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Breast Disease: Benign and Malignant

Angela L.W. Meisner, MPH[a],
M. Houman Fekrazad, MD[b],
Melanie E. Royce, MD, PhD[b,*]

[a]*Population Science, Cancer Health Disparities and Cancer Control, Cancer Research and Treatment Center, University of New Mexico, Albuquerque, NM 87131, USA*
[b]*Division of Hematology/Oncology, Department of Internal Medicine, Cancer Research and Treatment Center, University of New Mexico, Albuquerque, NM 87131, USA*

Breast diseases, both benign and malignant, are common. Typically, young women present with more benign pathologies; however, breast malignancies can occur in young women, especially in those harboring mutations in the *BRCA* genes, other inherited genetic syndromes associated with increased risk of breast cancer, or familial predisposition for breast cancer. In all women aged 40 and over presenting with abnormalities of the breast, a primary breast cancer should be ruled out because it is the leading cancer among women in developed countries.

Benign diseases of the breast

Epidemiology

Benign breast disease (BBD) is a heterogeneous group of pathologies with the majority related to benign fibrocystic breast changes. It is widely accepted that BBD is common, though the incidence is sparsely documented in the literature and is probably quite underestimated. It is challenging to approximate the incidence of BBD, given that it is not associated with a grave prognosis, and that not all women who have BBD see a physician. It is generally accepted that approximately 90% of women have fibrocystic changes, and that these are more pronounced in women of reproductive age. Prevalence and cumulative incidence rates of BBD may be estimated using

* Corresponding author. University of New Mexico, MSC 08-4630, UNM Cancer Research and Treatment Center, 900 Camino de Salud N.E., Albuquerque, NM 87131-0001.
E-mail address: MRoyce@salud.unm.edu (M.E. Royce).

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results from autopsy and cohort studies, respectively [1,2]. A forensic autopsy study by Bartow ands colleagues found benign cysts in 61% of the Caucasian women observed [3].

In 1997, Goehring and Morabia [1] conducted a meta-analysis to determine the incidence rate per 100,000 women-years for the two most common BBD in women: fibrocystic change and fibroadenoma. For fibrocystic change, the incidence rate per 100,000 women-years was 137 for ages 25 to 29 years, 411 for ages 40 to 44 years, and 387 for ages 48 to 49, producing a slightly skewed, bell-shaped curve. For fibroadenoma, the incidence rate per 100,000 women-years for fibroadenoma was 115 for ages 20 to 24 years, then a gradual decrease to less than 5 for women older than 50 years. Using this analysis, the study authors estimated the cumulative incidences were 8.8% and 2.2% for biopsy-proven fibrocystic change and fibroadenoma in women older than 65 years, respectively [1].

Etiology

Changes in hormone levels throughout women's reproductive cycles and lives contribute to the differentiation of the breast structure and cellularity. Therefore, risk of BBD is commonly associated with menopausal and hormonal status [2]. In premenopausal women who have BBD, underlying endocrinologic issues must be addressed. The following may be considered risk factors for BBD with differing degrees of association: oral contraceptives, age at first live birth, nulliparity, breastfeeding, age at menopause, socioeconomic status, education, race and family history of breast cancer [1]. For many women such changes are normal, without an identifiable cause.

Common symptoms and pathology in benign breast disease

Breast tissue is heterogeneous, containing ducts and lobules, stroma, and fat. Any one of these structures can be affected by benign processes. Fig. 1 illustrates the anatomy of the breast.

Mastalgia

Ninety percent of the time, mastalgia or breast tenderness/pain is benign [4]. There are two general types of mastalgia: cyclic or noncyclic. Cyclic mastalgia occurs because of hormonal changes during the menstrual cycle. Approximately 2 weeks before menses, hormonal changes trigger an increase in breast size and volume, and then they return to baseline a week afterward. The premenstrual changes in the breast can be heralded by mastalgia, and is often referred to as mastitis or fibrocystic disease; however, in reality it represents a normal condition of the breast. Some authors have found that symptoms associated with cyclic breast changes can be alleviated to varying degrees by reducing caffeine intake (coffee, tea, cola and chocolate), vitamin E cream application, or by taking evening primrose oil [5]. Relief may not be immediate, but symptoms generally improve

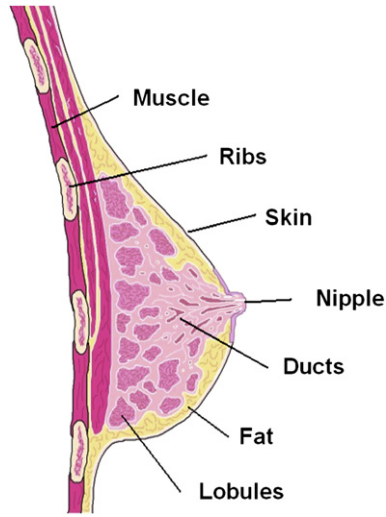

Fig. 1. Anatomy of the female breast.

within 3 to 4 months. Others, however, have suggested these treatments may be ineffective, and recommend instead a well-fitting bra, flaxseed, and topical nonsteroidal anti-inflammatory gel as treatments for mastalgia [6].

Noncyclic mastalgia is more common in older women and is not related to the menstrual cycles. It may be related to a variety of medications such as estrogen replacement, thiazide diuretics, and digoxin. Medications typically associated with mastalgia and those used to treat it are listed in Boxes 1a–b.

When a woman presents with mastalgia, a thorough history and physical examination is necessary to rule out any underlying pathology. Mammography, breast ultrasound or breast biopsy may be warranted for diagnostic purposes.

Box 1a. Medications associated with mastalgia

Oral contraceptives
Hormone replacement therapy
Antidepressants
Digoxin
Methyldopa
Spironolactone
Oxymetholone
Chlorpromazine

Box 1b. Medications used to treat mastalgia

Oral contraceptives
Danazol
Tamoxifen
Toremifene
Bromocriptine
Nonsteroidal anti-inflammatory drugs
Acetaminophen
Magnesium
Evening primrose oil

Mastitis

Mastitis is a condition in which the breast is inflamed, and it may or may not be caused by an underlying infection. The breast is often erythematous, warm, and tender. Mastitis is usually unilateral, and may be confused with inflammatory breast cancer. There are several types of mastitis, including, but not limited to, puerperal or lactational, periductal or mammary duct ectasia, and idiopathic granulomatous lobular mastitis (IGLM).

Puerperal or lactational mastitis is an acute infection of the mammary ducts, and is almost exclusively seen in lactating females. The inflammation is generally in a wedge distribution, but may eventually spread throughout the breast [7]. In addition to the tender, inflamed breast, other systemic symptoms may occur, such as fever, chills, fatigue, and body aches [8]. The organism responsible is usually *Staphylococcus aureus* and it generally enters the body through a dry, cracked nipple of a nursing mother. In most cases, the infant is the source of the infection by harboring the infectious organism in the oropharynx. The infection is treated appropriately with antibiotics, such as penicillins, cephalosporins, erythromycin, clindamycin, ciprofloxacin, or vancomycin. Left untreated, it may lead to breast abscess requiring surgical drainage. Necrosis may also develop, producing fibrous scars and nipple retraction, a presentation that can mimic an underlying breast carcinoma [7]. In nursing mothers, mastitis may also occur as a noninfectious inflammation caused by the increase in milk in the breasts.

Although mastitis mostly occurs in lactating women, it may occur at other times. Periductal mastitis, also called mammary duct ectasia, is not a disease and is not associated with lactation [8,9]. Perimenopausal and postmenopausal women are more likely to present with mammary duct ectasia than premenopausal women [8].

Mammary duct ectasia is a benign lesion of the breast that has been described in infants, prepubertal boys and girls, and adult men and women. In children and adolescents, the lesion is usually unilateral. The patient presents with nipple discharge, which may be bloody. Histologically, there is

dilatation of the mammary ducts, periductal fibrosis, and inflammation. Infectious and inflammatory causes have been implicated in the etiology. Ultrasound findings are usually suggestive, revealing dilated mammary ducts radially located around the nipple. The process is usually self-limited; therefore, surgery is not recommended if the diagnosis is certain [10].

IGLM is a rare benign breast disease that often mimics infection or carcinoma. Patients may present with impressive signs and symptoms that may include an irregular, inflamed, and painful breast mass, peau d'orange, nipple retraction, and no evidence of infection [11,12]. Despite dramatic findings in the breast, enlarged axillary lymph nodes are an uncommon sign of IGLM [12]. Care must therefore be taken not to confuse this condition with breast cancer to avoid inappropriate treatment. The exact etiology is unknown and response to treatment can be variable. Treatment often involves several months of anti-inflammatory medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) or prednisone. More severe or persistent cases may require a course of immunosuppressant such as cyclosporine or methotrexate. After medical therapy, some may require excision of any residual microabscesses.

Subareolar abscess, which typically affect smokers, presents with pain and redness of the nipple areolar complex. The abscess is generally polymicrobial. Treatment includes incision and drainage, and may occasionally necessitate antibiotics.

Nipple discharge and nipple abnormalities

Seventy percent of women have nipple discharge at some point during their lives. Many medications can be associated with galactorrhea, as enumerated in Box 2. Galactorrhea or milky discharge may be associated with hypothyroidism or pituitary adenomas, and assessment of thyroid stimulating hormone (TSH) and prolactin levels may be revealing of etiology.

Multiduct nipple discharge, especially if the discharge is milky, or cloudy green or yellow, is not an indication for surgical biopsy because the discharge is usually benign; however, a spontaneous bloody or serous nipple discharge is concerning for underlying problems. Approximately a third of these discharges are malignant, so evaluation should be more extensive. Galactography or mammary duct excision should be performed, and most often will reveal an intraductal papilloma, a benign growth of the breast ducts, which is the most common cause of a bloody nipple discharge. This lesion's appearance on galactography is that of a smooth, lobulated, intraluminal filling defect or a solitary obstructed duct [13].

Congenital inversion of the nipples occurs in many women, particularly those who have large breasts. It may be confused as a symptom of breast cancer [7]. Nipple inversion can also occur later in life as a result of scarring from acute mastitis. Nipple inversion, unless associated with other breast findings, is usually not a significant problem other than perhaps causing difficulty with nursing.

Box 2. Medications commonly associated with galactorrhea

Drugs that block dopamine receptors
- Butyrophenones
- Metoclopramide
- Phenothiazines
- Risperidone
- Selective serotonin reuptake inhibitors
- Thioxanthenes
- Tricyclic antidepressants

Drugs that deplete dopamine
- Methyldopa
- Reserpine

Drugs that inhibit release of dopamine
- Codeine
- Heroin
- Morphine
- Antihistamines
- Cimetidine

Drugs that stimulate lactotrophs
- Oral contraceptives
- Verapamil

Adapted from Leung AK, Pacaud D. Diagnosis and management of galactorrhea. Am Fam Physician 2004;70(3):544; with permission.

Skin conditions such as eczema or dermatitis may occur on the nipple and areola. Management approaches are similar to other parts of the body, with topical corticosteroids being the mainstay of treatment. Paget's disease of the nipple presents as a persistent dermatitis of the nipple with a red, oozing, crusted lesion, which is often unresponsive to topical steroid and antibiotics. Rarely, it can occur in both breasts [14]. This is an uncommon type of pathology that must not be dismissed simply as eczema, because over 95% are associated with an underlying breast cancer [15]. Most patients diagnosed with Paget's disease are over age 50, but a few cases have been diagnosed in women in their 20s [15]. Surgery is the most common form of treatment, but the specific treatment often depends on the characteristics of the underlying breast carcinoma. An algorithm for investigation of nipple discharge is shown in Fig. 2.

Fat necrosis

Fat necrosis presents as a firm mass generally associated with a history of trauma, surgery, or radiation therapy of the breast, though it can occur for

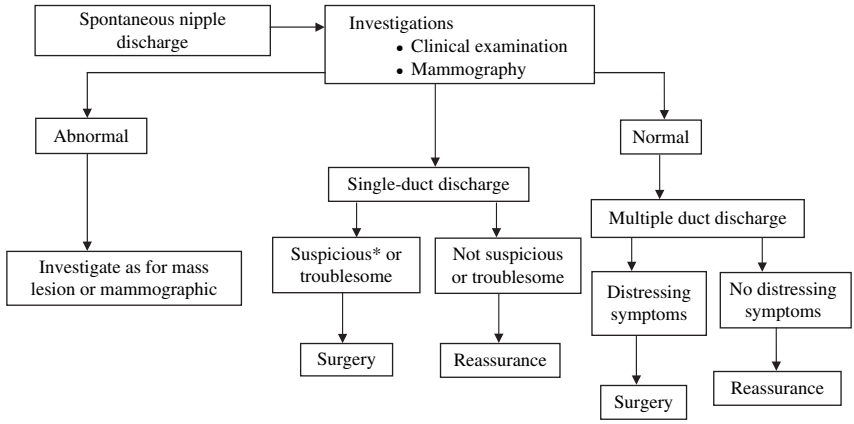

Fig. 2. Investigation of nipple discharge. * Suspicious means discharge that is bloodstained or contains moderate or large amounts of blood on testing, is associated with a mass, or is a new development in women older than age 50 and is not thick or cheesy. (*From* Dixon MJ, Bundred NJ. Diagnosis and management of benign breast diseases. In: Harris JR, Lippman ME, Morrow M, et al, editors. Diseases of the breast. 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 48; with permission.)

unknown reasons. Perimenopausal women who are obese and have large breasts are more likely to develop fat necrosis. It is typically found in the superficial region of the breast as a firm, nontender, irregular mass, which may result in skin retraction [8]. Clinically and mammographically, it may be difficult to distinguish it from a carcinoma of the breast. The diagnosis is usually made by breast biopsy.

Fibrocystic changes

Fibrocystic change is a heterogeneous group of changes rather than a single entity, affecting the stromal and glandular tissues of the breast. Pathologically, these changes are characterized by the formation of cysts, stromal fibrosis, and a variety of proliferative lesions [7]. The term ''fibrocystic disease'' is also commonly used to describe these lesions, but the morphologic changes that occur are not consistent with the definition of a disease. These changes are present in up to 90% of women and represent the normal changes in the breast, generally occuring between the ages of 20 and 40 years. Symptoms of fibrocystic change, such as palpable lumps or nipple discharge, may be initially confused with characteristics of carcinoma [7]. In premenopausal women, symptoms usually occur in conjunction with the menstrual cycle. Typically, postmenopausal women and adolescent girls do not experience symptoms related to fibrocystic changes, although it has been reported among in older women.

Fibrocystic changes can be classified as either nonproliferative or proliferative based on pathologic findings. Nonproliferative changes such as cysts, apocrine metaplasia, fibrosis, intraductal hyperplasia, and fibroadenomas

do not increase the risk of developing breast cancer. Proliferative lesions, on the other hand, may slightly increase the risk for breast cancer by 1.5 to 2 times that of the general population. Examples of proliferative lesions without atypia include florid hyperplasia, sclerosing adenosis, and intraductal papillomatosis. If a patient has epithelial ductal hyperplasia with moderate or florid proliferation of ductal cells, she has a 1.6 times higher risk of developing breast cancer. The relative risk increases to 2 if she has a family history of breast cancer [16]. Additionally, breast cancer risk increases if there are more than four layers of myoepithelial and epithelial cells [7]. When the proliferative lesion is associated with atypia, the risk for breast cancer is even higher. Women who have atypical ductal or lobular hyperplasia are at 4.5 to 5 times increased risk for developing breast cancer compared with the general population; or a hazard ratio of 5.80, after adjusting for breast density, ethnicity, and family history [17]. With the addition of a positive family history of breast cancer, the risk doubles to 8 to 10 times that of the general population.

Nonproliferative changes such as cysts and fibroadenomas are commonly encountered. Patients may experience symptoms for which they seek medical attention, or a discrete lesion may be seen on breast imaging. Cysts are fluid-filled lesions generally found in the terminal duct or lobule, and may appear with apocrine metaplasia [7,8,16,18]. Pain may or may not be a presenting symptom. Most women who report pain usually experience it in the upper and outer quadrant of the breast, and the pain is usually bilateral.

Fibroadenomas are grossly pseudoencapsulated lesions found in the stroma and ducts. Fibroadenomas are bilateral in about 10% of patients. Adolescent girls and young women are more likely to exhibit fibroadenomas than older adult women [8]. Fibroadenomas can vary in size from a few millimeters to several centimeters [19].

Epithelial hyperplasia is a type of proliferative change that is not obvious by physical examination. It is the result of proliferation of the myoepithelial and epithelial cell layer of the ductal system of the breast or, more frequently, the lack of apoptosis in the ductal lumen [7]. There are three levels of ductal cell proliferation: mild, moderate, and florid [8,20]. Atypia may or may not be present [7]. When present, atypia can be either an atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia [8]. These proliferative lesions share similar characteristics with their in situ counterpart [7]. Ductal carcinoma in situ (DCIS) is a noninvasive form of breast cancer and is discussed further under the malignant breast disease section of this article. Lobular carcinoma in situ (LCIS), although it sounds like cancer is in general considered a form of benign proliferative breast disease. Women who have LCIS are at a 15% to 35% increased risk for developing breast cancer over the next 15 years. Although many women have undergone bilateral prophylactic mastectomy for this condition, close clinical follow-up may suffice. Alternatively, chemoprevention, such as with tamoxifen, can be considered as a risk-reduction strategy. In women

who have LCIS and who subsequently develop a breast cancer, the most common histologic type is an infiltrating ductal carcinoma rather than an infiltrating lobular carcinoma, and the risk for developing breast cancer is equal in either breast.

Evaluation of benign breast disease

When evaluating breast abnormalities, one of the most important considerations is to exclude breast cancer. The clinical context may provide direction as to whether breast cancer should be low or high in the differential diagnosis, with the clear understanding that there are always exceptions to the rule.

Mammogram

Mammograms are radiographs of the breast whose sensitivity is highly dependent on breast density. As breast density increases, the sensitivity of a screening mammogram diminishes from 98% in women who have fatty breasts to 55% in those who have the densest breasts [20]. In general, denser breasts are found in younger compared with older women, and premenopausal compared with postmenopausal women. In a dense breast, a mass may be missed on mammogram. Thus, other breast imaging modalities such as an ultrasound or MRI may be required, especially in younger women, to better examine a lesion, especially if index of suspicion is high for a malignancy. Calcifications are best seen on mammogram. Fat necrosis [8] and fibrocystic change [7] on mammography may appear as a mass or dense tissue, with or without associated calcifications. In fibroadenomas, the calcifications often appear as "popcorn" [8,21]. The detection of microcalfications and other abnormalities on routine screening mammography has increased the rate of atypical hyperplasia diagnoses. An estimated 12% to 17% of biopsies performed for evaluation of a mammographic abnormality resulted in a finding of atypical hyperplasia [8].

Ultrasound

Ultrasound is often a useful adjunct in evaluating breast abnormalities, and may even be the initial breast imaging modality used, especially for a young woman who has very dense breasts. It can very easily differentiate between cystic and solid lesions, as in a simple cyst versus a fibroadenoma; however, it is not a good way to evaluate calcifications, especially when it is not associated with a mass. Ultrasound is not an effective method of screening the entire breast, and is best used to examine a targeted area of the breast.

Breast magnetic resonance imaging

MRI imaging is being used with increasing frequency by breast specialists for both diagnostic and screening purposes. This is because MRI imaging is quite sensitive and can help detect breast cancer that is both clinically and mammographically occult [22]; however, breast MRI is not a substitute

for mammography; rather it is an adjunct to it. Although quite sensitive, MRI has limited specificity, in the range of 65% to 79%, because of the enhancement of benign lesions such as fibroadenomas, fat necrosis, and certain types of fibrocystic changes. Indeed, women who are also screened with breast MRI tend to have more biopsies than women screened with mammography alone. Unfortunately there are reports of women undergoing unnecessary mastectomies on the basis of MRI findings without subsequent histologic demonstration of a malignancy in the resected breast specimen [23]. Cost is another important issue to consider regarding the use of MRI. Physicians should therefore use breast MRI only for a select group of women or clinical scenarios, and should recognize the benefits and pitfalls of this test when ordering it for their patients.

Current recommendations for the use of breast MRI are to evaluate a breast lesion in patients who have: (1) equivocal mammographic or physical examination findings;, (2) malignant axillary adenopathy and unknown site of primary tumor; and (3) extensive or locally advanced cancer undergoing neoadjuvant systemic therapy, typically chemotherapy [23]. As a screening tool, it should be limited to women at increased lifetime risk (greater than 20%) of developing breast cancer [23]. MRI is particularly helpful in women who have a high likelihood of developing breast cancer at an early age (eg, *BRCA* mutation carriers), because the denser breasts of young women generally decrease the sensitivity of a mammogram.

Tissue sampling

When the clinical examination or imaging of a breast abnormality are inconclusive, a tissue or cytologic diagnosis should be obtained. There are several ways to do this. One is to obtain a fine needle aspiration (FNA). Cysts are particularly amenable to this type of cytologic evaluation because it serves a dual purpose—for diagnosis and symptom management [16]. In many cases a lesion is not amenable to FNA, and a biopsy is required for tissue diagnosis. Core biopsy is preferred over excisional or incisional biopsy, unless the lesion is not amenable for this procedure or it is definite that the lesion is benign. For instance, when the symptom-causing lesion is clearly a fibroadenoma, it can be treated surgically by removing the lesion entirely.

Treatment strategies for benign breast disease

Treatment for BBD is directed at symptom control and prevention of more serious problems that might arise from the lesion if left untreated. In general, most fibrocystic changes in the breast do not require any treatment, and get better with time.

Lifestyle modifications

Lifestyle modifications can be encouraged, not only because they could alleviate the symptoms related to BBD, but also because of the benefits

related to general health and well-being. Eating a low-fat diet [24] and avoiding caffeine may be used to treat fibrocystic change, particularly if pain is exhibited [25]. Although a direct association has not been definitively established, smoking cessation and regular exercise is encouraged. Women who experience fat necrosis should wear an extra supportive brassiere.

Medications

BBD with infectious etiology, such as an abscess or mastitis, are treated with antibiotics; however, duration of therapy depends on the severity of symptoms and response to treatment. Commonly patients require at least 1 week of oral antibiotics. The choice of antibiotic depends on the suspected etiologic organism, usually gram-positive cocci. Acute mastitis is also treated with warm compresses. In lactational mastitis, breastfeeding should continue while the patient is treated for the mastitis [8].

Anti-inflammatory medications can also be used either as a pain reliever or to treat noninfectious forms of BBD. A brief course of NSAIDs can be very useful in managing pain related to fibrocystic changes as well as other BBD. In IGLM, NSAIDs and celecoxib can be quite useful, although the condition requires a longer duration of therapy compared with noninfectious mastitis.

Because several of the changes associated with BBD depend on hormonal fluctuations, oral contraceptives may be useful in its treatment. This may also help prevent development of further lesions, or at the very least, help modulate their size, thus further alleviating the symptoms [7].

In women who are deemed at intermediate to high risk of developing breast cancer, chemoprevention risk-reduction strategies include tamoxifen (for either pre- or postmenopausal women) [26] or raloxifene (for postmenopausal women only) [27]. Determination or calculation of breast cancer risk is discussed further under the section of malignant breast diseases of this article.

Surgery

Surgical drainage of an abscess is performed to prevent the spread of the infection and for symptomatic relief of discomfort/pain [7]. Fibroadenomas, when symptomatic, can be excised completely. Alternatively, if a patient is less than 35 years old and the breast mass is not disrupting quality of life, a core biopsy can be performed, primarily to establish that there is not a more ominous pathology to worry about, and then the condition can be managed conservatively [8,21]. Fig. 3 depicts an algorithm for evaluation and management of a palpable mass.

Less invasive forms of surgery to manage fibroadenomas are in use in certain centers in the United States. One such technique is cryoablation, which "freezes" the lesion in situ. The cells, which have been killed by the cryoablation procedure, are eventually cleared by macrophages. This process does

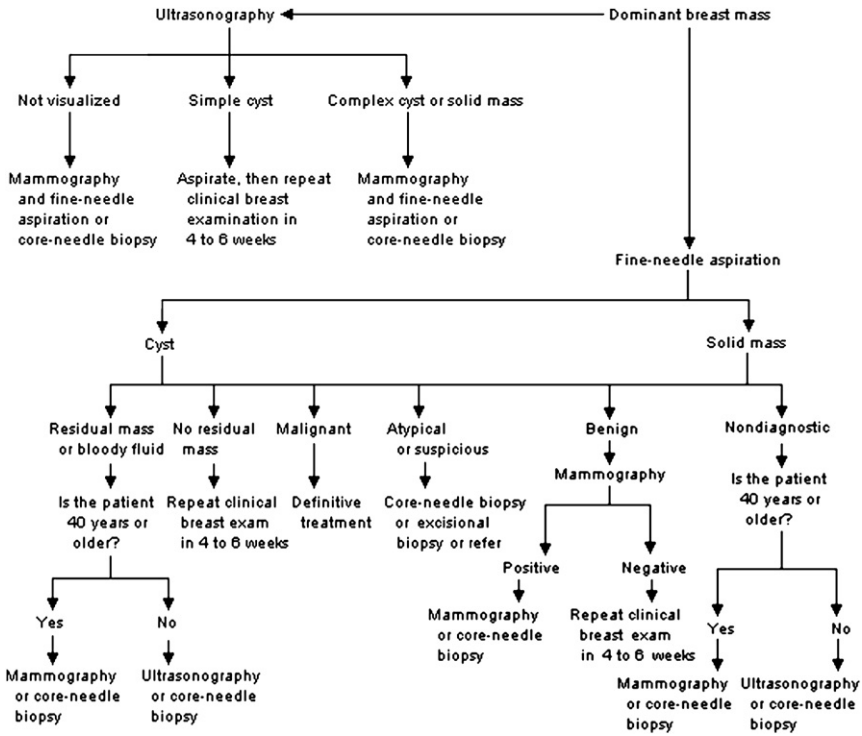

Fig. 3. Diagnostic algorithm for patients with palpable breast masses. (*Reprinted from* Evaluation of palpable breast masses. Am Fam Physician 2005;71:1736; with permission. Copyright © 2005 American Family Physicians. All Rights Reserved.)

take time, so the mass from the fibroadenoma may remain palpable for a long time after treatment.

Malignant diseases of the breast

Epidemiology

In the United States, breast cancer is the second most common cancer after skin cancers, and is the second leading cause of death from cancer in women after lung cancer. In 2007, 178,480 women will be diagnosed with breast cancer and 40,460 women will die of their disease [28]. At the current rate, 1 out of 8 American women will develop breast cancer at some point in their lifetimes [29,30]. After increasing since 1980, female breast cancer incidence rates leveled off from 2001 to 2003, likely a reflection of the saturation of mammography use and reduction in the use of hormone replacement therapy [28,31]. Even more noteworthy is that mortality from breast cancer has been on the decline since the early 1990s, partly because of early diagnosis and improvements in adjuvant therapy.

Etiology

Many factors influence the risk of developing breast cancer. Female gender and age are two risk factors that all too often are underemphasized, probably because there is nothing one can do to influence them. Other commonly recognized factors are genetics, family history of breast cancer, personal history of a prior cancer or prior biopsies disclosing atypia or LCIS, and use of hormone replacement therapy. The contributions to the risk of developing breast cancer by some of these factors are briefly described.

Personal characteristics

Female gender is the primary risk factor for developing breast cancer, with a female-to-male risk ratio of about 135 to 1. Age is the second leading risk factor. In American women, the probability of developing breast cancer is 1 in 210 at age 39 or younger, to approximately 1 in 25 for ages 40 to 60 years, to as high as 1 in 15 for those 70 years and older [28]. Age at first birth, early menarche, and late menopause are other factors that are weakly associated with an increased relative risk of developing breast cancer.

Prior personal history of cancer is another influencing factor. For instance, women who have a personal history of endometrial or ovarian carcinoma have greater than twice the risk of developing breast cancer as that of women who do not have such a history. Risk of a recurrence from a prior personal history of a breast cancer is clearly a concern, but it also puts the woman at a higher risk of developing a second breast cancer, either in the ipsilateral or contralateral breast. Women who have no prior history of breast cancer and who have had breast biopsies that reveal benign proliferative changes are also at increased risk of developing breast cancer. The risk is even more significant when proliferative changes are associated with atypia, especially if there is also a family history of atypical hyperplasia or breast cancer in first-degree relatives [16]. As previously mentioned, LCIS on previous biopsy is a marker for risk of developing invasive breast carcinoma in either breast.

Hormone replacement therapy

In postmenopausal women, the benefits of hormone replacement therapy (HRT) for menopausal symptoms are controversial, primarily because of the increased risk of developing breast cancer. On average, HRT use is estimated to increase the annual rate of breast cancer to approximately 2% above that for women not using it [32]. In the landmark Women's Health Initiative (WHI) study, more women taking HRT in the form of combined estrogen and progestin developed breast cancer than those taking placebo [33]. After an average of 5.6 years, 245 of the 8506 women on HRT and 185 of the 8102 women on placebo developed breast cancer. Of the total cancers, 349 cases were invasive; there were 8 additional cases of invasive

breast cancer for every 10,000 women over 1 year caused by HRT. Overall, the study authors found a 24% increase in the relative risk for breast cancer caused by HRT. HRT for management of problematic menopausal symptoms may be reasonable, but should be used for the shortest possible duration and with the lowest dose. Common and potential life-threatening side effects of HRT should be discussed with the patients.

Family history and genetic predisposition

The majority of patients who develop breast cancer, up to 85% of cases, do not have a family history of breast cancer; however, if a woman's mother, sister, or daughter has a history of breast cancer, her risk increases by approximately twice the population risk. Even more significantly, if a woman has two first-degree relatives affected, her relative risk increases by more than four to six times compared with someone without a family history. Moreover, bilateral breast cancer in a first-degree relative may increase risk by more than six times.

Only approximately 5% of breast cancer cases can be considered as inherited forms of breast cancer, and an additional 10% to 15% can be considered to have a familial predisposition. All are autosomal dominant and tend to be highly penetrant. Bilaterality is common, where breast cancer diagnosis can either be synchronous or metachronous. It is often forgotten that 50% of hereditary breast cancer is inherited from the paternal side. Carriers of a germ-line mutation have a 1.5% to 4% per year risk of developing breast cancer. The best-characterized genetic risk factors are represented by germ-line mutations in *BRCA1*and *BRCA2*. These tumor-suppressant genes are associated with a much higher risk of breast and ovarian cancers [34,35]. Claus and colleagues [36] estimated that 36% of breast cancer cases in women aged 20 to 29 years could be attributed to a single dominant susceptibility gene, whereas only 1% of women diagnosed with breast cancer over the age of 80 have such a gene mutation. The lifetime risk of breast cancer in female carriers of *BRCA1* mutation is estimated to be 36% to 87%, and 45% to 84% in carriers of *BRCA2* mutation. Additionally, *BRCA2* mutations are associated with a 6% lifetime risk of breast cancer among male carriers [34].

Breast cancer risk assessment tools

Optimal public health gains from breast cancer risk-reduction strategies depend on the ability to accurately assess an individual's risk for developing breast cancer. Several models of risk assessment exist. It is important to remember that these models assess probability of developing breast cancer, not of dying from it. Two currently accepted breast cancer risk assessment models are the Gail model and the Claus model. Both were designed primarily to provide risk assessments for Caucasian women, so caution must be taken when applying them to women of other races.

The Gail model estimates the risk of developing an invasive breast cancer over the next 5 years and a woman's lifetime [37]. It considers five factors: (1) current age; (2) age at menarche; (3) previous breast biopsies, taking into account if any of those biopsies demonstrated atypia; (4) age at first live birth; and (5) history of breast cancer in first-degree relatives. Disadvantages of this model are that it does not evaluate age at which a family member was diagnosed, and whether the disease occurred in both breasts. Thus, it underestimates the risk for patients who might harbor a *BRCA* mutation. Furthermore, the Gail model does not apply to women who have LCIS, DCIS, or personal history of breast cancer.

The Claus model is weighted toward identifying women at risk for breast cancers related to a genetically inherited risk. It calculates age-specific and cumulative risk of developing breast cancer for a woman who has a first-degree family history of breast cancer based on the age of the relative at diagnosis and the relationship to the woman at risk [36]. Like the Gail model, the Claus model does not consider other cancers that may signal a hereditary component, such as ovarian cancer and male breast cancer.

Of all the breast cancer risk assessment tools, the Gail model is the most user-friendly and readily available. For individuals who would like to personally assess their risk, a computerized risk assessment tool based on the Gail model is available on the Web at http://www.cancer.gov/bcrisktool [38]. The CancerGene software from University of Texas Southwestern, which estimates Gail risk, Claus risk, and the statistical model BRCAPRO, may also be found at http://www4.utsouthwestern.edu/breasthealth/cagene [39].

BRCAPRO is another program used to determine an individual's risk of carrying a *BRCA* mutation, but is not used to estimate the risk of developing breast cancer. BRCAPro assess the risk of a *BRCA* mutation based on personal and family history of breast cancer and ovarian cancer [40]. It also takes into account male breast cancer, ages of breast cancer onset, and the total number of family members who have never developed breast or ovarian cancer. The BRCAPRO software may be downloaded from http://astor.som.jhmi.edu/BayesMendel/brcapro.html [41].

The risk of harboring a genetic mutation is best determined by a genetic counselor rather than a general practitioner, mainly because of the extensive counseling that is required before genetic testing.

Malignant breast pathologies

There are several ways of classifying malignant breast pathologies. One method is to classify them as either invasive or noninvasive. Although some noninvasive forms of breast cancer may become invasive over time, invasive breast cancers are more concerning because they have the ability to metastasize to distant sites and other organs at the outset. Another way of classifying breast pathologies is by their histologic subtypes. The

most common histologic type of breast cancer is ductal, followed by lobular carcinoma. Some histologic types, such as tubular or mucinous, have a more favorable biology, whereas those with squamous or sarcomatous differentiation have a more aggressive behavior. Although often of ductal histology, a particularly aggressive form of breast cancer is inflammatory breast carcinoma. This type of breast cancer has a rapid course from a normal to abnormal looking breast in days to weeks, and is often misdiagnosed as mastitis, which often leads to delay in initiation of appropriate therapy. Fortunately, these aggressive histologic types and forms of breast cancer are less frequent than the "garden variety" type of breast cancer.

Noninvasive breast carcinoma

There are two subtypes of noninvasive carcinoma, DCIS and LCIS, although the latter is considered more frequently as a marker or risk rather than a cancer. DCIS is by far more common than LCIS, and more importantly, is clearly a malignant lesion.

In DCIS, cancer cells proliferate within the mammary ductal-lobular system. DCIS can present as either a mass or pleomorphic microcalcifications. Because it is noninvasive, it is less likely to produce overt changes in the contour of the breast or skin changes, but can occasionally be associated with nipple findings such as a discharge. Five pathologic subtypes have been identified: comedo, papillary, micropapillary, cribriform, and solid. A positive biopsy for DCIS increases the risk of subsequent development of an invasive ductal carcinoma by 8 to 10 times, possibly higher in comedo type DCIS. Standard of care is resection with negative margins followed by radiation therapy to the ipsilateral breast. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial, which prospectively randomized 818 patients to either radiation therapy or no radiation therapy following lumpectomy, showed that radiation after lumpectomy reduces the incidence of tumor recurrence in the ipsilateral breast by about half [42]. In women who have estrogen receptor or progesterone receptor positive (collectively referred to as hormone-receptor positive) DCIS, tamoxifen for 5 years is also recommended. The NSABP B-24 study, involving 1804 women who had DCIS randomized to receive either tamoxifen or placebo following their local therapy, showed that the addition of tamoxifen is more effective than local therapy alone in preventing invasive and noninvasive ipsilateral breast tumor recurrences [43].

In LCIS, solid proliferation of uniform small cells occurs within multiple breast lobules. There is diffuse involvement throughout the breast tissue, and it should be considered to be present in both breasts. Although LCIS shares features of its natural history with DCIS, LCIS is a more indolent form of in situ breast carcinoma than DCIS. For this reason, there is no compelling reason to surgically treat LCIS [44]. Negative surgical margins are not required, because it is presumed to be multicentric [45]. A woman

who has a finding of LCIS has 10 times the risk of developing invasive breast cancer compared with her counterpart without this diagnosis. Thus, these women are particularly good candidates for chemoprevention strategies with either tamoxifen or raloxifene, the latter recommended only in postmenopausal women. Additionally, elective bilateral mastectomy is an option, but because this is more invasive and a permanent procedure, it should be a personal choice for the patient. Furthermore, follow-up is more intensive, depending on age and clinical scenario, such as whether patients decide to take chemoprophylaxis, undergo a bilateral mastectomy, or choose close surveillance.

Invasive breast carcinoma

Invasive breast cancers usually are epithelial tumors of ductal or lobular origin. Infiltrating ductal carcinoma is the most common form of invasive breast cancer, and accounts for about 75% of patients who have breast cancers. Typically, it presents as a hard palpable mass, although with increasing use of screening mammography more cancers of this type are diagnosed at a nonpalpable stage. Infiltrating lobular carcinoma has a much lower incidence and composes about 15% of invasive breast cancer. It has a tendency to be more multifocal. Other invasive histologies of epithelial origin, such as tubular, medullary, and papillary carcinomas, as well as nonepithelial breast tumors such as breast lymphoma, are much less common, and together account for less than 10% of all invasive breast cancers.

Pattern and tempo of metastasis for invasive breast carcinomas can be quite unpredictable. In general, they metastasize to regional axillary lymph nodes first. Frequent sites of distant metastasis include the bone, lung, and liver. The brain as a sole site of metastasis is uncommon, occurring in less than 5% of patients presenting with a recurrence. Metastasis to the meninges (ie, leptomeningeal disease or LMD) can occur and is particularly difficult to manage. Similarly difficult to manage is metastasis to serosal surfaces or peritoneal carcinomatosis. This particular type of metastasis is more commonly associated with infiltrating lobular carcinoma.

Molecular markers in the tumor are increasingly used in clinical practice to discern both prognosis and probability of response to a given therapy. Currently, tumor expression of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are routinely assessed in every newly diagnosed breast cancer. All three have important prognostic and predictive implications. ER and PR are valuable markers of disease-free survival and potential response to hormonal therapy. Patients who have hormone receptor-positive breast cancers in general have a more indolent course with fewer numbers of recurrences; however, they also tend to have a long natural history, so that very late recurrences, 10 to 15 years later, are not uncommon. More importantly, treatment with anti-estrogen therapies such tamoxifen or an aromatase inhibitor can effectively decrease the risk of recurrence. Based on the results from the

Breast Cancer Prevention Trial (BCPT or P1 Trial), 5 years of tamoxifen compared with placebo reduced the risk of developing invasive breast cancer by 49% ($P < .00001$) in women at increased risk for breast cancer. The relative reduction in risk was greater in women who had a history of LCIS (56%) or atypical hyperplasia (86%) [46]. In patients diagnosed with breast cancer, treatment with tamoxifen improves breast cancer specific survival compared with placebo [47].

HER2 overexpression occurs in 20% to 30% of breast cancers, and is associated with increased incidence of recurrence and shortened survival. Patients who have HER2-positive breast cancer are candidates for treatment with the anti-HER2 monoclonal antibody trastuzumab. The addition of trastuzumab to standard therapy in early-stage and advanced disease has been shown to improve outcomes with fewer recurrences and deaths, respectively [48]. As more is learned about the biology of breast cancer, it is hoped that discovery of other molecular markers will be useful not only in providing prognosis, but also in tailoring therapy to specific abnormalities found in an individual's tumor.

Evaluation and diagnosis of breast cancer

Suspicious breast symptoms or findings must be carefully evaluated to rule out a malignancy. Several modalities may be used for evaluation, most of which are complimentary.

History and physical examination

History and physical examination are key to the evaluation and diagnosis of any lesion suspicious for a breast cancer. Other tests are important and useful adjuncts, but understanding the clinical scenario is a critical first step. Careful history will often lead a clinician to raise or lower the level of suspicion, and thus influence how vigorously additional testing is pursued.

Physical examination should include inspection of the patient in the upright as well as supine positions. Unless there is an obvious explanation, significant size discrepancy or asymmetry of the breast, dimpling, nipple retraction or inversion, scaling, skin erythema, edema (peau d'orange), or ridging should be considered abnormal and merit further evaluation. Examination of the supraclavicular, infraclavicular, and axillary lymph nodes is a part of routine physical examination. Once the patient is in the supine position with the ipsilateral arm extended over the head, the breast parenchyma can be compressed against the chest wall. This may reveal abnormalities not seen previously, such as a breast mass. Although not all breast cancers present with a mass, when a hard, often painless mass is noted, further evaluation is warranted. The same is true for a spontaneous bloody nipple discharge. In summary, all palpable breast masses should be evaluated by a physician to determine if further work-up is warranted.

Monthly self-breast examination (SBE) as a prevention strategy is still generally presented as an option for women beginning at age 18 years, although no strong data support its efficacy in the early detection of breast cancer. In fact, studies indicate that SBE increases the incidence of diagnostic interventions as well as patient anxiety without altering the incidence of breast cancer mortality. If a woman wishes to do monthly SBE, she should be carefully taught how to do it properly. Clinical breast examination in women age 19 to 40 years is recommended approximately every 3 years, and yearly for women aged 40 years and older [49].

Diagnostic mammogram and other breast imaging techniques

In the past, breast cancer most commonly presented as a palpable mass found by the patient. Currently most breast cancers are detected mammographically, when the mass may be quite small in size and nonpalpable. Thus, screening mammograms are important in the detection of breast cancer at an early stage. The American Cancer Society recommends that women in their 20s and 30s have clinical breast examinations every 3 years, and women aged 40 and older should have yearly bilateral mammograms and clinical breast examinations. In high-risk patients, such as *BRCA1* and *BRCA2* mutation carriers, heightened screening should begin at age 25, or 10 years earlier than the earliest age in which breast cancer presented in a family member. These women should best be followed at a high-risk breast clinic if one is available. (See the article by Zebrack and Brown elsewhere in this issue for additional breast cancer screening guidelines.)

Diagnostic mammography, which takes additional views of the breast or lesion, is commonly recommended for symptomatic patients or women who have abnormal screening mammogram. It is also recommended for breast cancer follow-up (ie, post-lumpectomy) and after breast augmentation surgery.

As an adjunct to mammography, ultrasonography can be particularly useful in younger patients or women who have fibrocystic breasts. Its main use remains in distinguishing solid from cystic lesions. It can be very operator-dependent, and is most useful when one can indicate which area of the breast needs further investigation. It is not a useful screening method for the entire breast because this would be quite time-consuming, and areas of the breast can be easily missed.

High-risk patients who are good candidates for MRI screening include women who have very dense breasts, women who have a personal history of breast cancer not initially visualized by mammography, and women who have a strong familial or genetic predisposition for breast cancer (eg, carriers of *BRCA1* or *BRCA2* mutation). As a screening modality, MRI is quite sensitive, but its specificity is significantly lower than that of mammography. As a consequence, more than twice as many unnecessary biopsies are performed, because many more abnormalities are picked up that turn out to benign on further evaluation [50]. When breast cancer is

diagnosed, MRI can be a very useful tool in determining the extent of the lesion, including assessment of whether there is chest wall or regional lymph node involvement. It is thus a useful adjunct for surgical planning and to determine whether the patient may be better served by undergoing neoadjuvant therapy initially, or for recommending mastectomy rather than lumpectomy.

Breast implants create limitations with regard to use of conventional breast cancer screening modalities. For instance, implants may make it difficult to adequately compress the breast during mammography for adequate viewing of the breast parenchyma. Given that the type, size, and placement of the breast implants differ, modification of screening practices depends on what finding/abnormality the clinician is investigating. Increasingly, MRI is used for evaluation of suspicious breast lesions in patients who have implants.

Diagnostic procedures for histologic diagnosis

Similar procedures used for BBD are also used in evaluating lesions suspected of breast cancer.

Although FNA remains a useful procedure for masses such as simple cysts, it is no longer the standard for initial evaluation of many palpable breast masses. It is still useful, however, in the evaluation of suspicious regional lymph nodes or in the younger patient who has a simple cyst. The reason FNA is used less frequently for evaluating suspicious masses is that cytology alone cannot distinguish invasive carcinoma from noninvasive disease, and histologic confirmation of invasion requires a biopsy. Core needle biopsy (CNB) is the preferred initial diagnostic procedure for breast lesions suspicious for a malignancy. The main advantage of CNB is the ability of a surgical pathologist to distinguish between invasive cancer and DCIS, based on architectural information provided by the larger tissue sample obtained in a CNB. Because a lesion can be heterogeneous, image-guided CNB is preferred over a ''blind'' biopsy even in palpable lesions, because this increases the probability of getting representative samples of the lesion. In a nonpalpable lesion, it is a way to assure that the appropriate area has been sampled. Ultrasonography, mammography, and MRI may all be used to perform image-guided CNB, although ultrasound is most commonly used.

Complete surgical removal of a palpable breast lesion is referred to as an excisional biopsy, whereas surgical sampling (or incomplete removal) of the lesion is referred to as an incisional biopsy. Excisional or incisional biopsies are indicated if the following situations arise: (1) neither CNB nor FNA is technically feasible, (2) nondiagnostic attempts by CNB or FNA, or (3) pathology is discordant with radiographic imaging. It is best to avoid excisional biopsy to establish histologic diagnosis of cancer, because this often means two different surgeries for the patient—one for diagnosis and the other for definitive therapy or axillary staging.

Staging

The standard staging system is that of the American Joint Committee on Cancer (AJCC). The system is based on primary tumor size (T), lymph node involvement (N), and whether there is evidence of metastatic disease on presentation (M) [51]. Breast cancer is broadly categorized into five stages, in which noninvasive disease is Stage 0 (Tis N0 M0), small tumors 2 cm or smaller without lymph node involvement is Stage I (T1 N0 M0), whereas metastatic disease is Stage IV (any T any N M1). Stage II is subdivided into a and b, and Stage III is subdivided into a, b, and c, to reflect increasing tumor size or number of lymph node involvement. The axilla is the principal drainage site for the breast. The size of the primary tumor has a positive correlation with the odds of nodal involvement. The number of metastatic axillary lymph nodes is a very significant prognostic factor in breast cancer. Among patients who have positive axillary lymph node involvement, those who have the least number of involved nodes (ie, one to three positive axillary nodes) do best. Immunohistochemistry staining for cytokeratin will detect an additional 10% to 20% of cases of carcinoma involving the lymph nodes originally assessed to be uninvolved by standard histology. Use of this technology is reflected in the current AJCC breast cancer staging (ie, N0 (i+)).

Staging workup in patients who have low probability of metastasis (ie, small tumors or negative nodes) requires only laboratory work and chest radiography; however, in higher-staged patients, staging workup may require CT and bone scans. Positron emission tomography (PET) scan is currently not recommended as a routine staging procedure for newly diagnosed breast cancer.

Treatment

Management of breast cancer requires a multimodality approach, including surgery, radiation, and systemic therapy. Surgery and radiation therapy are considered local therapies and are used for management of the primary tumor and to decrease risk of local recurrence. Systemic therapy modalities, such as chemotherapy, anti-estrogen therapy, and biologic therapy, are used to manage micrometastatic disease and decrease the risk of developing distant metastasis.

Surgical therapy

Initial surgical assessment involves determining whether the tumor is operable or not. This is predicated on whether the entire tumor, along with sufficient margins plus axillary nodes, can be removed without significant morbidity to the patient. If the patient is operable, then the next decision is to determine if the patient can be offered breast conservation surgery (ie, lumpectomy), or if a mastectomy is required. Lumpectomy is often followed with radiation therapy, and this must be taken into consideration

during the surgical planning. Total or simple mastectomy involves removal of the breast parenchyma, including the nipple-areolar complex, with no lymph node dissection. A modified radical mastectomy involves resection of the breast parenchyma and axillary nodes lateral to and behind the medial border of the pectoralis minor.

An essential component of breast cancer surgery is axillary assessment. There are two methods currently in use: sentinel lymph node biopsy (SLNB), and axillary lymph node dissection (ALND). Sentinel lymph nodes are the first nodes that receive drainage from tumors. The technique involves injecting radiocolloid, blue dye, or both, into the breast and allowing it to travel into the draining lymph nodes. Afterward, the initial draining lymph nodes are identified and removed. Additional lymph nodes are subsequently removed (ie, ALND) only if the SLN is found to have metastatic deposits of cancer. This procedure results in less morbidity to the patient compared with initially performing ALND, which involves removal of level I (closest to the breast) and II (bordering the pectoralis muscle) axillary nodes. ALND is required if there is clinical suspicion of lymph node involvement. After axillary surgery, patients may experience paresthesias or lymphedema, which may be a long-term problem for some patients. Fig. 4 illustrates the anatomy of the breast lymph nodes.

Radiation therapy

Radiation therapy is indicated for patients who have breast cancer who have: (1) undergone breast conservation, (2) large primary tumors greater than 5 cm, (3) skin or chest wall involvement, or (4) multiple lymph node involvement (four or more lymph nodes). Typically, the whole breast is

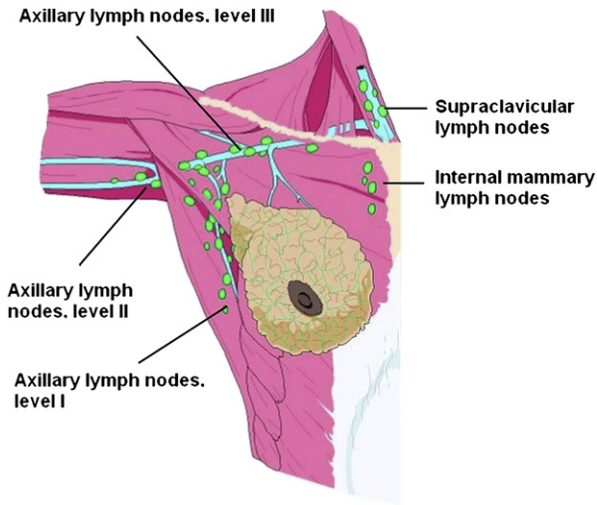

Fig. 4. Anatomy of the breast lymph nodes.

radiated, with a boost to the tumor bed. Regional lymph node-bearing areas such as the axilla and supraclavicular fossa are also radiated when a patient has multiple lymph node involvement, because these areas are at high risk for local recurrence. Newer techniques such as partial breast irradiation radiate only a select portion of the breast. Though used in some centers for selected patients, they are still considered investigational and should not be used routinely in clinical practice.

Common side effects of radiation therapy include skin changes and fatigue.

Systemic therapy

Breast cancer is considered a systemic disease; thus systemic therapy is an essential component of treatment to increase chances for cure and survival. Systemic therapy in operable breast cancer is typically given postoperatively or adjuvantly. Some patients who are candidates for systemic therapy may elect to receive all or some of their treatment in the preoperative or neoadjuvant setting. Often this is done to shrink the tumor and allow for an increased rate of breast conservation. This approach also allows for assessment of tumor response to a given therapy. In patients who are initially deemed inoperable, either because of locally-advanced or metastatic disease, systemic therapy is the mainstay of treatment.

Chemotherapy, anti-estrogen therapy (also referred to as endocrine or hormone therapy), and biologic therapy with molecularly targeted agents are all under the umbrella of systemic therapy. In the adjuvant or neoadjuvant setting, chemotherapy is typically given for a fixed number of cycles, whereas in metastatic disease the number of cycles is less defined, and depends on the patient's response and tolerance to the treatment. Chemotherapies commonly used in breast cancer include anthracyclines and taxanes. Examples of anthracylines include adriamycin and epirubicin; examples of taxanes include paclitaxel and docetaxel. Common side effects of chemotherapy include alopecia, nausea/vomiting, mucositis, lowering of blood counts, fatigue, and peripheral sensory neuropathy. Long-term toxicities include cardiomyopathy, secondary leukemia, and premature menopause.

Anti-estrogen or endocrine therapy is used in patients whose tumors are hormone-receptor positive—estrogen receptor (ER) or progesterone receptor (PR) positive. When used in the adjuvant setting, it is typically given for 5 years, though in some patients it may used for up to 10 years. As with chemotherapy, duration of endocrine therapy in the metastatic setting is variable from a few months to years. Commonly used endocrine therapies include tamoxifen, and aromatase inhibitors such as anastrozole, letrozole, exemestane, and fulvestrant. Common side effects of endocrine therapy include hot flashes, night sweats, mood lability, increased risk of thromboembolic events, increased risk of uterine cancer, and osteoporosis. Because endocrine therapy has a specific molecular target, the ER, it can be considered a form of targeted therapy.

To date, there are only two other molecularly targeted agents approved by the Food and Drug Administration (FDA) for the treatment of breast cancer: trastuzumab and lapatinib. Both target the HER2 receptor. Lapatinib also targets the epidermal growth factor receptor (EGFR), although a correlation between treatment response and EGFR targeting has not been clearly demonstrated in breast cancer. Trastuzumab is a humanized monoclonal antibody that has been shown to improve outcomes in both adjuvant [52,53] and metastatic treatment of breast cancer [54]. Common toxicities associated with trastuzumab include infusion reactions and cardiomyopathy. Rarely, it may be associated with pulmonary pneumonitis. Lapatinib is a small molecule tyrosine kinase inhibitor (TKI) that has been shown to be useful in the management of metastatic disease [55]. Common toxicities associated with lapatinib include diarrhea and rash. Other types of targeted therapy are currently being investigated, and should hopefully be part of the breast cancer armamentarium in the near future.

Breast cancer outcomes

Much progress has been achieved in the management of breast cancer. Women diagnosed with breast cancer today have a higher likelihood of surviving their cancer compared with women diagnosed in the 1970s or 1980s. Indeed, death from breast cancer has been declining since the 1990s. This is likely because of effective screening, with breast cancer being diagnosed at earlier stages, when there is a higher chance for cure, and development of effective adjuvant therapies. Because the curability of breast cancer is very much correlated to stage of diagnosis, it is essential for the primary care physician (PCP) to be vigilant about screening and early detection. It is also important for the PCP to make timely referrals when appropriate (eg, genetic counseling and screening in women who have strong family history, or further workup of suspicious breast lesions when there is uncertainty about how best to proceed).

Although much progress has been made, there is much that remains unknown. For instance, the recognition that not all breast cancers are the same has made it apparent that more needs to be known about the different "tumor biologies." New discoveries in this arena are likely to make a huge impact on the management of breast cancer in the future.

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