK2*) gene,[28–30] which doubles the risk of breast cancer.[28–31]

The phosphatase tensin homolog (*PTEN*) gene normally helps regulate cell growth. Inherited mutations in this gene can cause Cowden syndrome, a rare disorder that puts individuals at increased risk for both benign and malignant breast tumors, as well as growths in the digestive tract, thyroid, uterus, and ovaries.[29–31] Recently, the syndromes caused by PTEN have been combined into a single condition called PTEN tumor hamartoma syndrome.[29–31]

Inherited mutations in the cadherin-1 (*CDH1*) gene cause hereditary gastric cancer. Women with mutations in this gene also have an increased risk of invasive lobular breast cancer.[29–31] Defects in the serine/threonine kinase 11 (*STK11*) genes can lead to Peutz-Jeghers syndrome; people with this disorder develop pigmented spots on their lips and in their mouths as well as polyps in their urinary and gastrointestinal tracts, and have an increased risk of many types of cancer, including breast cancer.[29,31] The partner and localizer of *BRCA2* (*PALB2*) gene makes a protein that interacts with the protein made by the *BRCA2* gene.[12,29,31] Mutations in this gene can lead to an increased risk of breast cancer.[12] It remains unclear if the *PALB2* gene mutations increase the risk for ovarian or male breast cancer.[12,31]

Family History of Breast or Ovarian Cancer

A person's family history of breast cancer is another important nonmodifiable risk factor.[28] Of most importance is one's family history of breast or ovarian cancer, specifically first-degree relatives (e.g., mother/father, sister/brother, or daughter/son) with development of a breast or ovarian cancer prior to age 50.[28] A health history should include a minimum of first- and second-degree relatives with cancer, with an update annually.[28] The type of cancer, age at onset, and lineage should be documented. A woman with a health history that includes one first-degree relative with breast cancer has an increased relative risk of 1.8 (based on that one risk factor).[12] Thus, if a woman already has the average lifetime risk of 12% for the development of breast cancer, her personal risk has potentially increased to 21%.[12] The larger the number of first-degree relatives with breast or ovarian cancer, the higher one's risk is to develop either or both diseases. For example, a woman with two first-degree relatives with breast cancer has an increased relative risk nearly 3 times above normal, or nearly 40%.[29] Three first-degree relatives lead to an increased relative risk of 4, or nearly 50%.[29] The risk increases further when the affected relatives were diagnosed prior to age 50.[12]

The number of second-degree relatives (e.g., aunt/uncle, niece/nephew, grandchildren, half-siblings, or grandmother/grandfather) with breast or ovarian cancer is also a significant risk factor, even when no first-degree relatives have these diseases.[22,28] For example, when a woman has two second-degree relatives with breast cancer (e.g., two aunts diagnosed before age 50), her risk can be as significant, or higher than having a mother diagnosed with breast cancer before the age of 50.[22,28]

Race/Ethnicity

Non-Hispanic white women make up the largest group with breast cancer in the United States, followed by African American women, and then Asian/Pacific Islander women.[1] The risk of death from breast cancer is higher in African

American women than in non-Hispanic white women, especially in younger, premenopausal women.[32,33] For many years the increased death rate for African American women was blamed on their late presentation for medical care and lack of participation in adjuvant treatment. One of the most significant findings in modern breast cancer research, however, is the discovery that African American women are more commonly diagnosed with aggressive triple-negative breast cancer (TNBC). TNBC signifies negative estrogen and progesterone receptors and negative human epidermal growth factor receptor (HER2/neu) status.[32,33] These factors rule out the use of anti-estrogen or aromatase inhibitor drugs or targeted agents such as trastuzumab. This finding has encouraged researchers to identify factors related to triple-negative disease so that providers can administer personalized chemotherapy regimens specific to type of breast cancer, age, and race.[32,33]

Breast Density

Breast density is a risk factor for breast cancer development. Many premenopausal women have dense, fibrous breasts with significant amounts of firm glandular tissue. Higher density of breast tissue can also be found in postmenopausal women on hormone replacement therapy.[34] Breast density may be inherited, but is an independent risk factor for breast cancer development and may increase a woman's risk by 4 to 6 times the baseline risk.[34,35] Dense breasts are more difficult to examine due to the increased lumpiness inherent to fibroglandular parenchyma.

The radiographic appearance of breast tissue varies among individuals because of differences in cellular distribution of adipocytes, stroma, and epithelium.[34,35] The x-ray attenuation properties of each component in imaging are more difficult to discern in dense breasts due to white coloration of dense tissue.[34,35] In a mammogram, fat appears dark, while epithelium and stroma appear white, the appearance that the radiologist uses to define mammographic density.[34]

A number of factors can affect breast density including age, pregnancy, genetics, medications, and menopausal status.[36,37] Breast density is unmodifiable if a woman has done everything possible to modify her exogenous and endogenous estrogen sources, such as elimination of "natural," prescribed, over-the-counter, and food sources of estrogen, and the addition of tamoxifen, raloxifene, or an aromatase inhibitor, respectively.[38] The use of exogenous hormones may sustain or increase density, or women may continue to have dense breast tissues throughout their lifetime despite nonpharmaceutical interventions.[36,37]

Abnormal Biopsy Results

Breast tissue obtained with a biopsy procedure is thoroughly examined for any gross or cellular abnormalities. Pathological findings of atypia or lobular carcinoma in situ (LCIS) in breast tissue are nonmodifiable factors that may significantly increase a woman's risk of future breast cancer development.[37] Women with findings of atypical ductal or atypical lobular hyperplasia have a greater than 4 times risk of breast cancer development.[36,38] LCIS is an incidental biopsy finding that increases a woman's chance of breast cancer development by 7% to 12% in either breast.[36,39] Treatment for atypia or LCIS include an excisional biopsy in the event that the initial biopsy was a core-needle biopsy.[39] A larger biopsy is performed to ensure that foci of DCIS or invasive breast cancer are not located adjacent to the area of atypia or LCIS.[39,40]

Radiation Therapy to Chest

Women with a history of radiation therapy to the chest wall or mantle radiation for the treatment of Hodgkin disease when they were 10 to 30 years of age are at increased for breast cancer due to the inherent radiation-induced damage of tissues.[41] This risk increases every year; therefore, this group of women need to be screened after age 18 and followed very closely with early mammographic screening.[41]

Personal History of Breast Cancer

A personal history of breast cancer may increase the risk of a second breast cancer in the affected or contralateral breast, although it is not common.[42,43] In a retrospective study that examined the health records of 170 women with bilateral breast cancer and 1677 women with unilateral breast cancer, the following issues were significant ($p < 0.05$) in the bilateral group: young age at onset, premenopausal status, birth of first child after age 30, family history of breast cancer, history of benign mammary disease, and tumor size greater than 5 cm.[4] Women who were diagnosed with early-onset breast cancer (e.g., before age 40) or had a family history of breast cancer were significantly more likely to develop a second primary breast cancer in the ipsilateral or contralateral breast.[42] A personal history and known genetic predisposition in the *BRCA1* or *BRCA2* genes may contribute to the excess risk (e.g., 40% to 50%) of subsequent breast, ovarian, or fallopian tube cancers among women diagnosed at a young age.[19,22,42]

Endogenous Hormone Status

High endogenous hormone levels, including high levels of estrogen or testosterone, are another risk factor intertwined with the woman's genetic milieu that increases her risk 2 times as compared to those women with low endogenous hormonal levels.[43] High circulating estrogen levels are common in premenopausal women, but far less common in postmenopausal women unless obese or with chronic alcohol intake.[43–46] Endogenous hormone levels can typically be modulated by the addition or deletion of hormone-stimulating drugs (e.g., tamoxifen or raloxifene).

Women with an inherent high level of bone mineral density may also be at increased risk of breast cancer due to their stores of endogenous estrogen.[47] High bone mineral density is not an independent risk factor, but rather a marker of increased estrogen stores.[47]

Age at Menarche/Menopause

A girl's age at menarche, especially age younger than 12 years, and a woman's age (average 55 years) at menopause (the age when a woman undergoes a bilateral oophorectomy or when she has experienced 12 consecutive months without menstrual cycles) are time points at which endogenous hormone levels are important for breast cancer development.[44,48] These time points are considered somewhat nonmodifiable, although multiple interventions can be discussed to change a woman's endogenous hormonal level.[44,48] In some women, endogenous hormone levels can be decreased by surgery (bilateral oophorectomy), medications (tamoxifen, raloxifene), and first full-term pregnancy before age 30 with lactation.[46,48–52] Timing of pregnancy may or may not be altered depending on partner status, lifestyle, and ability to get pregnant and maintain a full-term pregnancy.

Age at First Full-Term Pregnancy

Pregnancy with the first full-term birth occurring after age 30 and nulliparity are risk factors that increase the risk of breast cancer due to their effects on endogenous estrogen levels.[48,49] When a woman experiences a full-term pregnancy prior to age 30, her endogenous estrogen levels are interrupted, which is protective and may decrease a woman's lifelong personal risk of breast cancer by 50%.[50,51] In contrast, the pro-inflammatory microenvironment that exists within the mammary gland after pregnancy may increase the risk of breast cancer, especially in a mother older than 35 years.[52] Multiple full-term pregnancies in younger women may confer greater protection from breast cancer, especially if lactation occurs with all of her children.[51,52] Pregnancy may or may not be modifiable, although in women with other increased risk factors, full-term pregnancy at a younger age may be of consideration as a prevention mechanism.[51,52]

Diethylstilbestrol Exposure

Diethylstilbestrol (DES) is a synthetic estrogen and a known carcinogen. DES was used in women during the 1940s through the 1970s to maintain pregnancy and prevent miscarriage.[53] Women whose mothers took DES have a 30% increased risk factor for breast cancer due to its effects on breast cellular structure.[53]

Personal History of Other Cancers

Hereditary cancer syndromes may occur in persons with a previous cancer diagnosis, including breast, ovarian, uterine, cervical, prostate (not in women), colorectal, melanoma, and pancreatic cancers. Women with a personal history of cancer need to be screened for these cancers to improve their chances of early detection and optimal outcomes.[42]

MODIFIABLE RISK FACTORS

Modifiable risk factors are those that individuals can do something to modulate, although the person is not always successful in achieving the desired outcome, or for some reason the person's physiologic outcome may not lead to the desired result. Modifiable risk factors are often important to disease prevention and should be taught to patients, although the healthcare professional must realize that each preventive intervention is the person's own prerogative, whether or not the professional agrees.

Exogenous Hormonal Level

Hormone Replacement Therapy

The use of exogenous hormones (estrogen, progesterone, testosterone) has been shown to increase the risk of breast cancer in postmenopausal women.[44,45] The risk may be even greater when hormones are taken in early menopause, as opposed to years later during full menopause.[45,46] The risk returns to its original level 5 years after cessation of hormone therapy.[46,47] The use of estrogen alone may or may not be an independent risk factor for breast cancer development,[45,46] although continued use of exogenous estrogen may hasten death in women with breast cancer due to an increased risk of metastatic disease.[45] High levels of free and circulating testosterone in premenopausal women may increase their risk of breast cancer by 80%,[43] an issue that is worrisome for women who use compounded hormone pills and creams.

Fertility Drugs

The use of fertility drugs and their relationship to breast cancer risk remain under study, as the number of women seeking help to achieve a full-term pregnancy continues to increase.[54] Of concern are the specific drugs that can alter fertility and the endogenous and exogenous hormonal levels, including luteinizing hormone (LH), gonadotropin-releasing hormone (GnRH) analogues/agonists, human chorionic gonadotropin (hCG), progesterone, and clomiphene citrate.[54–56] The precise effect of infertility hormonal treatment on development of breast cancer is difficult to determine as infertility itself may increase a woman's risk of breast cancer.[54]

Hormonal Contraception

Hormonal contraceptives include estrogen–progestin combination drugs prescribed in any manner of delivery: oral, transdermal, vaginal, or intrauterine.[57] The breast cancer risk associated with birth control hormones occurs secondary to their proliferative effect on breast tissue and potential direct carcinogenic effects on genes.[58] Oral contraceptives containing high doses of estrogen infer a higher percentage increase in breast cancer relative risk, although the link is uncertain for current low-dose estrogen preparations.[58] Ten years after women stop using birth control pills, they may have a similar risk for breast cancer as those women who did not take these pills.

Pregnancy

Younger age at first full-term pregnancy (i.e., prior to age 30) and a larger number of pregnancies are factors that may decrease a woman's risk of breast cancer as compared to nulliparous women or those seeking pregnancy after age 30.[48,52] Interestingly, there may be an increased risk of breast cancer development in the years immediately following pregnancy due to the pro-inflammatory microenvironment that occurs in the breast, an ideal environment for cancer development.[52]

Lactation

Breast cancer development in women with a history of lactation for 1 year is less common than in women who do not breastfeed.[50] Conversely, breast cancer development with its multiple cellular evolutions may be slightly increased during and immediately after lactation due to the effects of hormonal stimulation, especially in women with an unknown genetic risk.[52] Extended periods of breastfeeding do not qualify as an independent risk factor but may be associated with cumulative estrogenic exposures and decreased ongoing progesterone exposures.[49]

Increased Socioeconomic Status

High socioeconomic status (SES) is a risk factor for female breast cancer.[59] A study of early life stages and adult-onset breast cancer noted that a mother's educational level and family economic status are directly related to the incidence of breast cancer.[59] In another study using Surveillance, Epidemiology, and End Results (SEER) data, the SES of all racial and ethnic groups were reviewed. Survival was improved with higher SES for members of all racial and ethnic groups, but especially for non-Hispanic white and Asian/Pacific Islander women as compared to non-Hispanic black and Hispanic women.[60] In regard to mortality of non-Hispanic whites as compared to non-Hispanic blacks, survival was slightly higher among non-Hispanic black women in low-SES areas versus non-Hispanic white women in high-SES areas (7.1% and 6.8%, respectively).[60]

An inverse relationship is associated with the incidence of breast cancer morbidity and mortality and lower levels of socioeconomic status. Breast cancer outcomes in minority women with a lower socioeconomic status are typically worse than those in women with a higher socioeconomic status.[61] Differences in insurance status, race, and stage at diagnosis are important components of SES disparities and are associated with approximately two-thirds of SES disparities.[62]

Occupational Exposure

Overall, exposure to environmental pollutants has not been shown to confer an increased risk of breast cancer.[63] However, a study of Mexican women ($N = 2044$) living in northern Mexico and their exposure to arsenic in drinking water demonstrated an increased risk of breast cancer development, depending on the person's ability to methylate inorganic arsenic.[64] Occupational exposure to potential carcinogens may increase one's risk, as demonstrated in a study of Alaskan women ($N = 170$) and selected chemical exposure.[65]

Long-term (e.g., greater than 20 years) of night shift work may be a nongenetic risk factor for breast cancer in women.[66] Working at night with artificial light exposure may decrease melatonin production: melatonin is a tumor suppressor agent for estrogen exposure.[66] Such interrupted circadian rhythms commonly occur in nurses, flight attendants, and factory workers who work at least one night time shift per month.[67] In the United States and Europe, at least 15% to 20% of the population works at night and is exposed to artificial light.[1]

Lifestyle Risks

Several of the lifestyle risks for breast cancer have been targeted by *Healthy People 2020*, whose goals are to improve overall health, including that of patients with cancer.[68] Lifestyle habits that are predicted to be related to cancer development include diet, physical activity, weight management, alcohol moderation, smoking cessation, obesity, and stress reduction.[68–87]

Diet

A definitive relationship between diet and breast cancer risk remains unproven.[76] A few retrospective studies have indicated that a diet high in fruits and vegetables may be helpful for preventing estrogen-negative breast cancers, but more prospective studies are needed to confirm these relationships.[76] A colorful (e.g., fruits and vegetables) low-fat plate is promoted as heart healthy and remains important

in adolescent women as a potential preventive intervention for premenopausal breast cancer.[68] Soy has been extensively studied due to the low incidence of breast cancer in Asian women, although such studies have not yielded definitive results in Western women.[77] A plate with a high glycemic load or fat-laden diet may promote hyperglycemia, pre diabetes, or insulin resistance, all of which are risk factors for breast cancer development.[68,69]

Physical Activity

Evidence continues to mount that physical activity in postmenopausal women may decrease breast cancer risk.[16–18] This benefit may reflect the effect of exercise on energy balance, hormones and body mass.[16–18,78] Retrospective studies show that women who exercise regularly have a decreased risk of breast cancer, although prospective studies have not yet supported a long-term improvement.[78] A study of breast cancer–affected mice given chemotherapy compared exercise to no exercise and found that chemotherapy plus exercise was significant in delaying tumor growth ($P < 0.001$).[78] Future prospective studies need to be conducted with biologic measures to measure the optimal biologic effect of exercise.

Obesity and Weight Management

Obesity is a risk factor for the development of breast cancer due to potential increased estrogen stores in fat, and the potential increased insulin resistance secondary to carbohydrate and sugar metabolism.[68–70] Obesity rates are increasing rapidly in the United States.[68] Limited exercise habits and continual increases in adult-onset diabetes collectively point to necessary education for women and their personal commitment to weight reduction and a healthier lifestyle, ideally at a young age.[70]

Women who are overweight may have a 1.5 times increased risk of breast cancer, while women who are obese may have a 2.5 times increased risk due to greater estrogen stores in their fat.[69,70] Obesity itself is an independent risk factor and indicates a poorer prognosis in women with node-positive breast cancer.[82] Referral to a dietician who is knowledgeable about breast cancer, menopausal metabolism, weight gain with adjuvant therapy, and decreased activity may improve patients' ability to achieve weight loss.[85]

The development of central obesity (e.g., increased anterior to posterior girth) is one of the most concerning obesity-related conditions, as it may indicate deposits of fat around vital organs.[68] Central obesity is one of the diagnoses included in metabolic syndrome, another collective risk factor related to the development of diabetes mellitus and cancer.[69] Diabetes is a disease related to inflammation and insulin resistance, which are also factors related to to cancer development.[69]

Stress Reduction

Stressors related to inflammatory changes in the body are nonmodifiable risk factors, but stress related to stressful situations and distress may increase a woman's risk of breast cancer occurrence and recurrence. In one study, women with breast cancer ($N = 100$) undergoing treatment, at its end, and 3 and 6 months later self-reported moderate to severe distress at the first three time points, with a drop in stress being noted at 6 months after the end of treatment.[86] For women with extended treatments, the increased level of distress could endure for more than 18 months.[86] A study of survivors of stage II and III breast cancer ($N = 227$) over 11 years indicated that women who participated in structured focus groups had a significantly ($P = 0.03$) increased disease-free and extended life as compared to similar cohorts who were not in structured support groups.[87] These findings suggest that stress is a distinct issue requiring intervention to improve outcomes.

Alcohol Moderation

Alcohol consumption is positively associated with risk of breast cancer and breast cancer recurrence due to increases in endogenous hormones.[72,74,79,80] Consumption as low as one drink per day may increase a woman's relative risk, and more than one drink per day can significantly increase breast cancer risk and breast cancer deaths.[80] Alcohol increases androgen and estrogen levels, both of which are risk factors for breast cancer development.[72,74] Interactions between type of alcohol (e.g., wine, beer, liquor), dietary factors, and obesity need to be better understood before specific prevention recommendations can be made.[72,74,80]

Smoking Cessation

Studies have not proven a distinct link between breast cancer risk and smoking, as their results may be confounded by concomitant alcohol use.[75] In a recent meta-analysis ($N = 7388$), female smokers, both premenopausal and menopausal, experienced increased breast cancer development.[75]

MYTHS RELATED TO BREAST CANCER RISK

Several myths exist in regard to breast cancer development that can be barriers to screening or access to care, and that may increase patient's distress including false beliefs about ethnic and racial differences, frequency of abortions, antiperspirants, hair dye, and breast implants. The effect of breast cancer navigators in influencing African American women ($N = 69$) with breast cancer was studied to determine their effect on several psychosocial factors, including myths and stigma related to breast cancer.[88] This study demonstrated the positive effect of a navigator in explaining the breast cancer trajectory for optimal outcomes.[88] False knowledge about cancer in persons from Turkey ($N = 419$) was studied using self-reported questionnaires.[89] Researchers found that the majority of participants reported false information,

with this tendency being significantly correlated with level of education.[89] Knowledge of the beliefs held by members of different racial and ethnic groups is important to initiate a trusting relationship and appropriate treatment.[88–90]

Historically, abortions were thought to increase a woman's risk of breast cancer due to the failure to complete a full-term pregnancy. In a meta-analysis of 15 prospective studies, nonsignificant associations between breast cancer and abortion were found among several groups including in nulliparous women, women with first abortion after 30 years of age, women with abortion before or after first full-term pregnancy, and women with 2 or more abortions.[91]

The use of antiperspirants with aluminum additives has erroneously been thought to obstruct axillary lymphatic drainage and induce breast cancer. A detailed study of various genes in breast cancer showed no relationship between tissue aluminum concentrations and the development of breast cancer.[92]

The use of hair dye and its association to breast cancer is a persistent myth.[93] In a meta-analysis of 79 inclusive research articles, the link between hair dye and breast cancer was not upheld.[94] Exposure to various chemicals in aerosol hair products may be an occupational risk for hairdressers who are continuously exposed to these chemicals.[95]

Cosmetic breast augmentation with silicone filled implants or implants with silicone lining has been studied for its association with increased breast cancer risk. A meta-analysis of multiple studies confirmed there was no association between breast implants and breast cancer.[96]

BREAST CANCER RISK MODELS

Several risk estimation models for the development of breast cancer have been used for the past two to three decades. The various models are essentially based on two approaches: (1) chance of mutation in high-risk genes or (2) risks of developing breast cancer with or without gene mutations.[97,98] Two frequently used models are the Gail and Claus risk models. The Breast Cancer Risk Assessment Tool (i.e., Gail model) focuses on nongenetic risk factors and abnormal biopsy results, although information on family history is limited to first-degree female relatives.[99,100] The Claus model assesses the risk level based on extended family history of breast cancer.[101,102] A third model, the Ford model, is based on personal and family history characteristics to identify the presence of any germline mutation of the *BRCA* genes.[103] The International Breast Cancer Intervention Study (IBIS), or Tyrer–Cuzick model, and those models that are more specific to *BRCA1* or *BRCA2* mutations, such as BOADICEA and BRCAPRO, are also useful.[103–109] As new biologic information continues to be discovered (e.g., mutations in the *PALB2* and *RAD51* genes), risk models will account for these new data so as to assess the woman's true risk for the development of breast cancer. A review of existing models highlights key data related to the various risk models (**Table 47-2**).[1,28,34,36–38,97–104]

Gail Model/Breast Cancer Risk Assessment Tool

The Gail model, since renamed the Breast Cancer Risk Assessment Tool (BCRAT), is an interactive tool designed by scientists at the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) to estimate a woman's risk of developing invasive breast cancer.[98,99] BCRAT estimates a woman's absolute composite risk of developing invasive breast cancer for the next 5 years, and her absolute cumulative lifetime risk (e.g., 90 years of age) using an online computer program (http://www.cancer.gov/bcrisktool/). Lifetime risk estimates are higher than 5-year age interval estimates because breast cancer risk increases with age. While women's risk may be accurately estimated with this model, BCRAT is unable to precisely predict which woman will develop breast cancer.[99] Women who do not develop breast cancer may have higher risk estimates than women who do develop breast cancer, as the instrument is not specific to each woman.[99]

The BCRAT instrument is easy to use in the clinical setting as it is brief and concise. The assessed risk factors include history of abnormal biopsy (e.g., atypia or lobular carcinoma in situ), presence or absence of genetic mutation, current age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, previous breast biopsy, number of previous breast biopsies, number of abnormal biopsies (e.g., atypia or lobular carcinoma in situ), race, and ethnicity.[99]

Claus Model

The Claus model is based on empiric data from the Cancer and Steroid Hormone Study.[110] This model provides risk estimates for women with a positive family history of breast cancer using her age, number of first- and second-degree relatives (including paternal relatives), and their age at onset of breast cancer.[101] The Claus model does not account for more than two relatives with breast cancer, risk factors, or personal factors that may increase a woman's risk of breast cancer.

Tyrer–Cuzick/IBIS Assessment

The Tyrer–Cuzick/IBIS (computer program) breast cancer risk assessment is a more comprehensive risk assessment tool than the Gail model (BCRAT). This model includes additional information relative to breast cancer risk, age, extended family history of breast and ovarian cancer, child birth history, history of breast biopsy and related pathology, age of menarche and menopause, exposure to

TABLE 47-2

Models to Assess Breast Cancer Risk

Breast Cancer Risk Assessment Item	Gail Model/or Breast Cancer Risk Assessment Tool	Claus Model	Ford Model	Tyrer–Cuzick Model
1. Woman's current age	X	X	X	X
2. History of abnormal biopsy (e.g., atypia or lobular carcinoma in situ)	X			
3. Presence or absence of genetic mutation	X			
4. Age at menarche	X			X
5. Age at first live birth	X			X
6. Number of first-degree relatives with breast cancer	X	X	X	X
7. Has woman ever had a breast biopsy	X			
8. Number of breast biopsies	X			
9. Number of abnormal breast biopsies	X			
10. Race/sub-race	X			
11. Ethnicity	X			
12. Body mass index based on height and weight				X
13. Age at menopause				X
14. Presence of atypical hyperplasia in biopsy	X			X
15. Presence of lobular carcinoma in situ				X
16. Number of second-degree relatives with breast cancer		X	X	X
17. Age at onset of cancer		X	X	X
18. Presence of bilateral breast cancer			X	X
19. History of ovarian cancer			X	X
20. Male breast cancer			X	

Source: Data from American Cancer Society[1]; Melchor and Benitez[28]; Jung et al[34]; Neal et al[36]; Santen et al[37]; Visvanathan et al[38]; Evans et al[97]; National Cancer Institute[98]; Gail et al[99]; Constantino et al[100]; Claus et al[101]; McTiernan et al[102]; Ford et al[103]; Tyrer et al.[104]

postmenopausal hormones, Ashkenazi Jewish heritage, and height/weight.[104] A statistical curve is generated representing the person's lifetime risk compared to the "standard risk" and the chance of having *BRCA1* or *BRCA2* mutations.

Ford Model/BRCAPRO

The Ford model of breast cancer risk assessment is based on personal and family history to determine if a germline *BRCA* mutation exists. This model is linked with BRCAPRO, which also uses a version of the Claus model.[103]

Limitations of Current Models

A comparison of items assessed in the BCRAT, Claus, Ford, and Tyrer–Cuzick models is necessary to visualize the pros and cons of each model. Current versions of the models provide an accurate assessment of lifetime risk (Table 47-2). Unfortunately, none of the models accurately assesses which women will or will not develop breast cancer. Missing from the Gail model are measures of genetic risks and extended family history of breast cancer.[99,100,111,112] The Claus model assesses the risk level based on family history of breast cancer, whereas the Ford model includes personal and family history characteristics to identify the presence of any germline mutation of the *BRCA* genes. Both the Ford and Claus models lack the depth of information gained from the Tyrer–Cuzick model.[100,101] A recent study from the United Kingdom suggested that the BCRAT may under-predict a woman's actual risk as compared to the Tyrer–Cuzick model.[113] Another study was conducted to compare the four breast cancer risk assessment tools and a manual assessment of the patient's risk.[111]

The Tyrer–Cuzick model appears to consistently provide the most accurate risk estimation for high-risk women

based on family history and hormonal factors. The Gail, Claus, and Ford models all appear to have limited predictive validity in this cohort. Added features of the Tyrer–Cuzick model include broader family history (e.g., second-degree relatives), age of cancer onset in family members, and use of hormone replacement therapy.[97,101–109,111]

A new model that utilizes histologic information from benign breast biopsies with incorporation of the woman's individual demographic data and breast environment is an innovative approach to risk modeling.[114] The benign breast disease–breast cancer (BBD-BC) model predicts the risk of breast cancer using biopsy criteria that incorporate assessment of the breast cancer tissue at risk and a description of cellular characteristics.[114] Other models consider only the final pathological findings. Further testing of the BBD-BC model may yield a unique approach to risk assessment.

Recommendations for Improved Models

To rectify identified gaps in the existing models, additional risk factors should be added to current models and measured through prospective studies.[115,116] The most powerful risk factors, including mammographic density[34,35,52,116–120] and presence of single-nucleotide polymorphisms (SNPs),[111,116] estimation of hormone levels,[46] lifestyle factors, measures of body composition, and polygenic risks, should be incorporated and validated into risk assessment forms. Other important factors are plasma estrogen and androgen levels, bone density, weight and weight gain, BMI, height loss, age at menopause, and fracture history. These elements are not currently used in any comprehensive risk prediction model because of the lack of prospective validation.

Precision in measurement is necessary to determine whether a woman needs tamoxifen or raloxifene therapy or another prophylactic intervention. The development of a statistical model that can estimate each woman's probability of developing breast cancer would enhance providers' ability to identify high-risk individuals, allowing for earlier or more frequent screening and counseling of behavioral changes to decrease risk.[116] These models could guide the design of future chemoprevention and lifestyle alteration studies that include variables in the following categories: breast density, serum and breast tissue biomarkers, hormone levels, and polygenic risks.[116]

The influence of breast density is more difficult to ascertain when density is less than 50%, due to subjective evaluation. In clinical trials that measure breast density, it is necessary to have a measurement system that is both reliable and valid. Currently, no validated estimation methods exist for full-field digital mammography. Six density assessment methods showed that percent density (PD) was inversely associated with age, BMI, parity, and postmenopausal status for mammographic screening.[119,120]

Serum biomarkers have yet to illuminate factors that can be used to determine a woman's risk of developing breast cancer or actual presence of breast cancer. Ongoing research into circulating metastatic breast cancer cells continues to evolve in that setting, but the results remain inconclusive for utilization in breast cancer prevention models. Increased fasting insulin levels are associated with poor outcomes in breast cancer, but have not yet been confirmed as primary risk factors.[121,122] Although serum cytokines may indicate increased inflammation that correlates to cancer formation, they do not directly define breast cancer risks for prevention.[123] Micro-RNA (miRNA) can be identified in the serum that serves as a regulator of multiple proteins that are associated with breast cancer.[124,125] Extraction and quantification of specific miRNAs from serum may emerge as an accurate, noninvasive blood-based test of early-stage breast cancer detection in the future.[124,125]

Early mammary changes (e.g., ductal or lobular atypia) and advanced mammary changes (e.g., LCIS, DCIS) are pathologic changes in breast tissue that may be predictive of breast cancer risk, with or with or without family history or personal risk factors. The use of breast tissue biomarkers to predict a woman's risk of developing breast cancer is novel, yet pertinent to any risk model.[114] Changes in breast tissue can be observed as occult findings in biopsy specimens, in breast adipose tissue, or in cytological specimens from random periareolar fine-needle aspiration (RPFNA)[126] or nipple aspirate fluid (NAF).[127,128]

The measurement of endogenous hormones may provide another biomarker of risk status in postmenopausal women who are at increased risk of breast cancer development. In a recent study, plasma estradiol, estrone, estrone sulfate, testosterone, dehydroepiandrosterone sulfate, prolactin, and sex hormone-binding globulin were measured; the researchers determined that these endogenous hormone levels were pertinent to improving the risk prediction for postmenopausal invasive breast cancer.[129]

Breast cancer vaccines have been developed in mice and will soon be tested for human use. Data obtained from one mice study using combined vaccines demonstrated that stimulating antigen-specific T-helper (Th) cells composed of a limited number of immunogenic proteins as expressed in high-risk lesions can inhibit the development/progression of mammary cancer.[130] Ultimately, vaccination may be an effective strategy for breast cancer prophylaxis, targeted at high-risk and older women who may be harboring occult preinvasive disease. The data suggest that some chemoprevention agents may act synergistically with vaccines.[130]

Nurses working with populations at increased risk for breast cancer must be aware of the multiplicity of breast cancer risks to screen and educate women appropriately. Use of risk models may be common practice in high-risk clinics to highlight individual risks and provide counseling based on those risk factors. Nurses working in ambulatory

settings with breast cancer survivors can assess their patients for any changes in breast cancer history or any related risk factors. In addition, nurses should be prepared to answer the questions of family members who accompany patients with cancer to the clinic. Knowing the correct genetic test to order within each family requires an individualized approach and full knowledge of family history and any prior genetic tests.[131]

PREVENTION, SCREENING, AND EARLY DETECTION

The prevention of breast cancer includes a number of interventions catalogued as primary, secondary, and tertiary strategies. The *primary prevention* strategies for breast cancer are habits or activities to help avoid the onset of breast cancer and include the multitude of risk factors that were discussed in the previous section under "Etiology and Risk Factors." The prevention of breast cancer is not as clear-cut as the prevention of lung cancer (e.g., tobacco cessation) due to the heterogeneity of the disease and the lack of knowledge of what causes breast cancer in most women and men. There are often intersections between specific risk profiles and secondary or tertiary prevention strategies.

PREVENTION

Optimal risk reduction strategies for breast cancer have yet to be determined in large prospective studies, although results from smaller prospective studies indicate various healthy lifestyle habits may have a protective effect against breast cancer development.[69–76] Lifestyle modifications are also a significant part of tertiary prevention once a person is diagnosed with an abnormality that increases his or her risk, or with an actual cancer. Patients' health records should be scrutinized to ensure that every opportunity to improve outcomes is appreciated.

Identification of Individual Risks and Programming

Healthy People 2020, a national guide for health promotion and disease prevention in the United States, recommends that all Americans focus on smoking cessation, weight control, dietary improvements, exercise, and stress management to ensure good health.[132] This is an important area for nurses, advanced practice nurses, and providers in oncology and non-oncology practices to address; these topics are rarely discussed in daily practice with patients with cancer, yet they are important tertiary strategies to prevent recurrence or occurrence of a new cancer.[133]

The creation of cancer survivorship care plans is a more recent strategy of oncology professionals to focus on healthy lifestyle factors. The survivorship care plan consists of a treatment summary as well as a care plan that outlines health and wellness practices specific to each cancer,[134] congruent with the *Healthy People 2020* guidelines. In accordance with survivorship care as recommended by the American Society for Clinical Oncology[135] and the National Comprehensive Cancer Network's clinical practice guidelines in oncology for survivorship care,[136] the oncology team should review healthy lifestyle practices with reference to available programs at the area institutions and in the patient's community. These practices can include, but are not limited to, weight management programs, referral to a dietician, exercise sites or physical therapy programs, smoking cessation programs, alcohol cessation programs including Alcoholics Anonymous, and stress reduction strategies such as exercise, medication, or stress management programs.

Chemoprevention

Chemoprevention entails the use of agents to reduce the risk and delay the development or recurrence of cancer. Chemoprevention for breast cancer is provided by selective estrogen receptor modulators (SERMs), such as tamoxifen or raloxifene, or aromatase inhibitors (AIs), such as exemestane or anastrazole.[137,138] Chemoprevention is considered a primary prevention strategy in patients with a significant risk profile, such as those with an increased family history of breast cancer or in whom premalignant cells were identified during a breast biopsy. Chemoprevention in breast cancer can also be a part of the tertiary prevention of premalignant or malignant changes in the breast. Women with hormone-positive breast cancer take a SERM or AI to prevent metastatic cancer and a second primary cancer in the contralateral breast. The use of anti-estrogen pharmaceutical agents is an effective way to reduce a woman's risk of breast cancer development and may decrease the occurrence of a primary or contralateral estrogen-positive breast cancer by at least 38% over a 10-year period.[137–142]

Tamoxifen

Several prospective trials have been conducted to investigate the ability of tamoxifen to reduce the incidence of breast cancer in high-risk women. The Breast Cancer Prevention Trial (BCPT) was a randomized controlled study of women aged 35 to 59 years with a high risk profile, or women 60 years of age and older without any other risk factors. The risk reduction was 48% for estrogen-positive breast cancers and there was no effect on estrogen-negative tumors.[139]

A more current study, the International Breast Cancer Intervention Study I (IBIS-I), compared tamoxifen to placebo as breast cancer chemoprevention. The IBIS-I study was a randomized controlled trial in premenopausal and

postmenopausal women aged 35 to 70: Women were randomized to either tamoxifen or a placebo for 5 years. Estrogen-positive invasive breast cancers showed the largest risk reduction (34%) with the tamoxifen therapy, along with ductal carcinoma in situ (35%).[142] No effect was seen in the prevention of estrogen-negative breast cancers.[142]

Additionally, a meta-analysis was conducted to measure the effect of tamoxifen on the contralateral (e.g., unaffected) breast in women with *BRCA1* or *BRCA2* gene mutations. Tamoxifen was effective in preventing contralateral breast cancer in 44% of women with a *BRCA1* or *BRCA2* gene mutation as compared to a prophylactic mastectomy.[143]

Raloxifene

The Study of Tamoxifen and Raloxifene (STAR) trial found that tamoxifen and raloxifene produced similar outcomes, but women reported fewer side effects with raloxifene.[141] Raloxifene was 76% as effective as tamoxifen, but did not protect against ductal carcinoma in situ.[141] Similar data were noted in the concomitant Multiple Outcomes of Raloxifene Evaluation (MORE) study.[140]

Lasofoxifene

Lasofoxifene (dose of 0.5 mg/day) has demonstrated a superior protective effect (58%) for all types of breast cancer and DCIS.[144] The side effect profile of lasofoxifene is acceptable,[144] suggesting that additional study of this agent as breast chemoprevention is warranted.

Arzoxifene

A recent trial of arzoxifene demonstrated a 58% reduction in all breast cancers, although its effect was nonsignificant for the prevention of DCIS.[145] In addition to the SERMs, aromatase inhibitors have been tested for breast cancer prevention.[142,146–149] Breast cancer prevention has also been observed in several trials that are studying third-generation AIs (e.g., anastrozole, exemestane) for systemic treatment of early-stage breast cancer.[142]

Anastrazole

In the IBIS-II study, women were randomized to either anastrozole or placebo. After 5 years, a 53% overall reduction in breast cancer was seen in the intervention arm. After 7 years of therapy, there was a 69% reduction in the number of women with LCIS or atypical hyperplasia.[142]

Exemestane

The Mammary Prevention 3 trial (MAP3) showed a 65% reduction of breast cancer incidence in women taking exemestane as compared to placebo.[142]

In summary, the American Society of Clinical Oncology (ASCO) recommends that women aged 35 years or older and at high risk of breast cancer development should consider one of these potential life-saving interventions to reduce the incidence of estrogen-positive breast cancer.[38,142] Tamoxifen 20 mg/day for 5 years should be discussed. In postmenopausal women, tamoxifen or raloxifene 60 mg/day for 5 years or exemestane 25 mg/day for 5 years should be considered.[38] Despite the reduction in breast cancer incidence, these interventions do not demonstrate a reduction in mortality secondary to breast cancer.[38,142] Additional study is required to identify an agent that consistently protects women against estrogen-positive and estrogen-negative breast cancers.

Of note, only tamoxifen and raloxifene are approved by the U.S. Food and Drug Administration (FDA) for breast cancer prevention. While the statistics for breast cancer prevention are exciting, the use of these drugs remains much lower than expected. Women are reluctant to take these drugs (specifically tamoxifen) due to their side effect profiles, which include possible thromboembolism and uterine cancer. It is critical that nurses working with this population understand the relative risk of side effects as related to the benefits of taking a preventive drug such as tamoxifen. For example, the risk of uterine cancer is described as increased by 3% to 4%, which translates to 3 or 4 women per 1000, or less than 1%. Several investigational agents are also being studied to evaluate their effect on preventing breast cancer in high-risk women.

Metformin

Metformin is a drug widely used to treat non-insulin-dependent diabetes. It targets the enzyme (e.g., AMP-activated protein kinase) that regulates glucose uptake into the muscles.[122] In breast cancer prevention, metformin is being studied in obese, postmenopausal women with breast cancer.[122]

Bisphosphonate Clodronates

Bisphosphonate clodronates have demonstrated a 30% reduction in breast cancer recurrence.[138,150] These findings are preliminary and require further study. Women who receive bisphosphonates often have low bone density, a factor that is also associated with a decreased risk of primary breast cancer.[150]

Omega-3 Fatty Acids

A study of omega-3 fatty acids in mice indicated that diets enriched with omega-3 fatty acids inhibited early stages of HER-2/neu–mediated mammary carcinogenesis.[151] In addition, decreased development of mammary gland atypia (a histopathologic precursor to invasive cancer) was observed. Future human prevention trials of bioactive nutrients may seek the participation of women with premalignant conditions such as atypical ductal hyperplasia or carcinoma in situ.[151]

Vitamin D

The use of vitamin D as a prevention approach in solid tumors has been studied extensively.[152] Studies, including a Cochran review meta-analysis, indicate that vitamin D is not harmful, although its preventive properties may be minimal to nonexistent.[152]

Flaxseed

Flaxseed, the richest dietary lignin, is a phytoestrogen that has likewise been studied as a breast cancer mediator.[153] In one study, flaxseed intake and flaxseed bread were significantly associated with breast cancer reduction (odds ratio [OR] = 0.82, 95% confidence interval [CI] = 0.69–0.97 and OR = 0.77, 95% CI = 0.67–0.89, respectively).[153] These findings warrant a prospective randomized trial to confirm the outcomes. As dietary intake of flaxseed is modifiable, this finding may be an important breast cancer prevention strategy.[153]

Surgical Interventions

Surgery is a potential cancer prevention intervention for women at increased risk of breast cancer development, although it remains a difficult decision for many women. Varying situations or personal history may compel women to undergo bilateral mastectomy or oophorectomy, often due to fear or their increased risk factors. Despite the various systemic prevention options described previously,[154,155] many women choose surgery to eliminate their risks.

Bilateral Mastectomy

It is important that the oncology team fully discuss the pros and cons of prophylactic bilateral mastectomy. In the absence of a diagnosed malignancy, two to three appointments spaced a couple months apart may be helpful for the oncology team to embrace the woman's desires and goals. This allows a period of time for a woman to contemplate decisions about prophylactic surgery that she may make as a result of a new breast or ovarian diagnosis of a relative, or new information related to a personal or familial genetic mutation.

Despite removal of all visible breast tissue, breast malignancy may still occur in as many as 10% of patients, most commonly at the lateral chest wall, midaxillary line, below the clavicle, anterior chest, or supraclavicular or axillary lymph nodes.[156] Most women who undergo a preventive bilateral total mastectomy have the option to choose immediate or delayed reconstruction. When reconstruction is not an option due to health concerns or availability of a plastic surgeon, arrangements should be made to allow the woman to discuss future options. Prompt availability of external prosthetic options (e.g., postoperative prostheses/bras and permanent prostheses/bras) need to be provided to persons who do not undergo reconstruction. Otherwise, women may opt for bilateral saline expanders with permanent saline or silicone implants, or any of the various tissue-moving options.

Skin-sparing mastectomies will enhance restoration outcomes.[157,158] Consideration of preservation of the nipple and areolar complex may be contemplated as long as the woman realizes she must still undergo annual screening with mastectomy and twice-yearly clinical exams by the surgical team.[159] Surgical interventions will not include evaluation of the lymph nodes although a few nodes may be present in the tail of Spence, which extends into the axillary basin in some women.[158,160]

Bilateral Prophylactic Oophorectomy

Bilateral oophorectomy is a consideration for some women, depending on their family history and presence or absence of gene mutations.[161] Removal of both ovaries and fallopian tubes may bring great relief to those with a positive gene mutation, although a discussion must occur about the possibility of a cancer occurrence due to residual sloughed cells into the abdominal space or omentum.[161] The potential of acute menopausal symptoms needs to be reviewed, along with anticipated supportive interventions. Controversy remains as to the safety of systemic estrogen, although minimal concern exists for the use of local estrace cream or tablets.[162]

An estimated 15% of women are at increased risk for breast cancer development. Nurses and advanced practice nurses (APNs) working in primary care, gynecologic, and oncology offices should be familiar with simple risk models such as the Gail model/BCRAT or Tyrer–Cuzick online model and be able to calculate a woman's relative risk based on her family history of breast cancer, personal history of abnormal breast biopsy (LCIS or atypia), or genetic determinants.[116] One-to-one interaction between the woman and her provider yields increased knowledge of the risks and benefits of chemoprevention and sets the stage for ongoing dialogue.[154,163]

Nurses and APNs can have a significant impact during these stressful times in women's and their significant others' lives. Women who live with a significant risk do not wonder *if* they will develop breast cancer, only *when*. Women who are considering a prophylactic bilateral mastectomy may require significant emotional support as they make this difficult decision based on their high-risk profile. In women with lower-risk profiles, it is important for nurses to clearly explain individual risks, other potential interventions, and the permanence of bilateral mastectomy. Bilateral oophorectomy may hasten menopausal symptoms and physical changes such as atrophic vaginitis,[162] hot flashes,[164] and bone density issues.[165] Attention to symptom management and potential physical changes may aid the woman as she progresses through these stages.

SCREENING

The *secondary prevention* of breast cancer includes screening studies for asymptomatic women without clinical evidence of disease. Secondary prevention strategies include multiple radiographic screening techniques that can find a cancer at

its earliest stage or identify changes that warrant a biopsy. The choice of imaging studies is based on a woman's risk profile, although nearly always includes a mammogram due to the common risk factors of gender and increasing age.

Mammography

Mammography enables visualization of internal structures of the breast with minimal radiation exposure to the breasts (e.g., 1 rad per each breast). The American Cancer Society continues to recommend a baseline mammogram in women by age 40 to 50 depending on the woman's risk profile.[1] Mammograms are recommended as a choice for women at least every 1 to 2 years, depending on a woman's history and risk factors.

Since the publication of mammography guidelines by the U.S. Preventive Services Task Force (USPSTF), much unrest about the changing guidelines has occurred among the public and professionals.[166–169] The general female population has expressed difficulty understanding the new guidelines, which limit a woman's first mammogram to age 50, and possibly only every 2 years after that.[166–169] Professionals who traditionally have ordered mammograms for their patients starting at ages 35 to 40 and annually thereafter may have difficulty in changing their practice patterns. When an abnormality is found in a young woman age 40 to 50, the presumed value of mammography is supported without question. Young women, especially those with cancer, have voiced their concern about the changes in the guidelines and support annual mammograms due to their personal experiences. The Breast Imaging Commission of the American College of Radiology and the Society of Breast Imaging have reinforced that "every medical organization experienced in breast cancer (including the American Cancer Society, American Congress of Obstetricians and Gynecologists, American College of Radiology, Society of Breast Imaging, and National Accreditation Program for Breast Centers) recommend annual mammograms for women ages 40 and older."[166 (p.32)] Most importantly, women may avoid debilitating and life-changing breast cancer treatment when mammographic changes are detected early. The overall mortality rate may not change as suggested by the USPSTF, but the overall *morbidity* rate will remain improved as evidenced in current clinical practice.[169]

Dedicated mammography units provide high-quality images with a low dose of radiation that enable better images and a safer environment, respectively.[170] Conventional mammograms with screen film prints have been primarily replaced in the United States with digital mammography, which provides electronic images.[170]

Screening mammography in Western countries has expanded to full-field digital mammography, which offers several potential benefits as compared with traditional screen-film mammography.[171] Digital mammography is more accurate than conventional mammography due to the quality of the images, the ability of the radiologist to enlarge images and focus on areas of concern, the ease and quickness of the exam, the easy storage of files, and portability of files to other institutions.[170] Digital mammography is especially helpful in screening premenopausal women, women younger than age 50, and women with dense breast tissue due to the radiologist's ability to enlarge and manipulate images to view areas of concern.[170] New instrumentation is fitted with a photon-counting detector, which reduces doses of radiation by 40% to 60%, improves noise reduction, and has demonstrated a low mean glandular dose that further improves the safety of mammograms for women.[167–170] In addition, digital technology enables the use of advanced applications such as computer-aided detection (CAD) and tomosynthesis.[171]

Screening mobile mammography is an asset to any facility and community. Mobile mammography enables persons with access issues to take advantage of its presence and use cash, insurance, or state and federal funding to pay for their mammogram.[172,173] Most updated mobile units incorporate digital mammography devices that allow electronic transmission of the images to a radiology department.[173] One limitation of most of these units is the inability to perform special images, ultrasonography, or MRI on location. Therefore, in the case of recommended screening imaging beyond standard mammography or recommended additional imaging following the screening mammography, the woman must travel to the home institution to obtain additional films.

Computer-aided detection is a radiologic application to assist radiologists in the interpretation of digital mammography.[174] CAD implements software algorithms to analyze mammographic images, with the goal of improving the identification of underlying breast cancers.[174] The radiologist initially reviews the mammogram and develops an assessment. Next, CAD is applied and electronically marks potential abnormalities on the mammographic images, with the radiologist then reviewing these areas prior to making a final recommendation. A secondary advantage of CAD is its ability to convert film mammograms into digital images, which is helpful at sites that do not have digital mammography. While the film images are not the same as digital images, CAD does offer institutions the ability to digitally store their mammographic images.[174]

A retrospective study of data from 684,956 women with 1.6 million associated mammograms from 1998 to 2006 was done to examine the use of CAD at Breast Cancer Surveillance Consortium institutions.[175] Relationships between radiology performance, breast cancer prognostic characteristics, and cancer detection rates were compared to determine the efficacy and accuracy of CAD as well as its ability to assist radiologists in their interpretations.[174] Of note, all evaluated mammograms were traditional film mammograms that were converted to digital records. Researchers did not find significant improvements

($P > 0.05$) in the detection rates or prognostic characteristics of breast cancers with this technology as compared to the final assessment by the radiologists.[174] Further review of CAD must occur to evaluate its added cost to screening mammography. The application of CAD is being studied in hand-held ultrasonography as an approach to visualize abnormalities and store three-dimensional images,[175] as well as tomography.[176]

Ultrasonography

Ultrasound is an adjunct to other screening mechanisms, is less expensive that mammography, is readily available in breast centers, and requires no injected contrast or ionizing radiation. This technology has typically been a supplemental screening modality used to characterize smaller tumors in women with dense breasts as compared to mammography alone.[177] Ultrasonography focuses on an event that is palpable or seen on mammography or MRI. It is operator dependent, targets a specific area of the breast, and requires real-time presence of the radiologist to review images. Given these limitations, hand-held ultrasonography has not been widely used as a full breast screening modality.[178] In addition, hand-held ultrasonography can result in an increased number of false-positive results, lacks standardized techniques, and is nonreproducible.[179,180] Most recently, automated breast ultrasonography has been approved for use in the United States. It is intended for use in whole breast screening following a negative mammogram in women with dense breasts and no history of breast surgery or biopsy.[180]

Three-Dimensional Tomosynthesis

Newer modalities for breast screening will not immediately replace mammography but may provide the ability to diagnose early-stage cancer in women for whom mammography is less sensitive. The breadth of these breast screening tools has expanded beyond diagnostic interventions following mammography, to the point that they are now considered effective screening tools.[181] While the value of mammography as a screening tool has been well established, the false-positive (and false-negative) rates from screening mammography alone remain problematic. The benefit of additional screening tools for women with dense breasts, who have an increased risk for breast cancer development, or for women with a long-term history of personal breast cancer (e.g., 5 years or more since diagnosis) lies in the improved specificity of mammography as these women obtain screening versus diagnostic mammography.[181,182]

Digital mammography is the "gold standard" for breast cancer screening although tomosynthesis may add screening benefit. Tomosynthesis can decrease the false-positive rate and has better sensitivity than mammography alone for those women who have increased breast density.[183,184] Screening breast ultrasonography remains less common, although improvements in technology can allow for this modality to be an effective screening tool in women with dense breast tissue, particularly in young women who must obtain screening mammography due to a history of risk factors. MRI is the most expensive test to consider for breast screening, although it is recommended for young women with dense breasts with a strong family history of breast or ovarian cancer.[184]

Three-dimensional (3-D) mammogram films using tomosynthesis provide images that may eradicate many of the concerns related to two-dimensional (2-D) digital mammography.[183,185] Breast tissue density and small breast cancers have similar dense tissues that may overlap each other in regular mammograms. With 3-D tomography, additional views and recall rates are virtually eliminated, saving time, anxiety, and expense for the patient. Films are taken similar to digital mammography with low-dose cranial-caudal and medio-lateral oblique views.[184]

Several research studies have indicated that the integration of 2-D and 3-D mammography (digital mammography and digital breast tomosynthesis, respectively) can yield favorable outcomes.[183–187] In a population-based study of 12,631 women aged 50 to 69, a 40% improved detection rate for invasive cancer was obtained as compared to using digital screening mammography alone.[184] Another population-based study ($N = 7292$) of screened women, known as the Screening With Tomosynthesis or Mammography (STORM) study, found that false-positive recalls decreased by 17% and detection of cancers rose by 34% when tomosynthesis was used.[185]

Negative aspects of 3-D tomosynthesis include its increased cost, higher radiation dose, and workflow issues due to the additional radiology time required.[185,186] The increased radiation dose remains lower than safe limits, although the upper limits of radiation must be considered because millions of women are screened on an annual basis.[187] To compensate for this increase in radiation, digital breast tomography data can be used to reconstruct 2-D images, which may eliminate the need for the routine digital mammogram.[188] In a comprehensive breast center that is staffed by radiologists, films are read and the patient progresses to the next imaging. In the screening mode, once a patient is identified as having heterogeneously dense breast tissue or being at high risk for breast cancer development, the "routine" screening can be scheduled in advance.

Magnetic Resonance Imaging

Women who are at increased risk of breast cancer development may have MRI as an additional screening modality.[188] MRI is used to further define suspicious lesions, or to further evaluate dense breast tissue, especially in premenopausal

women at increased risk of breast cancer development. This imaging modality can also be used to examine the integrity of unilateral or bilateral breast implants.[189]

In women with dense breasts as the sole risk factor, a bilateral MRI has not shown specific benefit for screening. A review did indicate a paucity of clinical evidence, over-diagnosis of benign lesions, and increased, unjustified costs.[188] In high-risk women, MRI is recommended for those who received chest irradiation between the ages of 10 and 30. A bilateral breast MRI should be obtained by 8 years after the administration of chest irradiation, although not before the age of 25.[188] In women who have a high risk of breast cancer development, a bilateral breast MRI is recommended annually, to take place 6 months after a mammogram, as this schedule allows for radiographic surveillance every 6 months.[188,189]

Women with an inherited predisposition for breast cancer or a positive-gene profile that significantly increases (56% to 84%) their risk of breast cancer development may benefit from bilateral breast MRI. In a prospective study of 559 women at more than 20% risk for breast cancer development, MRI alone correctly identified more lesions than mammogram plus ultrasound plus MRI.[188] MRI had increased sensitivity in early detection regardless of patient age, breast density, or mutation risk status, as compared to mammogram or ultrasound.[188] An annual bilateral MRI is not recommended in women with an intermediate risk of breast cancer development (e.g., personal history of breast cancer, lobular carcinoma in situ).[187]

An emerging trend in imaging may improve the use of MRI and decrease the costs of screening—namely, the ultra FAST breast MRI.[189,190] This rapid, 3-minute scan deletes excessive screens and eliminates nonessential sequences. As a result, the ultra FAST breast MRI demonstrates high sensitivity, but improved specificity based on limited images. This type of MRI may improve patient tolerability due to its shorter scan times, decreased costs, and provide an adjunct to mammography.[189,191] A prospective study ($N = 443$) of 606 screening MRIs documented that with ultra FAST screening, patient time was reduced from 17 to 3 minutes, radiologist time was reduced from 30 minutes to 3 seconds, and cancer yield was increased to 18.2 cases per 1000 patients.[192]

In summary, optimal breast cancer screening is tailored to an individual's risk, with patient-specific application of the many available technologies. Personalization of screening considers advances in breast imaging modalities, risk assessment for breast cancer development, breast density, and the woman's own views about the risks and benefits of screening.[177] This approach requires a paradigm shift that differs from traditional guidelines in which all women are similarly screened starting at age 40 with annual mammograms. Other issues to consider include the financial cost of screening, lifetime radiation exposure of the breasts, and the medical, psychological, and financial challenges posed by false-negative or -positive results.[177]

EARLY DETECTION

Early detection strategies for breast cancer can include periodic self-breast awareness and annual clinical breast examination, despite the lack of robust level I statistical data that support their use.[193] Because imaging techniques are unable to identify all breast abnormalities, breast examinations should be performed in asymptomatic women starting at age 40 on a yearly basis. In women with a history of high-risk conditions, clinical breast examinations should begin at an earlier age, at least 10 years prior to the age at which the first-degree relative developed breast cancer. Women at increased risk of breast cancer development should have twice-yearly breast examinations.[193]

Breast self-examination (BSE) has been advocated for decades, although more recently the terminology has changed to self-breast awareness to reflect the inability of BSE to affect the mortality rate of breast cancer.[169] Nevertheless, self-breast awareness continues to be recommended for all women who are interested.[193] Nurses and APNs can encourage self-breast awareness in teenagers, young adults, and adult patients by offering a brief review of the anatomy of the breast, explaining how to know their own body, and encouraging them to observe and report any changes.

Breasts should be examined when they are nonpainful and ideally after the end of a menstrual cycle. Breasts often feel lumpy due to dense breast tissue, which is common in premenopausal and perimenopausal women. While these lumps can be confusing to both the woman and the examiner, the goal is to identify any changes, differences or unusual presentations. Should a new or unusual lump persist through another menstrual cycle, or for longer than a month, the woman should see her provider.[193]

Self-breast awareness includes looking at oneself in the mirror to observe if any changes are noted in aspects such as the shape, size, and color of the breasts and nipples. Changes of concern include dimpling, puckering, or bulging of the skin; differences in the nipples such as changed position; an inverted nipple; or any redness, pain, skin rash, or swelling of the breasts. While looking in the mirror, each arm should be raised to look for the same changes. As the chest wall muscles move, changes may be evident that were not previously observed. Women should also observe for any signs of fluid (clear, white, yellow, bloody) coming out of one or both nipples. Nipples should not be squeezed to accomplish this exam, as this action may induce a clear or bloody nipple discharge that is pathologically benign. A woman should also examine her inner bra lining for any evidence of nipple discharge, especially spontaneous bleeding.[193]

The next component of self-breast awareness is to develop an understanding of personal anatomy and how breasts feel throughout chronological life changes, including as a teenager during puberty, a young adult through further breast development, and an adult through pregnancy, lactation, perimenopause, and menopause. While lying down, the right hand is used to feel the left breast. This process is then repeated with the left hand feeling the right breast. The goal is to anatomically cover all areas of the breast tissue from the clavicle to below the breast (e.g., inframammary line), and from the sternum across to the opposite mid-axillary line (an imaginary line from the axilla down the flank).[193]

Clinical breast examination is performed in the same manner in which self-breast awareness is performed. The provider should observe the visual placement and orientation of the breasts while the woman is sitting at the end of the examination table while parting her gown. Breasts are often not symmetrical in size, shape, presentation, or nipple placement. It is especially important to note these differences in the medical record for future reference. The axillae are particularly easy to examine while the patient is sitting at the end of the exam table. While holding the arm in a relaxed position, use the opposite hand to thoroughly examine the axillae while swiping down the anterior, central, and posterior lymph node chains. In addition, the infraclavicular and supraclavicular lymph nodes should be examined.

Distress can be high in women who are undergoing their annual or twice-yearly screening and radiographic exams.[194] Breast centers that provide same-day services are excellent choices for these patients, especially in the event of abnormal imaging. Continuation of services until resolution is obtained all within the same day is advantageous to high-risk women. Persons who choose long-term surveillance may need to be reminded of their imaging appointments and physician consultations. A system should be in place to follow up with any missed appointments.[195]

Focused teaching and support of patients and family members for healthy lifestyles for cancer prevention may lead to encounters with siblings, children, and parents who have planned intentions, understand the perceived benefits, and voice confidence about eating a healthy diet, engaging in physical activity, and smoking cessation.[196] Nurses should take advantage of these teaching moments to engage in brief discussions, make referrals to classes, or recommend services in the community.

Women who are using pharmaceutical options to minimize their risk of breast cancer may need to be reminded of the importance of adherence to their agent.[194] Lapses in adherence to prescriptions may reduce the effectiveness, which may need to be discussed. Side effects must be assessed, discussed, and triaged, with interventions implemented as necessary to reduce or eliminate their symptoms.[195,197]

PATHOPHYSIOLOGY

BREAST ANATOMY

Humans develop a pair of complex mammary organs that evolve from the anterior chest in the early embryonic cycle. These organs have a thin layer of fascia that separate the chest wall muscles.[198] As a young adult the structures that support the functional characteristics of breastfeeding develop including extensive ductal, lymphatic, and vascular networks.[198,199] Lobules are present deep within the breast and link to the widespread ductal system to transport milk (**Figure 47-1**).[200] The female breast is considered in its final developmental stages when pregnancy and breastfeeding ensue.[198]

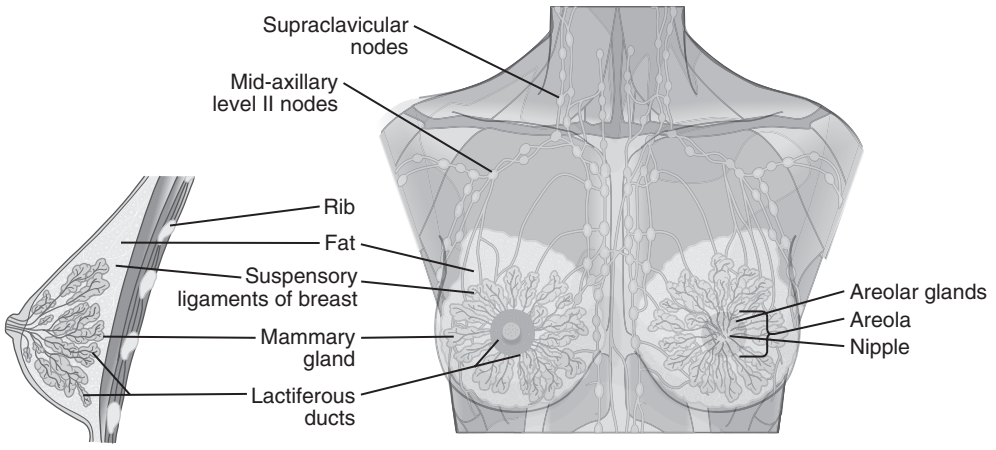

FIGURE 47-1

Anatomy of the female breast.

The female breast and its glandular and connective tissue, subcutaneous fat, and supportive Cooper's ligaments can significantly change depending on body weight and the presence or absence of endogenous and exogenous hormonal environments.[201,202] Externally, the breast lies atop the pectoralis major muscle and extends vertically from the posterior margin of the clavicle to the inframammary fold on the anterior chest wall.[201] Horizontally, breast tissue extends bilaterally from the mediolateral edge of the sternum to the mid-axillary line.[200]

The lymphatic system is responsible for removal of toxins and by-products. It includes three levels of axillary lymph nodes, inframammary and supraclavicular nodes, and interconnecting lymphatic vessels to drain the breast.[199–202]

Cellular Characteristics

Breast tumors can range from benign, fibrous tissue to invasive breast cancers with negative tumor markers. Multiple subtypes of breast cancers exist, characterized by individual genetic expressions and host characteristics. Several theories exist that explain the normal involutions of the mature breast and the process through which normal cells change to high-risk markers with or without further progression to invasive breast cancer.[203]

Breast cancer starts with a single cell that accumulates multiple mutations and learns to proliferate at a rapid pace, although little is known about the exact biologic processes that initiate and further these actions.[203] Each tumor includes heterogeneous cells (e.g., tumor heterogeneity), which allows the "fittest of the fit" cells to survive despite multiple treatment interventions.[203] These heterogeneous cells vary in size, shape, proliferation rate, cell-to-cell communication, metastatic potential, and sensitivity (or mutations) to systemic treatments.[203]

Atypia

Atypia in breast tissue is biologically related to breast cancer, although it can be reversed by prevention interventions.[204,205] Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) can be found on core or excisional biopsies based on the findings of palpable lesions or abnormality on imaging. When this atypia is found on core biopsies, it is important to obtain a larger piece of tissue, examine the surrounding tissues, and confirm malignant cells are absent. Removal of the atypical tissue may prevent progression of that actual group of cells, but does not remove the risk factor of the biopsy bed, which is theorized to contain embedded occult breast cancer cells, as breast cancers often form in the same area.[204,205] Compared to the contralateral breast, the ipsilateral breast remains at higher risk (2 times) for breast cancer development after removal of atypical tissue for 5 years, but then both breasts assume the same risk profile.[205] Overall, a woman diagnosed with breast atypia has a 4-fold increase in her relative risk of breast cancer development.[204] Women with a history of breast atypia who eventually are diagnosed with breast cancer typically have epithelial ductal cancers that are moderate or high grade, although tend to have positive estrogen receptors.[205] Considerations for risk factors of ADH and ALH include cessation of exogenous estrogens and close follow-up with the potential use of preventive agents such as raloxifene, tamoxifen, or aromatase inhibitors.[18,139,140,204,205]

Lobular Carcinoma in Situ

Lobular carcinoma in situ (LCIS) is an incidental finding that is typically not palpated on physical examination or found in imaging studies, although it can be linked to mammographic microcalcifications. LCIS can be multicentric (50%) and can involve the contralateral breast (30%).[206] When LCIS is identified, it is important to complete a needle-localization biopsy to confirm the absence of malignant disease, but it is not necessary to obtain clear margins due to its multicentricity.

Lobular carcinoma in situ itself will not turn into a cancer; rather, it is a premalignant change that represents a high-risk factor for breast cancer development in women.[206] Women older than 60 years with findings of LCIS have a higher risk of developing invasive cancer (25%) as compared to premenopausal women (8.3%) due to abnormal proliferation of cells.[18,206,207] Additionally, the presence of LCIS on core biopsy may predict a 25% to 31% presence of DCIS or invasive cancer.[206,207]A history of LCIS may be a woman's only high-risk factor, or it may be combined with a strong family history or a previous personal history of abnormal biopsies.

The future threat of an invasive cancer may dominate the decision making related to the diagnosis of LCIS.[16–18,206] Steps to control LCIS may vary from close follow-up, to chemoprevention (e.g., tamoxifen, raloxifene, or AIs), to bilateral mastectomy.[16–18,206,207] A unilateral mastectomy is no longer considered an appropriate intervention, as the diagnosis of LCIS can affect both the ipsilateral and contralateral breasts.[16–18]

Ductal Carcinoma in Situ

Ductal carcinoma in situ is a high-risk pathological breast finding that is noninvasive in nature and is the most common pre-malignant breast condition.[208] DCIS is classified as a stage 0 breast cancer because it occurs in the epithelial lining of the breast ducts and does not invade through the basement membrane.[36,206–209] This lack of invasion is important because the lymphatic and hematologic vessels are not in contact with cells that remain inside the duct,

which differentiates DCIS from an invasive ductal cancer.[208,209] DCIS virtually has no possibility of invasion or metastasis, two criteria that are necessary for a true cancer.[199,200,207]

Ductal carcinoma in situ frequently presents as a visualized cluster of microcalcifications on imaging, typically on a mammogram. DCIS can also be found on MRI or ultrasound, although mammography is the most reliable imaging modality in identifying the microcalcifications that are associated with DCIS.[210–212] Microcalcifications themselves are not malignant, but rather represent scarring near an area of active cell involution. When biopsied, they are classified as low-, moderate-, or high-grade DCIS.[208] The number of positive biopsies with DCIS has dramatically increased over the past two decades due to markedly improved imaging techniques and the establishment of dedicated breast radiology teams.[208,211] State-wide tumor registries include invasive breast cancers only, so the true number of DCIS cases can be difficult to track.[209–211]

Ductal carcinoma in situ has several different pathological and cellular classifications: flat or low papillary, papillary or cribriform DCIS, and comedo or solid DCIS. In DCIS with a high histologic grade, invasive breast cancer is likely to be found in a larger biopsy, or in the final pathology specimen of the lumpectomy or mastectomy.[208,209] Debate continues as to the extent of surgical intervention required to provide local control of low-, intermediate-, and high-grade lesions.[209,211,213,214]

Invasive Breast Cancer

Invasive breast cancer (IBC) is anatomically divided into three basic types; infiltrating ductal (60% to 80%), invasive lobular (7% to 15%), and inflammatory (2%); although multiple subtypes and characteristics are noted that validate the expanding heterogeneity of breast cancer to more than 30 separate histological types.[199,203,215] Diverse phenotypes of breast cancer cells, along with variations in anatomic location and intrinsic cellular subtypes with molecular characteristics, allow for personalized pathologic outcomes.[199,203] Traditionally, breast cancer treatment was driven only by the type of breast cancer and its few histologic features. Differentiation included cell type, pathologic and anatomic location of the breast cancer, and biomarkers such as estrogen (ER) and progesterone (PR) receptors, and in more recent years, human epidermal growth factor receptor type 2 (HER2/neu).[215–220]

CLINICAL MANIFESTATIONS

Breast cancer can be asymptomatic and found as a result of screening imaging tests; it may be palpated by the woman, man, partner, or provider; or it may be identified in routine imaging for breast cancer screening. Many variables related to breast cancer types and features govern the cancer's behavior, which are often not predictable or consistent. Therefore, any new finding or suspected abnormality of the breast, nipple, or axilla should be reviewed by the appropriate provider.

ASSESSMENT

PERSONAL HISTORY

Elements of personal history are essential to the initial evaluation of a breast abnormality. Information should be obtained about the woman's age at menarche, date of last menstrual cycle, age at first live birth, last pregnancy, end of most recent lactation, and if pertinent, date of menopause or cessation of menstrual cycle for 12 consecutive months. If she is menopausal, information about the use of hormone replacement therapies, including the type, route, and frequency, should be obtained. Information about pertinent surgery to the ovaries or uterus may be helpful. In addition, information about sexual activity, including number and type of partners (i.e., monogamous versus polygamous, gender of partner), as well as past and current birth control methods should be reviewed. Any hormonal replacement therapies or birth control pills will need to be stopped should a breast cancer diagnosis be verified. When she is at high risk of breast cancer development, the woman should also avoid perimenopausal and postmenopausal hormones.

A review of personal breast cancer risks is conducted to provide information about the potential diagnosis. It is important to emphasize that the patient did not "cause" the breast cancer as the etiology of this disease is multifactorial and out of one's definitive control, although a review may identify certain risk factors that can be eliminated from the patient's daily routine.

Information about past medical and surgical issues is requested, along with dates of onset, intervention, and resolution as noted by the patient or primary care provider. This information should be corroborated with the patient to ensure it is adequate and accurate if included in past medical records. Medications should be reviewed for the dose, route, timing, and frequency, along with the indications for use. The patient's social history should be explored with documentation of tobacco use, type, and length of time (in packs per year), as well as past and current use of alcohol and illicit drugs.

Socioeconomic information such as occupation, employer, marital status, number of children, race, ethnicity, and preferred language is often obtained by the registration personnel and should be reviewed prior to seeing the patient. Acculturation issues, including racial or ethnic differences, myths related to cancer, language

barriers, religious differences, or behavioral factors should be addressed early in the visit.[221] When misconceptions or myths mitigate necessary treatment, additional time with a trained nurse or APN is advisable to talk with the patient or family on a one-to-one basis.[222]

FAMILY HISTORY

Information about the patient's family should be reviewed including the status of all first- and second-degree relatives, age and cause of death if deceased, and any evidence of malignant disease. Of most interest is any family history of breast or ovarian cancer in first-, second-, and third-degree relatives. In the case of half-siblings or adoption, a notation should be made. In regard to surgical history, any anesthesia problems in the patient or first-degree relatives should be noted.

PHYSICAL EXAMINATION

Physical signs and symptoms of breast cancer include the following: breast lump or thickening; bloody nipple discharge; change in size, shape, or appearance of the breast or nipple; inverted nipple; dimpling of the breast (especially when raising the arms and looking in a mirror); pitting of the skin (e.g., similar to a pocked orange peel); or redness of the skin. Ulceration of the skin or nipple, or enlarged axillary, infraclavicular, or supraclavicular lymph nodes are of concern for advanced disease.[199,200,202]

The physical characteristics of a palpable breast cancer mass can include the following: hardness, irregularity, nodularity, asymmetric changes as compared to the other breast, fixation of skin to a nodule, or hard knots in the axillary, supraclavicular, or infraclavicular lymph nodes. Breast cancers can be movable, fixed, or both.[199,200,202] In reviewing this list of characteristics, one can see that breast cancers present in multiple forms. Therefore any new mass or abnormal imaging findings should be evaluated, regardless of the woman's age.

DIAGNOSTIC STUDIES

On imaging, radiologists and providers are looking for changes in one breast versus the other, with head-to-head comparison of vital features in the breast. Changes may appear as a circumscribed lump, microcalcifications, thickening, stellate lesions, or other changes.[199,200]

Mammography

Women often present with an abnormality found on their screening mammogram, or as the result of a mammogram done to identify a palpable lesion. As part of the primary workup of a new malignancy, a bilateral diagnostic mammogram is obtained to further examine the breast and lesion of concern, and to examine the unaffected breast in greater dimension.[169] A unilateral mammogram should not be accepted as the only source of mammographic imaging prior to the start of treatment for a newly diagnosed breast cancer.

Ultrasonography

Ultrasonography is an imaging technique that utilizes sound waves to determine whether palpable or nonpalpable breast masses are solid or fluid filled. Ultrasound waves are delivered through a wand and adapter specific to the body part being imaged. This imaging modality can also be used in conjunction with a variety of tasks, including ultrasound-guided biopsy for nonpalpable lesions, placement and preoperative identification of a localization clip to provide parameters of malignant lesions, and evaluation of microcalcifications in the breast.[178–180] Ultrasound is used to define and biopsy nonpalpable lesions, of which approximately 20% show evidence of cancer.[175] Ill-defined edges of lesions are 86% predictive of malignancy.[175] The ultrasound interpretation of a suspected malignancy may also be reported as a hyperechoic zone, indicating changes reflective of malignancy.[223]

In the case of nipple discharge, specifically spontaneous bloody discharge, a nipple–areolar complex ultrasound should be obtained to examine the internal structures of the ducts within the nipple. In the case of unilateral, spontaneous bloody nipple discharge, more than 30% of lesions are nonmalignant.[224,225] The duct is irritated by a papilloma that can easily be removed as an outpatient surgery.

Once a malignancy is identified, an ultrasound can verify the presence of a clip adjacent to the mass, or insert one for follow-up of a mass during neoadjuvant chemotherapy.[226,227] Should the mass completely disappear during chemotherapy, the clip can be used to guide the surgeon to the area that must be removed and pathologically examined.

Three-Dimensional Tomosynthesis

Three-dimensional tomosynthesis can also be useful during the workup of a suspicious mass or area of concern. Likewise, this technique is used to further evaluate suspicious microcalcifications or those that require biopsy.[186]

Magnetic Resonance Imaging

The routine use of MRI to evaluate the contralateral breast is not clinically recommended.[228] Comparative studies have shown that this additional imaging is costly but does not have any known benefit due to the minimal risk

of bilateral breast cancer that ultimately can be visualized with mammography.[228,229] The use of preoperative MRI does not decrease the risk of repeated excisions for clear margins, does not decrease recurrence, and is postulated to be partly responsible for the trend toward unilateral or bilateral mastectomy secondary to increased fears.[228] This phenomenon occurs following a bilateral MRI after which women must undergo additional imaging and possibly a breast biopsy due to the increased sensitivity, yet decreased specificity of the MRI images. Commonly, the additional workup is negative for cancer.

An exception to this criticism of MRI overuse is the reliance on this form of imaging after a new diagnosis of invasive lobular cancer that may have a risk of increased tumor size as well as an increased risk of bilateral presentation,[228] and for estrogen receptor–negative cancers in premenopausal women.[229,230] MRI exhibits increased sensitivity in detecting invasive lobular carcinoma as compared to mammography alone. These findings are secondary to the behavior of invasive lobular carcinoma, which has the ability to seep into the surrounding tissues, in contrast, invasive ductal carcinoma typically presents as a spiculated mass.[231] An MRI can provide data about the anatomic parameters as well as functional aspects of a tumor including visualization of neovascularity and peritumoral inflammation.[230,231]

Molecular Breast Imaging

Molecular breast imaging (MBI) is a dedicated nuclear medicine breast imaging modality that includes the addition of a pixelated tracer to any breast imaging technique (e.g., mammography, ultrasonography, 3-D tomosynthesis, MRI) to provide higher contrast and spatial resolution that enhances visualization of lesion characteristics.[232] Sestamibi is one of the most commonly used tracers in breast imaging,[232] and this radioactive substance has been used for decades in breast imaging, predating the development of breast MRI. The radiotracer is injected intravenously and accumulates in malignant cells of breast cancer, enabling MBI to detect occult breast cancers that defy detection by traditional mammography and ultrasonography.[233] Clinical trials continue to investigate the radiotracer of choice, best associated imaging modality, and ideal approach to obtain breast tissue for biopsy purposes.[233,234]

BREAST BIOPSIES

The type of breast biopsy performed depends on the lesion or area to be biopsied, the expected outcome, and patient-specific information (**Table 47-3**).[199,200,202,206,215,223,235–239] Breast biopsies are conducted as part of secondary prevention (i.e., as follow-up to abnormal imaging studies) and as part of the diagnostic process for breast cancer. Breast biopsies may be benign, in which case the area of concern is resolved and the patient returns to the baseline prevention protocol. Nevertheless, every biopsy, whether the results are benign, premalignant, or malignant, increases the risk of breast cancer development in either one or both breasts due to cellular activity or actual changes in the tissue. Breast biopsies are divided into palpable and nonpalpable lesions, with the appropriate biopsy technique being used to diagnose the abnormality (Table 47-3).

Fine-Needle Aspiration

If the examiner can feel the abnormality, a fine-needle aspiration (FNA) can be done to determine if the lesion is cystic or solid. If it is cystic, a 10-cc syringe is typically large enough to drain a simple cyst; a recheck of the area is done to ensure full aspiration.[199,200] In the case of a solid lesion, an aspiration of tissue can be done. When positive, the results indicate only that the lesion is cancerous: An FNA does not inform the examiner of any information beyond cytological diagnosis.[199] FNA can be used for axillary staging prior to the administration of neoadjuvant chemotherapy. In the event of negative findings, a core-needle biopsy should be completed to ensure negativity of the lymph node, which can ultimately be removed, if necessary, at the time of surgery.[199,200]

Core-Needle Biopsy

A core-needle biopsy can be done on a palpable lesion at the bedside, on a nonpalpable lesion with ultrasound guidance, or using a stereotactic approach. The core-needle biopsy utilizes a spring-loaded core needle apparatus (referred to as a biopsy gun due to its loud click). The apparatus has a large needle (10 to 16 gauge) that is encased in a protective sheath to decrease the possibility of tumor cell dissemination.[199,201] When the apparatus is withdrawn, the sample remains in the sheath.[201] For protective reasons, the needle exit site and sheath tunnel should always be excised at the time of definitive surgery, especially in cancerous lesions.[201,235]

Core-needle biopsies are typically done when the lesion is palpated or found on a radiographic examination.[199] The skin is sterilely prepped at the palpable or ultrasound-guided site; local anesthesia (lidocaine without epinephrine) is injected first in a circular manner, then deep into the tissue. A skin nick is made for entry of the core needle (as opposed to blunt entry) and the apparatus is inserted.[199] Several biopsies are taken to provide the most appropriate specimens for pathologic analysis. After every biopsy approach, the provider should extract the needle from the sheath and examine the material for evidence of white or off-white solid material, which indicates contact with solid

TABLE 47-3

Breast Biopsies

Type of Biopsy	Area of Concern	Outcome	Information
Fine-needle aspiration (by physician in clinic)	Palpable lesion	Cystic or solid mass. When a solid mass is positive for cancer, it indicates a need for definitive treatment. If the lesion is clinically suspicious and cytology is benign, consider another type of biopsy.	Cytology report to identify the etiology of a solid lesion, specifically cancer, or aspiration of a cyst with resolution. Cystic fluid is not sent to cytology unless bloody.
Core-needle biopsy (by physician in clinic or with ultrasound or MRI guidance)	Palpable or nonpalpable solid lesions. Lesion found on MRI that is identified with ultrasound.	Verifies the lesion and its properties. If the lesion is clinically suspicious and cytology is benign, consider another type of biopsy.	Pathology report with characteristics of mass, whether benign or malignant.
Stereotactic biopsy	Area near a cluster of microcalcifications, or a small lesion not well visualized on ultrasound. Woman must be able to lay flat in prone position.	Verifies the lesion and its properties. If the lesion is clinically suspicious and cytology is benign, consider another type of biopsy.	Pathology report with characteristics of mass, whether benign or malignant.
Excisional biopsy	Complex cyst or solid lesion. Often used to remove benign fibroadenomas in young women.	Area of concern is completely excised with confirmation of pathology.	Pathology report with characteristics of mass, whether benign or malignant.
Incisional biopsy	Large mass, especially if bloody or draining.	Verifies the lesion and its properties. Intent is to verify malignancy, followed by chemotherapy. If the lesion is clinically suspicious and cytology is benign, consider excisional biopsy.	Pathology report with characteristics of mass, whether benign or malignant.

Abbreviation: MRI: magnetic resonance imaging.

Source: Data from Carlson et al[199]; National Comprehensive Cancer Center[200]; Canadian Cancer Society[202]; Kounalakis et al[206]; American Cancer Society[215]; Durmus et al[223]; McClelland and Weiss[235]; Jankowski et al[236]; Feng et al[237]; Mayo Clinic[238]; Sala et al.[239]

tissue.[199,201,235] A tiny metal clip is placed at the biopsy site at the end of the procedure, which serves to mark the area of concern.[226] This marker is necessary not only for future imaging, but also if the area needs to be removed with an excisional biopsy or lumpectomy.[199] The samples are placed in sterile saline or formalin and sent to the pathologist for microscopic examination.

Core-needle biopsy can also be used to obtain tissue from enlarged axillary nodes, especially when administration of neoadjuvant chemotherapy is anticipated. This biopsy provides evidence of axillary metastasis for proper clinical staging should the chemotherapy result in a complete pathologic response of the axilla.[236,237] Following a core-needle biopsy, a 6-month imaging study (e.g., mammogram or ultrasound) is ordered in the case of benign or precancerous findings.[199]

Stereotactic Biopsy

A stereotactic core needle biopsy is performed when the area is not palpable or clearly visible with ultrasound. This type of biopsy is often performed in case of microcalcifications without an associated mass.[199,200]

In this procedure, the woman lies prone on a special table in radiology that has an opening in the table for the breast to hang through (**Figure 47-2**).[238] The breast is held securely between two mammogram plates and the area of concern is located using mammographic guidance. The area is prepped and infiltrated with lidocaine. Using the stereotactic mammographic images as a guide, biopsy specimens are obtained using a suction device. A tiny metal clip is placed at the biopsy site at the end of the procedure, which serves to mark the area of concern.[199] Following the procedure, a

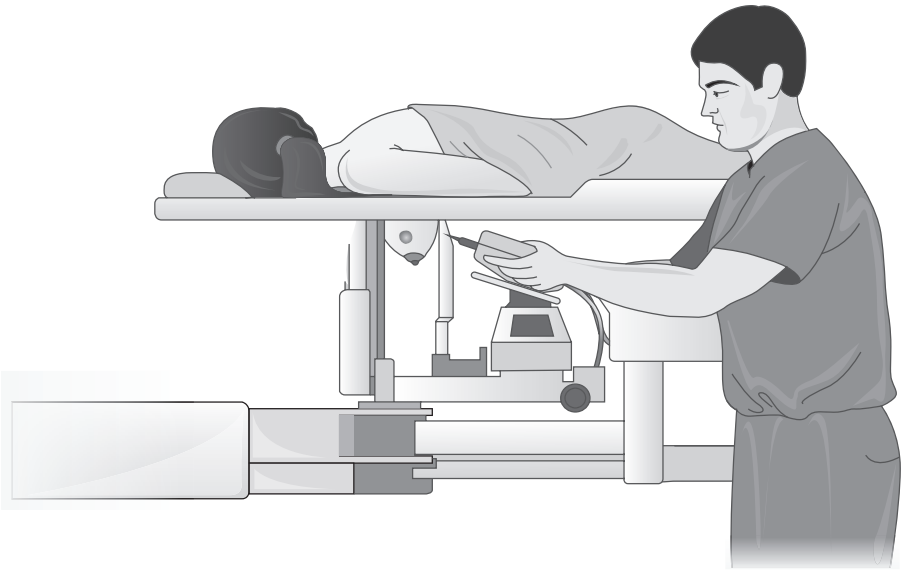

FIGURE 47-2

Stereotactic breast biopsy.

mammogram of the samples will be obtained to ensure the area of concern is present in the sample—typically microcalcifications that appear as little white specks. If the microcalcifications are not seen in the post-biopsy mammogram and not visualized by the pathologist, another biopsy may be performed at a later time to ensure the area of concern is free of abnormal cells, depending on the level of concern of the surgeon and radiologist.[199] At minimum, a 6-month follow-up mammogram is obtained to ensure there is no change.

Needle-Localization Biopsy

A needle-localization excisional biopsy is performed on nonpalpable lesions when a larger area of tissue must be removed and biopsied. This definitive procedure is performed when the core biopsy yields findings of concern (e.g., precancerous cells such as LCIS, atypical ductal hyperplasia, atypical lobular hyperplasia), or if the surgeon deems that the area or lesion should be removed.[199] In the case of precancerous cells, a larger area is removed to ensure a noninvasive (DCIS) or invasive malignancy is not adjacent to or surrounding the original core biopsy.[199,200]

On the day of biopsy, a mammogram is obtained of the area of concern. Using this image as a guide, the radiologist inserts a slender, bendable wire into the breast; the end of the wire should reach the lesion of concern, or approach the metal marker from the previous core biopsy.[199,223]

In the surgical suite, the patient's skin is prepped and infiltrated with lidocaine. Most commonly the patient receives conscious sedation or general anesthesia, although some surgeons are able to perform this procedure in the outpatient setting with local anesthesia. A small incision is made over the area of concern (e.g., palpable or needle localization) and the area of concern is removed. Dissolvable sutures are used to close the wound; steristrips are applied, along with a light, sterile dressing. Women are asked to keep this area clean and dry for at least 10 days. As with other biopsies, the breast is typically imaged again in 6 months.

Excisional/Incisional Biopsy

An excisional biopsy is typically performed to remove a small nonmalignant lesion such as a fibroadenoma or lipoma.[199,200,239] This procedure can be performed on an outpatient basis or with conscious sedation in same-day surgery. Following sterile preparation of the patient's skin, a small incision (2 to 4 cm) is made adjacent to or above the area to be excised. The incision is closed using subcutaneous absorbable sutures.

An incisional biopsy is performed on a large mass to obtain a portion of tissue for biopsy. This type of biopsy is not commonly done, although it may be performed in women with large cancers that have invaded the epidermis and are too friable for core-needle biopsy. Likewise in inflammatory cancers, a small section of skin may be taken with a piece of tumor to confirm an inflammatory breast cancer (e.g., one that involves the dermis and breast lymphatic channels).[199] Commonly, non-absorbable sutures or staples are used to provide closure and prevent bleeding; these are removed in 7 to 10 days, depending on the healing process.

A consult with surgical oncology and subsequent core-needle biopsy offered in the same day can induce anxiety in patients, despite their appreciation of the opportunity to move forward quickly. Women with preexisting episodes of depression or anxiety may have a higher risk and level of distress.[193] Nurses and the radiology ancillary team may be able to identify patient difficulties and distress early in the screening and diagnostic process, especially if they are aware that the patient's medical history includes prior depression or anxiety.[194] An oncology nurse navigator may serve to eliminate gaps related to psychosocial, information, and care coordination needs during the diagnostic workup for breast cancer and improve coordination of care. Fragmentation among departments can increase distress and frustration, especially when women are unsure of their diagnosis and struggling with the unknown and an inner fear of a positive breast cancer diagnosis.[240–242]

CLASSIFICATION AND STAGING

TYPES OF BREAST CANCER

Ductal Carcinoma in Situ

Ductal carcinoma in situ is a noninvasive cancer that is most commonly treated with lumpectomy or a total mastectomy.[200,243] A surgical lumpectomy is done to remove the area of concern with a clear margin of tissue and is generally followed with partial- or full-breast radiation therapy. The radiation further reduces the risk of local recurrence of DCIS or invasive breast cancer at the surgical site or ipsilateral breast. A mastectomy in the case of DCIS results in a 90% risk reduction.[200,243] On occasion, radiation therapy is warranted after a mastectomy in the case of diffuse DCIS with positive margins at the mastectomy site.[200,243,244]

Controversy surrounds the use of sentinel lymph node biopsy (SLNB) at the time of definitive surgery.[200,243] Some advocate the use of SLNB in association with high-grade lesions in the event that an invasive malignancy is found on the final pathology report,[1,199,200,243–249] while others advocate the use of SLNB only with mastectomy.[243,244] This would be necessary because once the breast is removed (and the bed of the tumor), SLNB cannot accurately be performed. Therefore, assessment of the axilla would require an axillary node dissection.[199,200,245]

Invasive Ductal Carcinoma

Invasive ductal carcinoma (IDC) is the most common type of breast cancer.[215] IDC arises in the ductal epithelial layer and invades beyond the ductal wall into surrounding tissues that contain lymphatic and blood vessels.[215] On clinical examination and imaging studies, invasive ductal carcinoma typically has defined margins. The projected size on imaging is generally close to the pathologic size excised at surgery. IDC provides a measurable tumor for neoadjuvant chemotherapy and for studies when an accurate size or response to therapy is required.

Invasive Lobular Carcinoma

Invasive lobular carcinoma (ILC) is the second most common type of invasive breast cancer, occurring in 7% to 15% of cases.[215] ILC arises in the lining of the lobule and invades into surrounding tissues that contain blood and lymphatic vessels. This type of cancer tends to spread into the surrounding tissue with multiple microscopic cancerous "fingers" and it often presents at a later stage than IDC, creating radiographic and surgical challenges.[231] ILC is not well defined on clinical exam or imaging, which explains the later stage typically noted at presentation. In IDC, an actual lump can be palpated (unless the tumor is identifiable only on imaging) and tumor margins can accurately be estimated from clinical exam and imaging. In ILC, a vague firm area is appreciated without palpable margins around the tumor. On imaging, the mass may disappear into dense mammographic tissue with a hint of asymmetry as compared to the contralateral breast.[231] MRI is often used to estimate the tumor size and determine the surgical approach versus neoadjuvant chemotherapy.

The surgical approach to ILC was traditionally a mastectomy because obtaining clear margins was challenging due to the compromised clinical exam and imaging studies. Once MRI was introduced to clarify ILC imaging, successful breast-conserving surgery became a reality.[231] The option to administer neoadjuvant chemotherapy for tumor size reduction enhances the surgeon's ability to estimate the reduced tumor size and obtain clear margins. Principles of breast-conserving surgery do not differ between histologic subtypes, in theory allowing for use of lumpectomy in women with ILC.

In a study of 998 women with ILC or IDC, breast-conserving surgery was offered to the participants. Women with ILC were initially more likely ($P < 0.001$) to have positive margins than women with IDC after breast-conserving surgery, resulting in significantly more re-excisions in the ILC group ($P = 0.02$). Following re-excision, the final margins between patients with ILC and those with IDC had significant similarities ($P = 0.88$).[246]

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is often found in younger and African American women and is the most lethal form of primary breast cancer.[247–249] Other risk factors associated

with development of IBC include obesity, young age at first delivery, rural residence, and shorter cumulative duration of breastfeeding.[247] IBC accounts for 1% to 5% of all invasive breast cancers and is considered more than a locally advanced tumor with a T4 classification.[215,248,249] It can occur as a primary diagnosis, or as a secondary diagnosis as a result of treatment for a primary IDC or ILC.[215]

Inflammatory breast cancer can appear as a case of acute cellulitis, or the classic peau d'orange that is often initially treated with antibiotics by the primary care provider. The antibiotics may offer improvement, which causes confusion of the etiology of the erythema.[248,249] The primary differential diagnosis in lactating women is typically mastitis. IBC should be considered a prime differential diagnosis in nonlactating or postmenopausal women when another source of infection cannot be found (e.g., insect bite). A recheck should occur after completion of antibiotics to assess response, with subsequent imaging being performed to ensure no underlying malignancy is present.[249] Imaging may be considered (ultrasound) with continued assessment.

Inflammatory breast cancer is an aggressive type of breast cancer. The overall prognosis for patients with IBC is poor.[248–250] The 10-year disease-free survival rate of IBC is 20% to 25%, a rate that has improved from 5% less than two decades ago.[250,251] Current multimodality treatment regimens are not robust enough for this virulent disease due to its specific clinical and biologic features, which include a high proliferation rate, negative hormone receptors, HER2 overexpression, high grade, and increased angiogenesis.[215,248–251] Specific molecular patterns may also exist in IBC such as epidermal growth factor receptor (EGFR) overexpression and high expression of oncogenes and proteins such as p53, mucin 1 (MUC1), the *ras* homolog gene family, member C (RhoC), calcium-dependent adhesion (E-cadherin), and transcription factors similar to a stem cell phenotype.[248] Circulating cancer cells are more evident in IBC, indicating its systemic involvement.[248,250]

Inflammatory breast cancer has distinct clinical features including a rapid onset, diffuse erythema, edema, a peau d'orange appearance of the skin, and generalized discomfort.[248,250] Palpable lymph nodes may be present as well as lymphedema of the breast and arm. The clinician can confidently palpate the thickened skin and obtain a punch biopsy to pathologically verify the diagnosis of IBC. The pathologic presence of dermal and stromal tumor emboli confirms the diagnosis of IBC.[248,250]

PROGNOSTIC FACTORS

Biomarkers

Biomarkers are functional or molecular indices of the biologic aspects of cancer and are used to predict, diagnose, or prognosticate outcomes.[220,252] Biomarkers represent gene expression, the process in which DNA is transcribed into RNA.[252] Biomarkers are used to configure treatment options in newly diagnosed or newly metastatic patients and to customize treatment to the specific cancer subtype and tumor.

Invasive breast cancer can be classified into five molecular subtypes that are indicative of gene-expression patterns: luminal A, luminal B, HER2 type, basal-like, and breast-like (normal-like) tumors.[216,218,219] Luminal breast cancers are secretory and stem from the inner lumen of ducts, while basal breast cancers are derived from outer-lumen epithelial cell types.[218,219] These molecular subtypes correspond to ER/PR positivity (luminal A and B), and triple-negative disease (ER/PR/HER2 negative).[218–220] Most tumors are estrogen receptor (ER; 73%) or progesterone receptor (PR; 70%) positive; HER2 positivity is observed in 20% to 30% of invasive cancers.[220] Molecular variants contribute to differences in clinical presentation and tumor behavior as well as response to therapy.

Basal-like breast cancers (BLBC) are aggressive and are often refractory to treatment.[253] Specific risk factors can be associated with certain breast cancer subtypes. For example, BLBC most commonly occurs in premenopausal African American women, suggesting that biomarkers may include age, stage at diagnosis, grade, delay in diagnosis, and various socioeconomic factors.[253] Other related risk factors include high parity, earlier onset of menarche, first full-term child at younger age, lack of protective breastfeeding, increased use of lactation suppressants, and increased waist-to-hip ratio.[253] BLBC is most likely to metastasize to the brain and lung, and has the poorest survival rates. These tumors typically lack estrogen or progesterone receptors or HER2/neu on their cell surface, resulting in triple-negative disease. In addition, BLBC is typically high grade, poorly differentiated, and with a high mitotic index, reflecting the tumor's doubling time. BLBC tumors are typically treated with neoadjuvant and platinum-based chemotherapy.[253]

Another biomarker, Ki-67, correlates with other markers such as ER, PR, HER2, EGFR, topoisomerase II-alpha (TOP II-α), and p21.[254] Ki-67 is a prognostic determinant and indicates a poor prognosis in triple-negative IDC inflammatory cancer with early recurrence and demise.[254] In the future, micro RNA (miRNA) may be utilized as a marker for breast cancer risk and the development of invasive disease.[254–256]

Inclusion of socioeconomic determinants, disparities, and demographic variants are also important considerations for successful outcomes.[161,248] Timing of surgery, and timing and types of chemotherapy, targeted therapies, and hormonal therapies are driven by these markers.

Triple-negative disease in African American women indicates differences in the biology of the cancer. The use of molecular profiling to guide treatment or predict outcomes is not cost-effective, however, and does not lead to changes in treatment.[257,258] Survival related to triple-negative disease

has improved in European-heritage women, but not in African American women; many of whom also suffer from advanced disease presentation, comorbid disease, disparities in income, lack of access to screening and cancer care, and overall delays in treatment of their breast cancer.[61,247,256] Disparities that may influence African American women's survival in the face of triple-negative disease include considerations of inequitable unsafe neighborhoods with increased biopsychosocial challenges, lack of access to grocery stores, increased stress, and exposures to environmental carcinogens due to inadequate housing.[61,247,256]

Locally Advanced Breast Cancer

Locally advanced breast cancers (LABC) present with inoperable disease. Despite aggressive treatment with neoadjuvant chemotherapy, surgery, radiation therapy, and targeted therapy the majority of women with LABC will relapse and eventually die of their disease.[259] LABC includes large primary tumors with clinically evident lymph nodes that are matted or fixed, or supraclavicular or infraclavicular lymph node enlargement, or tumor extension to the chest wall. The histopathology of LABC includes both infiltrating ductal and lobular types, although tubular or medullary breast cancer is rarely seen.[259]

Lymph Node Status

Physical examination, imaging studies, and surgical evaluation of the axillary, infraclavicular, and supraclavicular lymph nodes provide important indicators of the metastatic activity of breast cancer and indices of prognosis. Local metastatic disease to the lymph nodes indicates potential tumor invasion into adjacent lymphovascular structures with the potential for dissemination of cancer cells throughout the body via the vast network of lymph vessels. This concept underlies the prophylactic systemic treatment of breast cancer with hormonal agents, chemotherapy, or targeted agents, or a combination of therapies to preemptively assume dissemination of cells and treat the patient for potential system-wide disease.[200] At the current time, there are no other confirmatory tests that can provide the same information gained from lymph node assessment. Of note, it is important to test any positive lymph nodes for characteristics of the primary tumor to ensure they are related, rather than stemming from two (or more) simultaneous primary cancers.[260] The organ or anatomic structure adjacent to enlarged lymph nodes is not always the source of the malignant adenopathy.

Receptor Status

As previously discussed, various molecular markers are associated with breast cancer and its outcomes, including estrogen, progesterone, and HER2/neu receptors. The estrogen and progesterone receptors are proteins found inside breast cells. Circulating hormones can bind to these receptors, stimulate proliferation of breast cells, increase cell division and DNA replication, and lead to deleterious cellular mutations with rapid growth of breast cancer cells.[220,230] The receptor status of a tumor can be confirmed with a biopsy core of malignant tissue. The receptor status of the largest piece of tumor is what generally dictates the final test results.

HER2/neu Receptor

The HER2/neu receptor is another molecular marker related to breast cancer. A member of the tyrosine kinase family, HER2/neu defines part of the genetic makeup of the breast cancer. Nearly 70% of breast cancers are termed HER2/neu negative, meaning that the tumor does not amplify or overexpress this oncogene. Those persons who have HER2/neu-positive tumors (approximately 30%) overexpress the oncogene located at human chromosome 17.[220] Tumors characterized by overexpressed HER2/neu carry an increased risk of disease recurrence and poorer prognosis than HER2/neu-negative tumors. Testing is performed to obtain prognostic information and determine suitability for targeted therapy with trastuzumab or pertuzumab.

HER2/neu testing is performed by the pathologist using immunohistochemistry, which measures the amount of HER2 protein in the tumor. For equivocal outcomes (values of 2), additional testing is done using fluorescence in situ hybridization (FISH) to measure the number of copies of genes in the tumor. FISH is more sensitive and specific than immunohistochemistry; therefore the FISH results dictate the final HER2/neu results.[220]

Estrogen/Progesterone Receptors

Estrogen and progesterone receptor status is a prognostic indicator for breast cancer and is used to select part or all of the patient's systemic treatment. In addition, the receptors are used as prognostic data. Nearly 80% of women have tumors that are estrogen or progesterone receptor positive and are amenable to use of SERMs or AIs for systemic treatment.[220] The other 20% to 25% of women with breast cancer are diagnosed with estrogen- and progesterone-negative tumors, which rules out the use of SERMs or AIs for systemic treatment.

Histologic Factors

Histologic factors of the tumor include the status of additional molecular markers that indicate prognostic outcomes and drive systemic treatment. As scientists learn more about the intricacies of cancer cells, various histologic markers are coming to light. The tumor grade and Ki-67 status are two common indices that oncologists currently review, along

with cellular invasion of associated structures such as perineural structures, and invasion of neural structure, blood, and lymphatic vessels.

Grade

The grade of a tumor describes the cellular makeup of the cancer and indicates how the cancer cells resemble or have deviated away from their parent cells. In the case of breast cancer, the pathologist examines the breast cancer cells and describes the cells' similarities to or differences from normal breast cells. This comparison also aids the pathologist in identifying the primary tumor source in the case of metastatic disease.

For purposes of grading, pathologists typically use a scoring system to determine the grade. In breast cancer, the Nottingham grading system (also termed Elston-Ellis modification of the Scarff-Bloom-Richardson grading system) is used with evaluation of tubule formation (breast duct structures), nuclear grade (size and shape of the nuclei), and mitotic rate (rate of cellular division). Each of these three categories receives a score between 1 and 3. The scores are then summed to give a total score of 3 to 9.[261] It is important to not confuse grade with the stage of disease, as the two numeric values are not related.

Several synonymous terms are used to describe the grade of tumor. Low grade, well differentiated, and grade 1 (G1) with a Nottingham score of 3 to 5 are all terms that infer the breast cancer cells have not significantly deviated from parent breast cells. Intermediate grade, moderately differentiated, and grade 2 (G2) with a Nottingham score of 6 to 7 infer significant changes; whereas high grade, poorly differentiated, and grade 3 (G3) with a Nottingham score of 8 to 9 infer significant changes that indicate the tumor is rapidly growing and has significantly deviated from the parent tissue.[261] Anaplastic, undifferentiated, and grade 4 (G4) indicate the cells do not resemble breast tissue. If these types of cells are found in the breast, most likely the breast mass originates from another parent cell group, whose cells have metastasized to the breast. Such presentations could include a grade 4 sarcoma or lymphoma that originated in another part of the body, although this is a rare occurrence in the breast.

Ki-67

Another molecular marker is Ki-67, a cancer antigen that can be found in growing, dividing cells. Ki-67 is not observed when cells are in the resting phase of the cell cycle. Both premalignant breast cells (e.g., ADH, ALH, LCIS, DCIS) and malignant breast cells (invasive breast cancer) can receive a Ki-67 score. Evaluation of Ki-67 is performed on a sample of tumor tissue, with the results then being used to predict prognosis and guide treatment decisions. High levels of Ki-67 indicate more aggressive changes in cellular growth, indicating a poorer prognosis.[220]

Perineural Invasion

The pathologist examines the tumor tissue to observe if the cancer has spread into the local space surrounding nerves in the breast tissue. Perineural invasion (PNI) is associated with a poorer prognosis as it indicates aggressive behavior of the tumor.[220,262]

Lymphovascular Invasion

Evidence of lymphatic invasion of the tumor represents another indicator of aggressive tumor behavior.[220] Lymphovascular space invasion (LVI) is observed under the microscope and demonstrates invasion of the tumor into blood or lymphatic vessels.

Comorbid Disease

Comorbid disease in persons with breast cancer is also used to evaluate the body's response to the disease and any associated cofactors that may affect treatment and outcomes. Comorbid factors associated with breast cancer include older age, more advanced tumor stage and grade, estrogen-receptor–negative status, and preexisting comorbid conditions.[263] In a retrospective study of 19,160 patients with either non-Hodgkin lymphoma and breast, colorectal, lung, ovary, and gastric cancers, comorbid conditions were reviewed to determine the risk of first cycle chemotherapy-induced febrile neutropenia without granulocyte colony-stimulating factor (G-CSF) prophylaxis. The comorbid conditions included chronic obstructive pulmonary disease, congestive heart failure, HIV infection, autoimmune disease, peptic ulcer disease, renal disease, and thyroid disorders.[264] This study represents only one example of how comorbid conditions are associated with tumor activity, prognosis, and expected outcomes.

Disparate Conditions

Traditionally, disparate conditions have been considered only in terms of outcomes of cancer treatment, associated comorbid conditions, and morbidity and mortality rates. Disparate conditions are also associated with types of breast cancer and their associated molecular markers. Racial and ethnic disparities are responsible for more aggressive and fatal types of breast cancer (e.g., inflammatory, triple-negative disease).[61,247,256,265]

STAGING OF BREAST CANCER

The stage of a breast cancer includes components of tumor size, lymph node status, and the presence or absence of metastatic disease. The TNM staging system is the universal staging system used for breast cancer, with T representing the tumor size in centimeters, N representing the presence

(and number) or absence of disease in ipsilateral axillary lymph nodes, and M indicating the presence or absence of distant metastatic disease (e.g., bone, liver, lung, brain). The TNM staging system groups these three variables to determine the final stage of disease, ranging from stage 0 to IV. Stage 0 indicates noninvasive disease only (ductal carcinoma in situ), whereas stage I to stage IV (metastatic disease in distant organs) indicate invasive disease.[266] The stage of a breast cancer is then combined with the outcomes of molecular markers as described earlier to predict prognostic outcomes and determine treatment.

Tumor Size

The tumor size in breast cancer is measured by the pathologist at its greatest dimension and is represented by one of the following classifications:

- T0: no evidence of primary tumor
- Tis: carcinoma in situ or Paget disease of the nipple with no associated tumor mass
- T1 a, b, or c: 0.1 to 2 cm
- T2: 2.1 to 5 cm
- T3: greater than 5 cm
- T4 a, b, c, or d: involves all quadrants of the breast, or evidence of disease in structures of the chest wall[266]

Lymph Node Status

The axillary lymph node status is determined by the pathologist and is reported as one of the following classifications:

- N0: no evidence of cancer
- N0 (i+): minute (less than 2 mm) evidence of cancer identified by using either routine or special stains
- N1 a, b, or c: 1 to 3 positive axillary nodes
- N2 a or b: 4 to 9 positive axillary nodes
- N3 a, b, or c: 10 or more axillary nodes[266]

Within these classifications, invasion of tumor into ipsilateral, infraclavicular, or supraclavicular nodes can also be described.

Metastatic Disease

Evidence of metastatic disease is not determined by the pathologist in the breast sample, but rather by the oncology team through clinical, radiographic, or pathologic examination of disease in other organs beyond the breast. MX indicates evidence of metastasis cannot be assessed, a designation often provided by the pathologist when reviewing the primary breast tumor only. Other designations include M0 (no evidence of distant metastasis) and M1 (evidence of distant metastasis).[266]

Clinical and Pathological Stage

The clinical presentation of a breast cancer is determined by physical examination of the breast and axilla, imaging studies, and pathological verification of a breast cancer, typically from breast or axillary biopsy specimens.[199,236,237] Documentation of the clinical stage is most important when neoadjuvant therapy is administered, as the clinical stage (cTNM) represents the initial and overall documented stage of disease prior to administration of any systemic therapies.

The pathological stage of a breast cancer is determined by the pathologist based on samples of breast tissue or axillary sampling/contents. Systemic treatment is often based on the pathological stage except in the case of neoadjuvant therapy. In this situation, the pathological stage (pTNM) of disease indicates the response to neoadjuvant therapies and the amount of residual disease following definitive surgery. In addition, the assessment of the disease after hormonal therapy, chemotherapy or radiation therapy can be indicated by yTNM.

THERAPEUTIC APPROACHES AND NURSING CARE

In early-stage breast cancer, surgery is typically the first intervention for a newly diagnosed breast cancer. Nearly all surgical options are available for an early-stage breast cancer, with few exceptions.[199,200,267–270] The standard of care is lumpectomy, extended resection with quadrantectomy, or skin-sparing mastectomy that includes removal of breast tissue, the nipple and areolar complex, and biopsy scar with preservation of the remaining skin and inframammary fold.[199,200,270] Breast conserving treatment may be contraindicated in the following situations: prior history of radiation therapy to the chest or breast, current pregnancy, diffuse microcalcifications with concern of widespread DCIS, or positive margins that were not cleared with repeat lumpectomy.[199,200] In addition, if the remaining breast tissue is less than the amount of tissue to be removed, the woman may cosmetically benefit from a total mastectomy. Breast conserving treatment may be suboptimal in women with connective tissue disorders (e.g., scleroderma, lupus) or when complete removal of breast tissue is warranted for prophylactic control, such as prophylactic contralateral mastectomy, positive genetic results that identify a woman as being at high risk for breast cancer, or biopsy results indicating lobular carcinoma in situ.[199,200]

In older patients, a geriatric assessment should be performed that will provide additional information about preexisting comorbid conditions, life expectancy, activities of daily living, and any required tailored activity needs. The information gained through this assessment may help guide

geriatric patients to the best course of treatment to maximize control of the tumor and minimize the effects of their current comorbid conditions.[271,272] Procedures for control of breast cancer can be planned similar to those offered to their younger-aged counterparts, including reconstruction following a mastectomy.[273]

LOCAL TREATMENT OF BREAST CANCER

Lumpectomy

Breast conserving surgery with adjuvant radiation therapy remains a landmark in breast cancer management in this last century. Nearly 30 years of randomized trials provide sound evidence that breast conservation surgery does not compromise mortality and that it reduces long-term morbidity to an extent comparable to mastectomy.[274] Mastectomy is equivalent to lumpectomy plus whole-breast radiation therapy for stage I and II breast cancers.[274] A radiation boost to the lumpectomy site adds to the absolute gain for local tumor recurrence in the breast, especially in younger patients due to their anticipated longer life span.[274]

A lumpectomy alone is a same-day surgery. A small incision is made over the palpable tumor, or adjacent to needle-localization wires. The breast tissue is dissected down to the tumor, which is then removed through dissection around the area of concern with a clear margin of tissue. The tumor may or may not be exposed, although all areas of concern to the naked eye are removed and marked (e.g., inked) as specific margins of the tumor. All tissue is submitted to the pathology department for examination of the lumpectomy margins. A second lumpectomy may be required to remove residual invasive cells or DCIS; a lumpectomy is considered successful when the margins around the tumor are clear of disease.[275] A total mastectomy is recommended when a surgeon is unable to obtain clear margins.[199,200]

A lumpectomy immediately behind the nipple usually results in a poor cosmetic outcome due to the central defect and scarring around or behind the nipple with resultant nipple retraction. The one exception may be in the case of a large, pendulous, ptotic breast (found in older or overweight women) in which the nipple is barely visible due to the overall size of the breast and resulting ptosis (drooping of the breast due to lack of connective tissue). In this case, a central lumpectomy can be performed with excellent cosmesis.

A surgical technique to accomplish a nipple-sparing lumpectomy is the round block mastopexy reduction, which allows a small breast reduction and discreet scar.[276] This procedure may still result in a substantial lumpectomy, but may be a surgical option for the woman who does not desire a mastectomy with or without reconstruction.[273,277]A small external prosthesis (with or without a prosthetic nipple) can be worn in the bra to equal the volume of the contralateral breast.

Total Mastectomy

A total simple mastectomy is performed for local control of newly diagnosed multicentric or recurrent DCIS, or a new or recurrent invasive breast cancer. A total mastectomy may also be recommended by the surgeon due to several potential factors, including the size of tumor, tumor directly under the nipple–areolar complex, compromised cosmesis, or inability to clear margins with a lumpectomy.[199,200] Anatomic margins of tissue removal in a mastectomy are as follows:

- Anterior: fascia over the pectoralis major/minor muscle
- Superior: clavicle
- Inferior: inframammary line
- Medial-to-lateral: sternal border
- Lateral: midaxillary line[199,200]

Once healed, the wound appears as a flat incision on the anterior chest wall. Part of the lateral rib cage may be visible under the skin in very thin women, although the defects traditionally observed with a radical mastectomy are no longer apparent.[278] Immediate or delayed reconstruction can be performed to restore the natural look of a breast as visualized in a bra.[279]

Clear margins are essential for loco-regional control of the breast cancer. The American Society of Clinical Oncology (ASCO) endorses the use of ink to mark specific margins within the tumor bed, whether using a different color of ink or "a," "b," and "c" labels to indicate the defined location of each margin.[280] Wider margins often do not preserve cosmesis and do not improve the loco-regional control and tumor recurrence, even in aggressive tumors.[281] A second lumpectomy may be necessary in as many as 40% of initial surgeries to remove residual tumor tissue, either invasive cells or noninvasive DCIS.

Ultrasound guidance during surgery may be used to provide direct visualization of the tumor. This guidance enables the surgeon to obtain clear margins, with intraoperative identification from pathology noting any close margins that require additional dissection. Intraoperative ultrasound guidance may eliminate the need for painful preoperative needle localization.[282,283]

Total Skin-Sparing Mastectomy

A total skin-sparing mastectomy (TSSM) is often performed when immediate or delayed reconstructive surgery is planned.[158] There are several surgical approaches to the TSSM including inframammary, superior periareolar, radial, or lateral.[158] Both TSSM and nipple-sparing

procedures can be combined in the same surgery, which results in optimal outcomes with reconstructive procedures.

Nipple-Sparing Mastectomy

Nipple-sparing procedures are less commonly used in mastectomy for the control of invasive disease than in prophylactic mastectomy.[159] Criteria for a nipple-sparing procedure include tumors smaller than 3 cm, tumors more than 2 cm from the nipple–areolar complex, absence of palpable nodal involvement, absence of skin involvement of tumor, and prophylactic mastectomies.[159] At the time of surgery, the tissue beneath the nipple–areolar complex must be biopsied with a frozen section for tumor involvement. If the intraoperative frozen section is positive for tumor, then the procedure must be aborted to preserve local control of the tumor.[159]

Bilateral Mastectomy

Women are increasingly electing to undergo mastectomy, both unilateral and bilateral, versus breast conserving surgery (e.g., lumpectomy), perhaps due to their desire to prevent a second breast cancer occurrence, recurrence of their original cancer, or previous decision making based on family deaths from breast cancer.[284,285] Many women report fear of a second primary cancer in the contralateral breast.[286] Given this multitude of concerns and attitudes, the decision-making process regarding type of surgery can be very difficult to navigate.

The risks involved with bilateral mastectomy followed by immediate reconstruction include increased rate of infection, extended anesthesia time, and ischemic tissue secondary to decreased oxygenation.[287–290] While the decision of which of the various surgical options to pursue is always left to the woman, the oncology team is responsible for fully explaining the reality of recurrent systemic disease versus the low risk of ipsilateral recurrence or contralateral occurrence.[287,288,290] The nurse must ensure that the woman understands a bilateral mastectomy will not impact her risk of recurrent systemic disease and that her risk of contralateral breast disease is very low.

In recent years, the rate of contralateral prophylactic mastectomy has significantly increased in younger women by 3- to 4-fold.[287,288] This increase is not questioned in women with genetic mutations (e.g., mutations in *BRCA1* or *BRCA2*), although the etiology of the rapid increase in women diagnosed with breast cancer remains somewhat unknown in regard to the absolute benefit of the procedure.[287,288] A survey of participating institutions associated with the Young Women's Breast Cancer Study identified 159 (29%) women aged 40 or younger who underwent a contralateral prophylactic mastectomy. Of these women, 123 participated in the contralateral prophylactic mastectomy study, which consisted of questionnaires addressing decision making, risk perception, breast cancer knowledge, and breast cancer worry. Women ranked their desire to improve survival, extend life, and prevent metastatic disease as reasons to do contralateral prophylactic mastectomy, although they also acknowledged an understanding that their survival would not be extended.[290]

Axillary Surgery

Surgical assessment of the axilla remains one of the most important prognostic variables in the systemic treatment planning of a newly diagnosed breast cancer.[199,200,291] Tumor in the axilla indicates local metastatic spread and is a poor prognostic factor as compared to a negative axilla.[199,200,260] In the era of the radical mastectomy, the level 1 (low), 2 (mid), and 3 (deep) axillary lymph nodes were routinely removed as part of the anatomic markers of dissection. Once the modified radical mastectomy gained popularity as the preferred surgical intervention, however, the axillary dissection was typically confined to only level 1 and 2 lymph nodes unless the burden of tumor required a level 3 dissection to improve local control.[199,200] As breast conserving treatment became more popular, again only the level 1 and 2 lymph nodes were removed at the time of lumpectomy. In the 1990s, clinical trials were completed using sentinel lymph node biopsy instead of an axillary dissection, which enabled the surgeon to sample a few of the first draining lymph nodes of the tumor.[291,292] The positive or negative result of this biopsy indicates the status of the axilla, information that is used in local control of the tumor as well as to guide systemic treatment.[291,292]

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy is now the standard of care unless the burden of disease requires more extensive surgery with an axillary dissection.[293–297] Women with early-stage breast cancer should not undergo an axillary node dissection that is not preceded by SLNB.[199,200,294] Breast surgeons routinely perform SLNB, although in some institutions the general surgeon remains unpracticed in this procedure; in such a case an axillary dissection is performed, which significantly increases healing time and morbidity.[294] The use of SLNB has reduced the incidence of lymphedema as compared to axillary dissection, although any surgery in the axilla carries the risk of lymphedema in the surgical arm.[297]

The emergence of SLNB is a major milestone in the treatment of breast cancer, as it has been associated with a significant decrease in cancer-related morbidity. The sentinel lymph node is the first draining lymph node of the tumor; the rationale of SLNB is that if the first draining node is free of disease, then the nodal chain behind that first draining node will likewise be free of disease.[294–297]

In the case of palpable axillary lymph nodes, the patient is not eligible for SLNB.[294] A fine-needle aspiration or

core-needle biopsy can confirm the presence or absence of malignancy, especially if neoadjuvant chemotherapy is planned. Following neoadjuvant chemotherapy a SLNB can be performed even in patients who presented with non-palpable, biopsy-proven node-positive disease.[295,296] This procedure is most reliable if three sentinel lymph nodes are examined, as compared to one or two.[297] The premise is that neoadjuvant chemotherapy can contribute to axillary cancer control.[292,293]

The SLNB is most commonly performed at the time of definitive surgery, although it may also be performed prior to and after neoadjuvant chemotherapy to assess the stage of the malignancy.[292,293] Prior to surgery, the patient receives an injection of radioactive technetium into the bed of the tumor. This substance is injected adjacent to the palpable tumor or via the needle that is inserted to localize the tumor. Over the following 1 to 2 hours, the technetium travels to the nodal basin of the first lymph node that is draining the breast tumor. During surgery, the tumor basin is injected with blue dye. The breast is gently massaged over 5 minutes to enhance the rapid uptake of blue dye.[294,297] The anatomic location of the sentinel lymph node is not related to the location of the breast tumor, a reality that emphasizes the importance of the technetium injection and blue dye to locate the first draining node of the tumor.[294]

Prior to the axillary incision, a gamma probe is traversed over the axilla to locate the sentinel lymph node. Once it is identified, the gamma probe emits a high-pitched signal and a high reading appears on the probe screen indicating uptake in the first draining lymph of the tumor.[298] A small incision is made over the "hot" area in the case of lumpectomy and the incision may be slightly extended in the case of mastectomy. The gamma "hot" and visible blue lymph nodes are removed for immediate frozen section with pathological examination.[199,200,294]

The frozen section results guide the subsequent intraoperative decisions[291–297]:

- If the lymph nodes show no pathologic evidence of tumor, the remaining nodes are left intact.
- If one or two pathologically positive lymph nodes have microscopic disease (versus macroscopic), an axillary dissection may be performed, or the procedure may be aborted and the remaining lymph nodes may be left in place.
- If there is evidence of tumor in three or more lymph nodes, then an axillary dissection is performed.
- If there is microscopic evidence of tumor in non-sentinel lymph nodes, an axillary dissection is typically performed.
- If palpable adenopathy is found after the SLNB performed, then an axillary dissection is performed.

Controversy persists regarding these decisions despite multiple clinical trials that support preserving the axillary nodes despite frozen section positivity.[295]

Even if the intraoperative frozen section is negative, the final pathology report may indicate microscopic disease in one or more of the sentinel lymph nodes. In such a case, the patient may need to return to surgery for an axillary dissection or the oncology team may reason that such a procedure is not necessary given that adjuvant therapy is planned.[293,295] A return to surgery is particularly difficult following a total mastectomy with immediate reconstruction, especially with a flap-perforator procedure, as the reconstruction may be altered by another surgery. When other worrisome tumor characteristics are found including high-grade disease, lymphovascular invasion, or triple-negative disease, an axillary dissection may be recommended, but may be deferred until after adjuvant therapy is complete.

The use of SLNB following neoadjuvant chemotherapy remains controversial as it may not provide reliable results.[293,294] A retrospective review of data from the American College of Surgeons Oncology Group Z1071 study ($N = 689$) noted that an accurate sentinel lymph node status was obtained following neoadjuvant therapy.[295] Additional studies continue to assess these difficult situations, as some women may undergo an axillary dissection that provides no additional survival benefit, but significantly increases surgery-related morbidity.[199,200,294]

Disparities related to SLNB exist throughout the United States. SLNB has been a routine procedure in academic settings for 20 years, although some institutions still perform axillary dissections on all women or men with breast cancer. Differences in the options available may be present in various geographic areas of the United States, including those related to race.[299] Black women often have multiple disparate conditions: less access to screening, potentially more aggressive tumors, and worse outcomes.[299] In some regions, surgeons may not be proficient or well practiced in this type of surgery and therefore, may choose not to perform SLNB.[199,200,300]

Axillary Node Dissection

An axillary node dissection is performed at the time of definitive surgery, either following an aborted SLNB or as a planned procedure. An accurate description of the axillary basin whether provided by SLNB or axillary dissection is an important factor in the staging and prognosis of breast cancer.[199,200,291,294] The role of axillary node dissection remains controversial in the case of early-stage, estrogen-receptor–positive disease given the odds of a negative axillary basin.[295]

Lymphedema of the arm is a result of blocked lymph flow, which promotes swelling and accumulation of plasma proteins in interstitial tissues. This adverse reaction often occurs in the affected limb, breast, or chest wall of women with breast cancer who have undergone either a SLNB or axillary node dissection.[301] In addition, the level of disease is a significant risk factor when axillary lymph nodes are

affected by cancer that blocks the flow of lymph fluid. Other factors that increase the risks of lymphedema include metastatic disease to the axilla, frequent arm infections, and as a secondary effect of chemotherapy or radiation therapy.[301]

Preventive measures, identification steps, and monitoring of preoperative and postoperative assessments are required to prevent or manage lymphedema. Incidence rates of lymphedema are as high as 50% following a mastectomy and 28% with lumpectomy, although the degree of lymphedema varies within patients who receive these treatments.[301] It was initially claimed that SLNB would prevent lymphedema, but the incidence of this complication is currently as high as 17% with this type of axillary surgery.[301]

Breast Restoration

Reconstruction of the breast has proven psychological benefits for women.[284] The number of women seeking breast reconstruction significantly increased from 1998 to 2007 and continues to rise.[287,288] The Women's Health and Cancer Rights Act in 1999 mandated insurance coverage for women to complete reconstruction on either or both breasts, and to maintain symmetry to the contralateral native breast.[289] This law enables reconstruction for women for life, although disparities still exist in practices that refuse to take Medicare or Medicaid, as well as among African American women. Despite the mandated legislation in 1999, widespread geographic availability of qualified personnel remains inadequate to fulfill women's needs.[302]

A retrospective study from 2005 to 2011 examined women who underwent a mastectomy ($N = 44{,}497$) using the American College of Surgeons' National Surgical Quality Improvement database. The study indicated that 37% of women had immediate reconstruction; 84% received prosthetic implants, 15% had pedicled-autologous procedures (attached flap), and 5% underwent free-transfer autologous reconstruction.[302] In comparison to white women, only one-third of Asian women received reconstruction, 57% of blacks, and 60% of Hispanics. Both Asian and black women were more likely to undergo free-transfer autologous reconstruction. The differences among white, Asian, and black women were statistically significant ($P < 0.001$) with more white women being offered reconstruction as an option compared to Asian or black women.[302]

Women often seek immediate reconstruction to maximize their surgery experiences with the same episode of general anesthesia, or to wake up with a partially or fully reconstructed breast versus a flat mastectomy incision.[284] Women may be forced to forgo immediate reconstruction due to surgeon preferences, patient risk factors (e.g., advanced age, elevated body mass index, smoking history), or the need to proceed initially with breast cancer–related interventions such as chemotherapy and radiation therapy.[303]

The use of immediate or delayed breast reconstruction has significantly increased over time, and it continues to rise given the increased rate of bilateral mastectomies despite lack of disease in the contralateral breast or the presence of genetic mutations.[304,305] It is important to discuss a number of points with patients preoperatively, including the stage of disease, low possibility of contralateral breast cancer development, extent of surgery, potential side effects in the contralateral side, and possibility of adjuvant radiation therapy on the ipsilateral chest wall and axilla depending on the outcome of surgery.[305] The timing of reconstructive surgery may need to be planned around adjuvant treatment for the breast cancer (e.g., radiation therapy) to achieve the best outcomes.[306]

Alloplastic Implant-Based Reconstruction

Restorative breast cancer surgery after mastectomy with saline-filled expanders, also known as alloplastic implant-based surgery, is the most common type of reconstruction used throughout the United States. Alloplastic implant-based reconstruction is based on a plan of two surgeries: The first inserts saline expanders intraoperatively under the chest wall muscle immediately following the mastectomy, and a second surgery replaces the expanders with saline- or silicone-filled implants into the expanded muscle and chest wall. Additional minor surgical procedures can smooth any unwanted tissue bulges or provide for nipple reconstruction.

Radiation therapy following implant-based reconstruction is generally without negative side effects provided the skin and muscle are expanded prior to the radiation. When chemotherapy follows surgery, sufficient time is available for expansion procedures to occur, resulting in optimal outcomes. This extended postoperative time is not available when neoadjuvant chemotherapy is administered, followed by definitive cancer surgery and then radiation therapy. Complications in such a case may include incomplete expansion (prior to or after radiation therapy), capsular contracture, breast distortion, or infection.[306] Therefore, expansion is often delayed in a time frame similar to waiting for delayed reconstruction after the end of all cancer treatments. This allows the oncoplastic surgeon to adequately evaluate the radiated skin prior to further surgery, avoid implant explantation (loss of implant), and help the woman choose the most appropriate reconstructive surgery.[305,306] As an alternative, a latissimus dorsi flap can be fashioned as a sling-type tissue transfer with insertion of a permanent saline or silicone implant.

Implant Reconstruction in Augmented Breasts

Breast cancer can occur in women with breast implant augmentation, as the number of augmented women in the United States is greater than the annual breast cancer occurrence rate.[307] Women with previous augmentation are

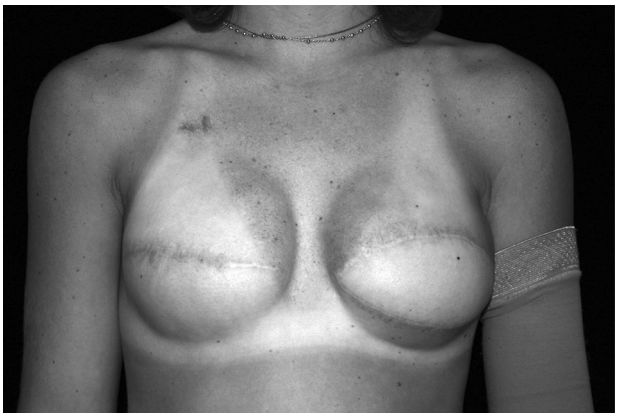

FIGURE 47-3

Latissimus flap with implant reconstruction on left in radiated field.

Source: Courtesy of Joseph Serletti, MD. Department of Plastic Surgery. Hospital of the University of Pennsylvania.

likely to choose an implant-based reconstruction. In a retrospective review, women with previous augmentation were compared to women without augmentation prior to their mastectomy and reconstruction with saline expander or silicone implant. Both physical and psychological outcomes were similar for these groups, indicating that implant reconstruction in women with previously augmented breasts is as successful and satisfying as it is in women without previous augmentation.[307]

Autologous Breast Reconstruction

Autologous breast reconstruction uses a woman's own tissue that is surgically transferred to the chest wall, often using microvascular surgery to transfer a preserved blood supply (or the blood supply can remain at the donor site). Several types of autologous reconstruction procedures are performed, including latissimus dorsi flap, pedicled transverse abdominal (TRAM) flap, and free tissue transfer flap (i.e., perforator flap).[308–310] The latissimus dorsi flap (**Figure 47-3**) is a combined tissue transfer and implant-based reconstruction. It can be either performed as an immediate reconstruction option or delayed following radiation therapy.[309]

Transverse abdominal reconstruction can likewise be performed in an immediate or delayed fashion with either the free full muscle TRAM or muscle-sparing TRAM that utilizes the rectus abdominus muscle.[308] The TRAM is an autograft (e.g., the woman's native tissue) crafted as a pedicled flap in which the tissue is tunneled underneath the anterior upper abdominal and lower chest walls to the mastectomy site. In this surgery, the blood supply remains at the donor site and the rectus abdominus is used to support the graft.[309] The most common negative side effect related to the TRAM flap surgery is a gradual development of a lower abdominal hernia.

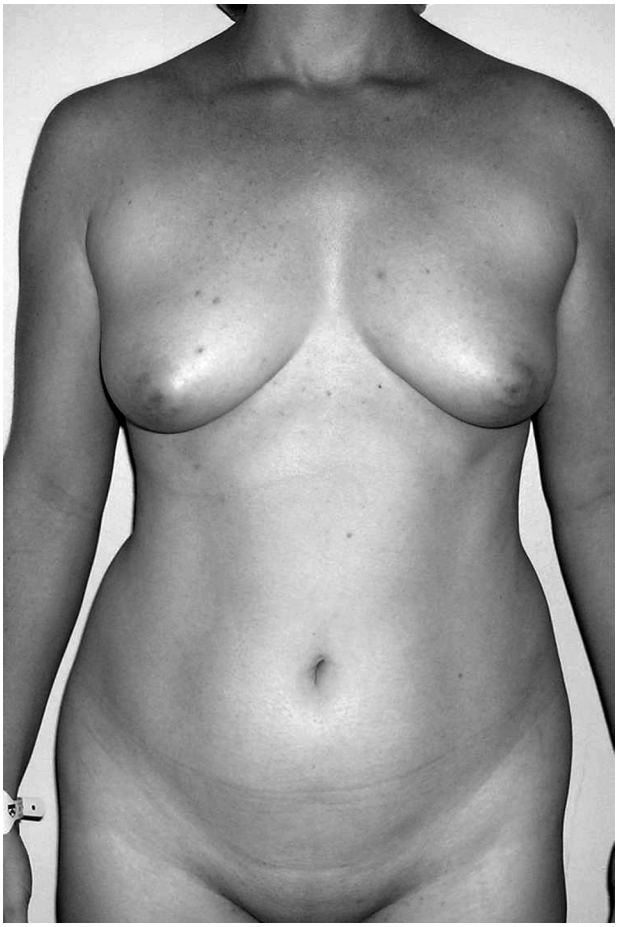

FIGURE 47-4

Pre-surgery reconstruction.

Source: Courtesy of Joseph Serletti, MD. Department of Plastic Surgery. Hospital of the University of Pennsylvania.

The perforator flap can be utilized as an immediate or delayed procedure using a deep inferior epigastric perforator (DIEP) flap, thereby sparing the abdominal muscle.[310] **Figure 47-4** and **Figure 47-5** show "before and after" photos of this surgery.

Microvascular breast reconstructions are lengthy procedures adding up to 12 to 15 hours of operative time and are technically challenging. Specialized immediate postoperative care is essential to monitor tissue perfusion and ensure maximum blood flow across the microvascular anastomosis, while preventing platelet accumulation that might result in flap pedicle thrombosis (a surgical emergency).[310–312] Although platelets are essential to the healing process, excessive accumulation can occlude the pedicle vessels and ultimately lead to loss of the free flap. The critical factor that prevents excess accumulation of platelets is the force of blood across the anastomosis. Thus, an uninterrupted high flow of blood through the microvascular anastomosis is

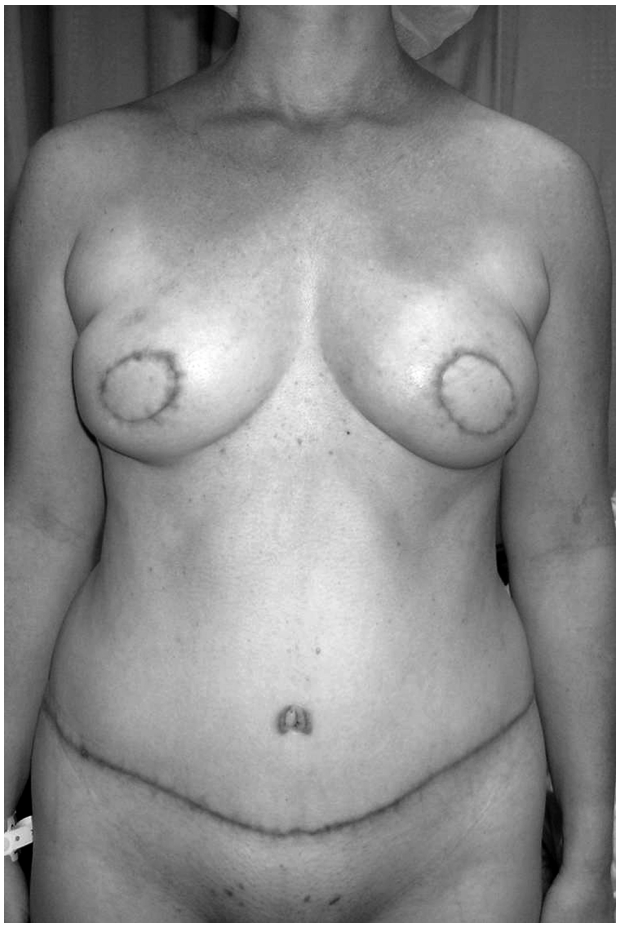

FIGURE 47-5

Bilateral free flap reconstruction.

Source: Courtesy of Joseph Serletti, MD. Department of Plastic Surgery. Hospital of the University of Pennsylvania.

essential to sustained patency.[310–312] The advantages of the DIEP flap (or other possible donor sites) is the creation of a breast mound with its own blood supply, a tummy tuck (or other anatomic site), and long-term aging of the tissue that is similar to the aging of the contralateral breast.

Post-mastectomy radiation therapy may increase the risk of fat necrosis, skin contracture, parenchymal induration, and hyperpigmentation with an autologous implant.[310] In addition, the presence of a reconstructed breast may compromise the optimal delivery of radiation therapy.[310,313] Oncoplastic surgeons prefer that patients complete radiation therapy before undergoing delayed reconstruction.

Future Considerations

With the advent of improved loco-regional control of the tumor as well as potential delays in systemic recurrence, the use of radiation therapy to the mastectomy site or axillary lymph nodes has significantly increased over this last decade. These changes in radiation therapy practice offer new challenges to the management of post-radiation tissue changes in women with autologous breast reconstruction. A reconstruction algorithm includes the preservation of native skin, which can improve long-term outcomes such as skin and scar quality, breast shape and contour, and aesthetic outcomes.[314,315] A novel reconstructive surgery allows immediate post-mastectomy formation of a skin pocket with insertion of a saline expander, which is then expanded to its fullest during the breast cancer treatment sequence.[315] Following the completion of all cancer treatments, the patient can either opt for a silicone or saline expander or choose to fill the pocket with natural tissue.

The use of absorbable mesh is an area of interest in alloplastic implant-based reconstruction. Vicryl mesh is used to extend the subpectoral pocket with complete coverage of the implant.[316] In a comparison of reconstructions with and without mesh, fewer revisions were observed in the mesh group ($P = 0.05$), and a large implant could be used with the mesh ($P = 0.01$). In addition, fewer subsequent contralateral mastopexies were performed ($P = 0.01$) to provide symmetry.[316] Smaller breasted women who want to preserve their petite shape postoperatively may be eligible for a permanent device that is both a saline expander and an implant. A remote port is located just beneath the skin, allowing any fills that are required for symmetry. The port is easily removed when expansion is completed.

The surgical decision-making process is difficult for women with a newly diagnosed breast cancer. In the case of neoadjuvant chemotherapy, the woman has added time to consider her options and to prepare a plan of action. It is important that nurses explain breast cancer from both its local and systemic aspects, including discussion that a contralateral prophylactic mastectomy will not improve the patient's overall chance of cure, although it may contribute additional comorbid conditions. Sometimes, however, bilateral mastectomy with bilateral reconstruction may be exactly what the woman wants[314]; in that case, nurses should be supportive and discuss postoperative care.

ADJUVANT RADIATION THERAPY

Adjuvant radiation therapy is an important breast treatment for the local control of breast cancer following a lumpectomy with radiation being given to the breast and possibly axilla, or after a mastectomy with radiation being given to the chest wall and axilla for locally advanced disease. Radiation therapy is intended to prevent a local recurrence of the cancer or to prevent development of a second cancer. Nearly 30 years of evidence exists that supports the use of lumpectomy and radiation therapy for the local control of an early cancer.[200,317,318] A lapse in utilization of the recommended course

of radiation therapy may seriously compromise the local and systemic control of the primary breast cancer.

Whole Breast Radiation

External beam radiation utilizes 25 fractionated treatments and 5 to 10 additional treatments that provide a "boost" to the lumpectomy site.[200] In the case of a lumpectomy with 4 or more positive lymph nodes, the axilla is also radiated.[200] External beam radiation therapy is well tolerated, although patients may have complaints of fatigue, tenderness, and skin erythema toward the end of the radiation course. Traditional whole breast radiation therapy can be difficult for women due to the required extended time period of 5 to 7 weeks, Monday through Friday. This regimen may be complicated by the need for time off from work, transportation challenges, financial issues, childcare responsibilities, and difficulties in accessing care.[319]

Partial Breast Radiation

Hypofractionated radiation therapy with accelerated partial-breast irradiation therapy (APBI) has gained popularity over the past 5 to 10 years and may be a solution to the barriers associated with whole breast radiation therapy, without changing outcomes.[319,320] APBI essentially provides the same overall amount of radiation therapy to the tumor bed, but over 5 to 15 days in an accelerated schedule as compared to whole breast irradiation.[320,321]

A number of APBI techniques have been used including brachytherapy (e.g., interstitial and balloon), intraoperative (e.g., one large intraoperative dose), and the more novel approach of three-dimensional conformal external breast irradiation, and prone positioning to minimize cardiac exposure.[319–335] There are a number of reasons why patients might prefer APBI, including geriatric patients who do well with the shortened regimens.[323,331] Nevertheless, tissue damage and reduced cosmesis can result from volume effects of APBI, such that this approach is recommended only for small tumors.[330]

Many radiation centers at rural, urban, and academic sites have offered APBI despite a lack of head-to-head comparisons among the various types of APBI and most importantly, a comparison to whole breast irradiation, which has a history of success spanning more than 30 years. Until results of current clinical trials are completed, it is important that clinicians consider some of the following criteria to determine if APBI is a reasonable approach as compared to whole breast radiation therapy[319,322,334,335]:

- Tumor size (3 cm or less)
- Negative nodal status
- Patient age greater than 50 years
- Favorable tumor histology
- Negative tumor margins
- Absence of multifocality or multicentricity
- Absence of calcifications on postoperative mammogram
- No prior history of radiation therapy to the chest wall or breast
- No history of connective tissue disorders
- No significant family history that may suggest genetic mutations

Larger, randomized clinical trials in the United Kingdom have compared various APBI applications with more than 10 years of evidence to whole breast radiation, but no study has compared all types of APBI in a head-to-head trial.[330]

Interstitial APBI is the oldest delivery mode and uses multiple thin catheters implanted intraoperatively or postoperatively in the lumpectomy bed. The number of implanted catheters ranges from 7 to 20 depending on factors related to the tumor location, tumor size, and breast size.[316,331] Once the lumpectomy site is healed, the radiation source is delivered twice daily for 5 days and the catheters are then removed.[331,333]

The balloon-based implant delivers radiation to the lumpectomy site using the intraluminal balloon, which is inserted by skilled surgical and radiation oncologists. The balloon-based implant was developed to eliminate the multiple catheters, as the device is implanted in the lumpectomy site. Upon healing when the balloon is ready for use, the water-filled vessel is inflated, which allows it to physically adapt to the lumpectomy space. The radioactive source is delivered twice a day for 5 days (i.e., for 10 total treatments).[319,329] The balloon is removed after the last treatment.[329]

Three-dimensional conformal radiation therapy (3DCRT) utilizes an external beam linear accelerator to irradiate the quadrant of resection and provide the required total dosage. This approach is noninvasive, does not require an implantable device, and may have promising applicability. The treatment is administered twice a day for 5 days, with a total of 38.5 Gy of radiation.[315,335]

Intraoperative accelerated partial-breast irradiation is a single fractionation that uses low-energy x-rays to deliver radiation to the lumpectomy site. This type of APBI is used in Europe, and final study outcomes are pending.[72]

Prone Positioning

Prone positioning for the treatment of left breast cancer is under study as a means to reduce ipsilateral lung and heart doses when radiation is given to the left breast.[336,337] Patients who may be eligible for prone positioning include those with large pendulous breasts and those who will receive significant treatment to their heart as visualized on computed tomography simulation.[337]

In a phase I/II study, 20 postmenopausal women with node-negative breast cancer, excised tumors smaller than

3.0 cm, negative sentinel lymph node biopsy, and surgical clips demarcating the lumpectomy cavity underwent prone external beam radiation with accelerated partial-breast radiation in 10 fractions (38.5 Gy) over 5 days. Dose constraints for the whole breast, lungs and heart were met. Acute toxicities included grade 1 erythema (80%); and grade 2 erythema, fatigue, and breast pain occurred in one participant. At a median follow-up of 18.9 months (range: 12–35 months), 95% of patients had good to excellent cosmesis, 40% had grade 1 fibrosis, and 30% had grade 1 hyperpigmentation. All study participants remained free of disease.[338]

Skin Care

Skin reactions following breast radiation therapy and subsequent skin care vary with each person depending on the total radiation dose, boost to the lumpectomy site, and additional radiation to the axillary or inframammary nodes. Most patients who receive whole or partial breast radiation experience some level of skin irritation and erythema,[319,339] especially as they reach the middle to end of their treatment phase. In addition, women may experience fatigue and alterations in their activities of daily living.

Skin care is dependent on three variables: adherence to the prescribed skin care regimen, patient satisfaction with the products, and skin condition before and after radiation therapy.[339] The prescribed skin care differs for each facility and radiation oncology program, although generally patients are taught to cleanse their skin twice a day with a prescribed wipe, and apply a moisture-rich adherent lotion to the radiation field. The goal of any intervention is to prevent grade 3 and 4 skin reactions that result in painful moist or wet desquamation.[339]

ADJUVANT SYSTEMIC TREATMENT

Systemic treatment of early-stage breast cancer (e.g., stage I, II, or III) consists of chemotherapy, endocrine, and human epidermal growth factor receptor 2 (HER2)–directed therapies, with the intent being to control or eradicate micrometastatic disease. The various combinations of systemic therapies are responsible for the decline in breast cancer mortality observed over the past several decades.[1,340]

Adjuvant Chemotherapy

The systemic treatment of early-stage breast cancer is termed adjuvant chemotherapy. This therapy is used to treat micrometastatic disease that may remain despite aggressive local treatment with surgery alone or surgery plus radiation therapy. Adjuvant treatment is a critical component of primary breast cancer treatment and may be administered prior to definitive surgery (neoadjuvant chemotherapy) or after surgery following adequate healing of incisions (adjuvant chemotherapy). The administration of adjuvant therapy is based on the stage of disease, histologic and molecular markers, and the patient's health and preexisting comorbid conditions.[341–343] Chemotherapy administration has significantly changed over the past 30 years, with regimens being changed from cyclophosphamide, 5-fluorouracil, and methotrexate to anthracycline-containing regimens in the late 1980s, followed by the introduction of taxanes for adjuvant treatment in the mid-1990s.[342–344]

The evolution of growth factors to support the bone marrow and prevent profound neutropenia has enabled the practice of dose-dense chemotherapy, chemotherapy administered every 2 weeks instead of every 3 to 4 weeks. Dose-dense chemotherapy delivers the standard-dose chemotherapy with shorter intervals between the cycles in patients with high-risk, early-stage breast cancer.[345]

A variety of data are now used to determine the best course of adjuvant or neoadjuvant chemotherapy including genomic data; tumor, histologic, and biologic markers; and host characteristics.[343,344] The exact time to initiate chemotherapy is not clear, although clinicians generally agree that chemotherapy should be started within 2 months of surgery.[346] The exception is triple-negative disease, for which neoadjuvant chemotherapy can be initiated.[344,345] Systemic chemotherapy has evolved into a tailored, personalized approach, as information from molecular assays and drug toxicities is available to inform treatment regimens and personalize care so as to ensure provision of the right therapy to the right patient.[344,345]

Commonly used regimens include doxorubicin and cyclophosphamide (AC); docetaxel and cyclophosphamide (TC); cyclophosphamide, doxorubicin, and fluorouracil (CAF); cyclophosphamide, epirubicin, and fluorouracil (CEF); cyclophosphamide, methotrexate, and fluorouracil (CMF); epirubicin and cyclophosphamide (EC); fluorouracil, doxorubicin, and cyclophosphamide (FAC); fluorouracil, epirubicin, and cyclophosphamide (FEC); docetaxel, doxorubicin, and cyclophosphamide (TAC); and docetaxel, carboplatin, and trastuzumab (TCH).[344–346]

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is increasingly prescribed to evaluate its sensitivity or resistance through quantifiable measurement.[347,348] Neoadjuvant chemotherapy is administered prior to definitive surgery based on treatment goals, quantifiable markers, treatment goals, and personal input. The goal of neoadjuvant chemotherapy is a complete pathological response.[347] Retrospective and a few prospective studies have provided promising data on this approach, although additional prospective data are necessary to ensure these outcomes occur consistently.[347,348] Neoadjuvant chemotherapy continues to gain popularity not only as a way

to reduce the size of tumors prior to surgery, but also as a means to observe the response of various types of breast cancers to the drugs.[347,348]

Adjuvant Targeted Agents

Targeted agents have been utilized in multiple adjuvant clinical trials, with or without paclitaxel. Trastuzumab is an accepted targeted agent in both metastatic and adjuvant breast cancer care. In the adjuvant setting, the standard is to administer trastuzumab every week for 52 cycles (e.g., 1 year) or every 3 weeks for 17 cycles.[349] Trastuzumab typically is started after the cessation of any chemotherapeutic drugs with potential cardiac toxicities (e.g., doxorubicin, epirubicin) to reduce the chances of concomitant cardiac damage.[349,350] Trastuzumab in adjuvant breast treatment clearly shows evidence of improved survival even in patients with node-negative disease.[350]

Adjuvant Hormonal Agents

Nearly 80% of newly diagnosed women with breast cancer are positive for estrogen or progesterone receptors, enabling the use of adjuvant hormonal therapies as part or all of their systemic treatment. Multiple agents are available that require personalization to each woman and her cancer requirements and that offer differing side effect profiles.[351–356]

Molecular Assays

The use of molecular assays to guide the type of adjuvant chemotherapy or hormonal therapy is an increasingly important aspect of personalized care. Women who are eligible for hormone treatment alone, without adjuvant chemotherapy, should be tested to determine their cancer's metastatic potential.[351] Oncotype DX is a 21-gene reverse polymerase chain reaction assay that can determine the metastatic potential of a breast cancer and predict outcomes related to the use of adjuvant therapy.[352] Women who have a newly diagnosed stage I or II node-negative breast cancer who are estrogen receptor-positive and HER2/neu negative are potentially eligible for Oncotype DX testing.[352] A low score demonstrates a low risk of systemic recurrence with hormonal therapy alone, whereas a high score underlines the importance of adjuvant chemotherapy and hormonal therapy.[352] Tools such as Oncotype DX can predictably guide treatment toward maximal outcomes and avoid unnecessary exposure of patients to chemotherapy.

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator has been the mainstay of adjuvant hormonal therapies for decades. Today it remains an important component of adjuvant treatment in premenopausal women, in postmenopausal women with significant decreased bone density with or without a fracture history, and in premenopausal women who cannot tolerate any of the aromatase inhibitors. Tamoxifen has tissue-specific activity and exerts an anti-estrogenic effect in the breast and vaginal mucosa through inhibition of estrogen dimerization.[351] Tamoxifen has an estrogenic effect on several tissues (e.g., endometrium, coagulation, bones, lipids, liver), which can cause negative side effects including endometrial hyperplasia, thromboembolic events, and hepatotoxicity. Tamoxifen can prevent fractures related to osteoporosis as well as minimize the risk of hyperlipidemia.[351]

Tamoxifen is primarily metabolized by the CYP2D6 and CYP3A4 enzymes to form endoxifen, which binds estrogen receptors to block their actions.[353] Therefore, concomitant use of certain drug classes should be avoided due to their potential interference in drug metabolism, specifically groups of antidepressants that rely on the CYP2D6 and CYP3A4 enzymes (cytochrome P450, family 2, subfamily D, polypeptide 6 and cytochrome P450, family 3, subfamily A, polypeptide 4, respectively) and that may result in an under-response to tamoxifen.[353] Notable strong inhibitors of CYP2D6 that should be avoided include the antidepressants venlafaxine and citalopram.[351,353]

The side effects of tamoxifen may be limited in premenopausal women. If they are still experiencing menstrual cycles, tamoxifen may decrease the amount of menstrual flow and the number of cycle days. Conversely, because tamoxifen can stimulate proliferation of the endometrium, mid-cycle spotting can occur, especially in perimenopausal women.[351,354] Women taking tamoxifen must see their gynecologist on an annual basis and report any unusual bleeding or prolonged amenorrhea. A pelvic ultrasound may reveal a thickened endometrium and require an endometrial biopsy to determine the status of the lining. Although it is rare, tamoxifen can increase a woman's risk of endometrial cancer.

Tamoxifen also carries a higher risk of blood clot formation, with the typical presentation being a deep vein thrombosis (DVT) event, typically in the calf. Women who smoke have an increased risk of DVT. Tamoxifen is not indicated for women who have a clotting history.[351]

Aromatase Inhibitors

Members of another class of hormonal drugs, the aromatase inhibitors (AIs), are often prescribed for postmenopausal women with breast cancer. Aromatase inhibitors inhibit enzyme activity that converts androgens to estrogen.[351] These agents are often used as primary adjuvant hormonal treatment in estrogen receptor–positive breast cancers. Aromatase inhibitors are indicated over tamoxifen for premenopausal women in conjunction with a gonadotropin-releasing hormone agonist (GnRH-a) that will block

ovarian production and induce a menopausal state.[351,354] The use of AIs has demonstrated improvements in disease-free survival of postmenopausal women and estrogen receptor-positive premenopausal women with concomitant ovarian suppression as compared to tamoxifen alone.[351] **Table 47-4** summarizes the various treatment options for breast cancer based on stage of disease, and local and systemic treatments.[1,199,200,244–253,259–261,265–269,272–274,340–352]

Women may suffer from multiple side effects of hormonal drugs, depending on their personal experience with menopause and their hormonal status prior to their diagnosis. Commonly noted symptoms include vasomotor changes (hot flushes), sexual dysfunction, vaginal dryness, insomnia, weight gain, bloating and swelling. Musculoskeletal symptoms are also common including arthralgia, bone pain, and joint stiffness; all symptoms that are associated with the blocking of endogenous estrogen. Hot flashes can often occur and can induce sleep disturbances; these symptoms are most pronounced in the first 1 to 3 months of hormonal therapy. Discussion of possible side effects with ongoing assessment is necessary for optimal symptom management with attention to daily adherence to treatment.[351,353,354,356] If one type of hormonal drug creates significant side effects, another may not. Therefore, a switch in drugs can occur without negative effects on the antitumor activity.

Women who receive neoadjuvant or adjuvant therapies to provide both local and systemic control may experience a number of short- and long-term side effects that can significantly alter their lifestyle. Nurses must review these potential side effects with women to gauge their knowledge base and ability to problem solve if symptoms occur. Chemotherapy can cause alopecia, fatigue, peripheral neuropathy, neutropenia, thrombocytopenia and anemia. Severe bony pain may occur for 1 to 2 days following the use of marrow growth factors. Chemotherapy can induce premature ovarian failure in premenopausal women secondary to chemotherapeutic agents that cause follicular destruction.[351] Frustration can occur in women during their extended length of adjuvant therapies and require much supportive care.[356-358] Women with early-stage breast cancers have excellent results following local and systemic therapies, although they may experience changes in their body, lifestyle, and quality of life. Nurses often create relationships that enable them to impart wisdom and knowledge as women traverse the challenges of multiple surgical options, systemic treatment, radiation therapy, and ongoing survivorship care.

Psychological Impact

The psychosocial impact of a cancer diagnosis and side effects from treatment are often underestimated by the patient and family, as well as the healthcare team. A cancer diagnosis followed by extensive surgery and lengthy adjuvant treatment can elicit intense emotional responses that interfere with activities of daily life. Increased levels of distress are observed in these interventional periods, along with fears, worry, and anxiety about the future. Nurses need to listen to their patients to discern their needs and provide comprehensive survivorship care with symptom management and episodic assessment of psychosocial needs. Anxiety and anxiety-related emotions such as worry, fear of recurrence, and fear of dying can negatively affect daily life, relationships, and work-related issues. High levels of anxiety have been observed in as many as 30% of patients with cancer.[86] Anxiety prior to a surgical procedure can increase biophysical stress changes that may impede initial healing and recovery. Anxiety does not typically resolve quickly after surgery, as the survivor and family must anxiously wait for the surgical pathology results and perhaps worry over these findings and future treatment.[356,357]

Distress

Patients with breast cancer report feelings of vulnerability, loss of control, uncertainty, stress, and loss of energy.[86] Psychosocial support prior to and after surgery from family and friends may not be effective if the group is also experiencing emotional responses that impede their support mechanism for the survivor. Therefore, it is important for nurses to understand the experiences of survivors and to play an active role by screening for distress, assessing identified sources of distress, and providing interventions and referrals to help patients move forward and gain control of their situation.[86]

Self-Image

Breast cancer survivors can suffer from multiple self-image issues before and after surgery related to body image and body dissatisfaction.[359] Appearance issues may include a defect in remaining breast tissue or a loss of breast(s) secondary to surgical interventions. Other issues in regard to self-image may include tissue damage, decreased range of motion, lymphedema, and persistent seromas. Bothersome matters may also include changes in muscle definition secondary to surgery, breast tenderness, and frustration that the body looks and functions differently than it did before surgery.[359]

It is important for the oncology team to recognize the potential myths and concerns associated with new diagnoses. A discussion with the patient and family members is recommended to help patients move forward. Habits from the past cannot be altered or changed, but can certainly be improved after a cancer diagnosis. Some patients or families may require a referral to psychology services should psychological issues persist beyond the early diagnostic period.

TABLE 47-4

Examples of Stages of Breast Cancer and Treatment Choices

TNM Stage of Disease	Choice of Local Control	Type of Systemic Treatment	Comments
T0 N0 M0 ER+ PR+ Low grade No metastasis Stage 0	Lumpectomy with radiation therapy to breast, or total mastectomy No nodal assessment	Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy	In the case of widespread disease, total mastectomy with or without immediate reconstruction
T0 N0 M0 ER– PR– High grade Node negative No metastasis Stage 0	Lumpectomy with radiation therapy to breast, or total mastectomy Sentinel lymph node biopsy	None; may be treated with tamoxifen or aromatase inhibitor as prevention to unaffected breast	As above in regard to widespread disease Sentinel lymph node biopsy is performed to provide axillary staging if invasive cancer is found on final pathology
T1 N0 M0 ER+ PR+ HER2/neu– Negative lymph nodes Stage I	Lumpectomy with radiation therapy, or total mastectomy Sentinel lymph node biopsy	Oncotype score to determine future metastatic potential. If medium or high score, chemotherapy with 4 cycles dose-dense anthracycline with or without cyclophosphamide, or dose-dense or weekly × 12 taxane Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	
T1 N0 M0 ER– PR– HER2/neu+ High grade Negative lymph nodes No metastasis Stage I	Lumpectomy with radiation therapy, or total mastectomy Sentinel lymph node biopsy	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide) Followed by dose-dense or weekly × 12 taxane Herceptin weekly or every 3 weeks × 1 year	May consider mastectomy with or without reconstruction if invasive component is not identified in lumpectomy specimen pathology report Oncotype ineffective due to node-positive disease Aromatase inhibitors preferred in all patients
T1 N0 M0 ER+ PR+ HER2/neu+ (triple positive) Negative lymph nodes Stage I	Lumpectomy with radiation therapy, or total mastectomy Sentinel lymph biopsy	Chemotherapy with 4 cycles of dose-dense anthracycline and cyclophosphamide Possibly taxane Herceptin weekly every 3 weeks × 1 year Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	May consider mastectomy with or without reconstruction if invasive component is not identified in lumpectomy specimen pathology report Oncotype ineffective due to node-positive disease
T1 N0 M0 ER– PR– HER2/neu– (triple negative) Negative lymph nodes Stage I	Lumpectomy with radiation therapy, or total mastectomy Sentinel lymph node biopsy	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane	May consider mastectomy with or without reconstruction if invasive component is not identified in lumpectomy specimen pathology report Oncotype ineffective due to node-positive disease Aromatase inhibitors most effective

T0 N1 M0 ER– PR– HER2/neu– (triple negative) Positive lymph nodes (1–3) No metastasis Stage IIA	Lumpectomy with radiation therapy or total mastectomy Sentinel lymph node biopsy; probable axillary node dissection if macroscopic disease in nodes	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane	May consider mastectomy if invasive component is not identified in lumpectomy pathology report, with or without reconstruction Oncotype ineffective due to node-positive disease Tamoxifen or aromatase inhibitor alone if oncotype score low *or* woman chooses no chemotherapy Aromatase inhibitors most effective Oncotype score ineffective in estrogen-negative disease Oncotype ineffective with HER2/neu+ status Aromatase inhibitors most effective Oncotype ineffective due to estrogen-negative disease
T1 N1 M0 ER+ PR+ HER2/neu– Positive lymph nodes (1–3) Stage IIA	Lumpectomy with radiation therapy, or total mastectomy Sentinel lymph node biopsy with probable axillary node dissection if macroscopic disease in nodes	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	Oncotype ineffective due to node-positive disease May have fine-needle aspiration, core-needle biopsy, or sentinel lymph node biopsy to accurately stage axilla if neoadjuvant chemotherapy administered If positive lymph nodes, may give neoadjuvant chemotherapy Aromatase inhibitors most effective
T1 N1 M0 ER– PR– HER2/neu+ High grade Positive lymph nodes (1–3) No metastasis Stage IIA	Lumpectomy with radiation therapy, or total mastectomy Sentinel lymph node biopsy with probable axillary node dissection if macroscopic disease in nodes	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane Followed by dose-dense or weekly × 12 taxane Herceptin weekly or every 3 weeks × 1 year	Oncotype ineffective due to node-positive disease May have fine-needle aspiration, core-needle biopsy, or sentinel lymph node biopsy to accurately stage axilla if neoadjuvant chemotherapy administered If positive lymph nodes, may give neoadjuvant chemotherapy
T1 N1 M0 ER+ PR+ HER2/neu+ (triple positive) Positive lymph nodes (1–3) Stage IIA	Lumpectomy with radiation therapy, or total mastectomy Sentinel lymph node biopsy with probable axillary node dissection if macroscopic disease in nodes	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane Herceptin weekly or every 3 weeks × 1 year Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	May have fine-needle aspiration, core-needle biopsy, or sentinel lymph node biopsy to accurately stage axilla if neoadjuvant chemotherapy administered If positive lymph nodes, may give neoadjuvant chemotherapy Aromatase inhibitors most effective

(*continues*)

TABLE 47-4

Examples of Stages of Breast Cancer and Treatment Choices (*continued*)

TNM Stage of Disease	Choice of Local Control	Type of Systemic Treatment	Comments
T1 N1 M0 ER– PR– HER2/neu– (triple negative) Positive lymph nodes (1–3) Stage IIA	Lumpectomy with radiation therapy, or total mastectomy Sentinel lymph node biopsy with probable axillary node dissection if macroscopic disease in nodes	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane	May have fine-needle aspiration, core-needle biopsy, or sentinel lymph node biopsy to accurately stage axilla if neoadjuvant chemotherapy administered If positive lymph nodes, may give neoadjuvant chemotherapy
T2 N0 M0 ER+ PR+ HER2/neu– High grade Negative lymph nodes No metastasis Stage IIA	Lumpectomy with radiation therapy, or total mastectomy Sentinel lymph node biopsy	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide) May be followed by dose-dense or weekly × 12 taxane Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	Neoadjuvant chemotherapy may be administered to decrease tumor size and increase chance of lumpectomy in smaller breast May have fine-needle aspiration, core-needle biopsy, or sentinel lymph node biopsy to accurately stage axilla if neoadjuvant chemotherapy administered Aromatase inhibitors most effective
T2 N1 M0 ER– PR– HER2/neu– (triple negative) Positive lymph nodes (1–3) Stage IIB	Lumpectomy with radiation therapy or total mastectomy Sentinel lymph node biopsy; probable axillary node dissection if macroscopic disease in nodes	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane	May have fine-needle aspiration, core-needle biopsy, or sentinel lymph node biopsy to accurately stage axilla if neoadjuvant chemotherapy administered Neoadjuvant chemotherapy may be administered due to disease burden
T3 N0 M0 ER– PR– HER2/neu– (triple negative) Negative lymph nodes No metastasis Stage IIB	Total mastectomy axillary node dissection (e.g., modified radical mastectomy). Will require radiation therapy to chest wall.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane	Fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy administration Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy should be administered due to disease burden
T3 N0 M0 ER+ PR+ HER2/neu– High grade Negative lymph nodes No metastasis Stage IIB	Total mastectomy Sentinel lymph node biopsy; axillary node dissection depending on surgical size of tumor following neoadjuvant chemotherapy. Will require radiation therapy to chest wall.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide) Followed by dose-dense or weekly × 12 taxane Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	Fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy administration Neoadjuvant chemotherapy should be administered due to disease burden Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Aromatase inhibitors most effective

T2 N2 M0 ER+ PR+ HER2/neu– Positive lymph nodes (4–9) Stage IIIA	Lumpectomy with radiation therapy, or total mastectomy. Due to level of disease, may receive radiation therapy to axilla); axillary node dissection.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	May have fine-needle aspiration, core-needle biopsy, or sentinel lymph node biopsy to accurately stage axilla if neoadjuvant chemotherapy administered Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy may be administered due to disease burden Aromatase inhibitors most effective
T2 N2 M0 ER+ PR+ HER2/neu+ (triple positive) Positive lymph nodes (4–9) Stage IIIA	Lumpectomy with radiation therapy, or total mastectomy with axillary node dissection (e.g., modified radical mastectomy). Radiation to chest wall and axilla necessary.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane Herceptin weekly or every 3 weeks × 1 year. May add additional target agents. Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	In N2 disease, may have palpable nodes Fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy administration Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy may be administered due to disease burden Aromatase inhibitors most effective
T3 N1 M0 ER– PR– HER2/neu+ Positive lymph nodes (1–3) Stage IIIA	Total mastectomy Axillary node dissection (e.g., modified radical mastectomy). Will require radiation therapy to the chest wall and axilla.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide) followed by dose-dense or weekly × 12 taxane Herceptin weekly or every 3 weeks × 1 year. May add additional targeted agents.	Fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy administration Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy should be administered due to disease burden
T3 N1 M0 ER– PR– HER2/neu– (triple negative) Positive lymph nodes (1–3) No metastasis Stage IIIA	Total mastectomy with axillary node dissection (e.g., modified radical mastectomy). Will require radiation therapy to the chest wall and axilla.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane	Fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy administration Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy should be administered due to disease burden
T4 N0 M0 ER+ PR+ HER2/neu– Negative lymph nodes Stage IIIA	Total mastectomy Axillary node dissection (e.g., modified radical mastectomy). Will require radiation therapy to chest wall.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane. May add additional targeted agents. Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	Fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy administration Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy should be administered due to disease burden Aromatase inhibitors most effective

(*continues*)

TABLE 47-4

Examples of Stages of Breast Cancer and Treatment Choices (*continued*)

TNM Stage of Disease	Choice of Local Control	Type of Systemic Treatment	Comments
T4 N3 M0 ER+ PR+ HER2/neu– Positive lymph nodes (10 or more) Stage IIIC	Total mastectomy with axillary node dissection (e.g., modified radical mastectomy). Will require radiation therapy to the chest wall, axilla, and other nodal basins.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention strategy and systemic treatment. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	In N3 disease, may have palpable axillary nodes May perform fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy administration Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy should be administered due to disease burden Aromatase inhibitors most effective
T4 N3 M0 ER– PR– HER2/neu+ Positive lymph nodes (10 or more) Stage IIIC	Total mastectomy with axillary node dissection (e.g., modified radical mastectomy. Will require radiation therapy to the chest wall, axilla, and other nodal basins.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide) followed by dose-dense or weekly × 12 taxane Herceptin weekly or every 3 weeks × 1 year. May add additional targeted agents.	In N3 disease, may have palpable axillary nodes May have fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy should be administered due to disease burden
T4 N3 M0 ER+ PR+ HER2/neu+ (triple positive) Positive lymph nodes (10 or more) Stage IIIC	Total mastectomy with axillary node dissection (e.g., modified radical mastectomy). Will require radiation therapy to the chest wall, axilla, and other nodal basins.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane Herceptin weekly or every 3 weeks × 1 year. May add additional targeted agents. Tamoxifen (premenopausal or postmenopausal) or aromatase inhibitor (postmenopausal only) as prevention. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	In N3 disease, may have palpable axillary nodes Fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy administration Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy should be administered due to disease burden Aromatase inhibitors most effective
T4 N3 M0 ER– PR– HER2/neu– (triple negative) Positive lymph nodes (10 or more) No metastasis Stage IIIC	Total mastectomy with axillary node dissection (e.g., modified radical mastectomy). Will require radiation therapy to the chest wall, axilla, and other nodal basins.	Dose-dense chemotherapy with an anthracycline (with or without cyclophosphamide); possibly carboplatin or cisplatin; followed by dose-dense or weekly × 12 taxane	In N3 disease, may have palpable axillary nodes Fine-needle aspiration or core-needle biopsy to accurately stage axilla prior to neoadjuvant chemotherapy administration Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Neoadjuvant chemotherapy should be administered due to disease burden

T (any) N (any) MI ER+ PR+ HER2/neu– Stage IV disease with distant metastasis	Surgery may be performed in future, but not at time of diagnosis May ultimately have radiation therapy to metastatic sites Major goal is to treat systemic disease and slow its course	Chemotherapy regimen may vary depending on condition of patient, comorbid conditions, and effect of breast cancer May receive a variety of targeted agents, although different agents than for HER2/neu+ tumors May start with hormonal control if woman is relatively asymptomatic Tamoxifen (premenopausal or postmenopausal, although *rarely* used in this setting) or aromatase inhibitor (postmenopausal only) as prevention and systemic care. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	Chemotherapy administered due to disease burden Sentinel lymph node biopsy not indicated in palpable axillary adenopathy or extensive disease burden Despite stage IV status, women may live longer than 10 years given their hormonal status Aromatase inhibitors most effective
T (any) N (any) MI ER– PR– HER2/neu+ Stage IV disease with distant metastasis	Surgery may be performed in future, but not at time of diagnosis May ultimately have radiation therapy to metastatic sites Major goal is to treat systemic disease and slow its course	Chemotherapy regimen may vary depending on condition of patient, comorbid conditions, and effect of breast cancer Will receive Herceptin throughout disease; may receive a variety of combined or individual targeted agents	Chemotherapy administered due to disease burden Despite stage IV status, women may live longer than 10 years given their HER2/neu+ status
T (any) N (any) MI ER+ PR+ HER2/neu+ (triple positive) Stage IV disease with distant metastasis	Surgery may be performed in future, but not at time of diagnosis May ultimately have radiation therapy to metastatic sites Major goal is to treat systemic disease and slow its course	Chemotherapy regimen may vary depending on condition of patient, comorbid conditions, and effect of breast cancer Will receive Herceptin throughout disease; may receive a variety of combined or individual targeted agents Tamoxifen (premenopausal or postmenopausal, although *rarely* used in this setting) or aromatase inhibitor (postmenopausal only) as prevention. If premenopausal, may receive ovarian suppression and take aromatase inhibitor.	Neoadjuvant chemotherapy administered due to disease burden Aromatase inhibitors most effective Despite stage IV status, women may live longer than 10 years given their HER2/neu+ and hormonal status
T (any) N (any) MI ER– PR– HER2/neu– (triple negative) Stage IV disease with distant metastasis	Surgery may be performed in future, but not at time of diagnosis May ultimately have radiation therapy to metastatic sites Major goal is to treat systemic disease and slow its course	Chemotherapy regimen may vary depending on condition of patient, comorbid conditions, and effect of breast cancer May receive a variety of targeted agents, although different agents than for HER2/neu+ tumors	Neoadjuvant chemotherapy administered due to disease burden This situation is most difficult due to triple-negative status. Long-term survival is not common.

Abbreviations: ER: estrogen receptor (positive or negative); HER2/neu: human epidermal receptor (positive or negative); PR: progesterone receptor (positive or negative); TNM: tumor, nodes, metastasis.

Source: Data from American Cancer Society[1,266]; Carlson et al[199]; National Comprehensive Cancer Network[200]; McCormick et al[244]; Kumar et al[245]; Braunstein et al[246]; Dietze et al[247]; Mohamed et al[248]; Dushkin et al[249]; Mego et al[250]; Masuda et al[251]; Van Poznak et al[252]; Leidy et al[253]; Tryfonidis et al[259]; Zhao et al[260]; National Cancer Institute[261]; Daly and Olopade[265]; Mamounas[267]; Garg and Buchholz[268]; Lillie et al.[269]; Rizzo and Wood[272]; James et al[273]; Fisher et al[274]; von Minckwitz and Loibl[340]; Jamieson et al[341]; Pietri et al[342]; Murialdo et al[343]; Yazilitas et al[344]; Colleoni and Gelber[345]; Bourdeanu and Liu[346]; Berruti et al[347]; Haddad and Goetz[348]; Brower[349]; Tolaney et al[350]; Reinbolt et al[351]; McVeigh et al.[352]

The nurse navigator often plays a critical role in preventing disparities that can occur in patients of Asian, African American, and Hispanic ethnicity.[195,240,241] Barriers to care created by low socioeconomic status, lack of health insurance, fragmented continuity of care, lack of a primary care provider, challenges in communication, low educational level, minimal social or family support, personal and family health priorities and healthcare practices, and cultural beliefs may all be addressed by a nurse navigator.[195,240,241]

The types of breast cancer, biologic markers, genetic changes, risk factors, and related treatment options may be difficult to learn, although a greater understanding of the relationship of these indices may improve the nurse's ability to explain the tumor's characteristics to the patient and family. As scientists continue the art of deconstructing the clinical and molecular heterogeneity of breast cancer, a greater understanding of these terms will be required of nurses and APNs to meet the informational needs of women and men diagnosed with specific breast cancer types.[203,215,219,231]

Newly diagnosed breast cancer requires prompt treatment, although the treatment options will rely on the size, type, and extent of the tumor. A multimodality approach is commonly used to care for patients, including care given by oncologists from the surgical, medical, and radiation teams, as well as consultation with oncoplastic surgeons, as needed. This can result in a personalized approach with individualized care, supportive care strategies, and overall improved quality of life and safety.

Nurses are integral in maximizing understanding of persons from minority groups who may need information specialists, translators, and additional guidance with a nurse navigator. Variations in ethnic beliefs and needs must be addressed and barriers minimized to help women understand the concepts under discussion and the various options in their own language.[195,240,241,269]

CONCLUSION

Early breast cancer encompasses prevention, screening and early detection, diagnosis, therapeutic approaches and nursing care based on a breadth of research, practice, and patient responses. Nearly 89% of women diagnosed with early-stage breast cancers reach their 5-year survival mark without evidence of recurrent disease.[1]

Our challenge is to continue research and testing of interventions related to survivorship of this disease, as we must take responsibility for the short- and long-term effects of the life-saving treatments that change the lives of women and men. We must learn about the multiple disparate conditions that women bring with their diagnosis and investigate ways to overcome them in an effort to improve patient outcomes. Furthermore, nurses need to take responsibility to learn and teach the *Healthy People 2020* guidelines to their patients and families in an effort to reduce morbidity and mortality. Control of diet, weight management, exercise, stress reduction, and smoking cessation will be future concerns in the reduction of recurrent breast cancer or reoccurrence of a second breast cancer or another primary cancer(s). We must be proud of what we have accomplished, but cannot stop. Above all, we must significantly increase research efforts to prevent a disease that stumps the finest scientists, learning how it starts and exactly what makes it happen.

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