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Editors

Breast Disease

Diagnosis and Pathology, Volume 1

Second Edition

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Preface

The goal of *Breast Disease: Diagnosis and Pathology* is to provide a comprehensive, scholarly appraisal of contemporary basic science and diagnosis. Because of advances in molecular medicine and therapeutics, this appraisal requires a more extensive understanding of the basic science of oncology than was required in the past. This book is organized into 18 chapters, and a brief summary of their content is provided below. In addition, we highlight some of the various important points in this second edition of the book.

The topic of *Benign Breast Diseases* covers a wide variety of conditions, both common and unusual, that may require additional work-up, excision, or surveillance. In addition, some benign conditions may confer an increased risk for future disease, and this risk should be explained to the patient during treatment for these entities. This section attempts to provide a basic understanding of some of the most frequently encountered benign breast conditions and various rare types, including current recommendations for work-up, management, differential diagnoses, and future surveillance. The specific conditions that are explored in this chapter include fibroadenomas, intraductal papillomas, lipomas, hamartomas, radial scars, and gynecomastia in males.

Age, family history, and both endogenous and exogenous ovarian hormone exposure have important effects on risk and have been incorporated into models that predict the individual *risk of breast cancer*. Diet, alcohol use, and other factors play smaller roles. BRCA mutation-associated breast cancer differs from sporadic breast cancer in that BRCA mutation carriers exhibit an increased risk of breast and ovarian cancer and differential sensitivity to chemotherapeutic agents. Because BRCA genetic testing is readily available, BRCA mutation status should be evaluated in high-risk women, including women who were diagnosed with breast cancer at an early age and women with a strong family history or triple-negative tumors. Given the high rate of contralateral breast cancer and ovarian cancer, mutation carriers with newly diagnosed breast cancer may choose to undergo contralateral prophylactic mastectomy or bilateral salpingo-oophorectomy. In addition, two selective estrogen receptor modulators, tamoxifen and raloxifene, and aromatase inhibitors can be used to decrease the incidence of invasive breast cancer in women who are at high risk of this condition.

Breast imaging is an essential component of breast cancer diagnosis and guides surgery and treatment options. Imaging techniques, such as mammography, ultrasound (US), and magnetic resonance imaging (MRI), enable the detection of breast cancer at earlier stages. Mammography remains the standard screening examination; however, additional imaging studies are useful in evaluating the breast. US is utilized primarily in the diagnostic setting to characterize mammographic or palpable findings and assess axillary lymph nodes. Supplemental US screening may also be useful in patients with an intermediate risk for developing breast cancer and dense breasts to increase cancer detection. In addition to mammography, high-risk patients may also have annual MRI or US screening if they are unable to undergo MRI. MRI is also performed to evaluate the extent of disease, the response to neoadjuvant chemotherapy, and the silicone implant integrity. In addition, these imaging modalities are also used to guide percutaneous biopsy, enabling minimally invasive tissue diagnosis.

In *nuclear medicine* practice, there have been many diagnostic tools developed for primary detection, staging, and evaluation of treatment response in breast cancer. In this edition, a new

chapter outlines the role of nuclear medicine both in imaging and treatment of patients with breast cancer.

Lobular carcinoma in situ (LCIS) is a high-risk indicator lesion for and a non-obligate precursor of the development of invasive breast carcinoma. The loss of E-cadherin is the hallmark pathological feature of lobular entities. Effective clinical management of LCIS requires good communication among the radiologist, surgeon, pathologist, and medical oncologist and entails surgical excision, subsequent surveillance, and systemic and surgical strategies to reduce the risk of future invasive cancer.

Ductal carcinoma in situ (DCIS) is defined as abnormally proliferating malignant cells confined to the breast milk ducts by the basement membrane. DCIS is diagnosed most commonly as a mammographic abnormality but can occasionally present as a palpable breast mass. Overall survival after breast-conserving therapy is equivalent to that observed for mastectomy. Patients undergoing mastectomy for DCIS should have sentinel lymph node biopsy (SLNB). Immediate breast reconstruction should be considered for patients undergoing mastectomy. Endocrine therapy, such as tamoxifen, is offered for 5 years to women with estrogen receptor-positive DCIS.

The topic of *Biology and Genetics of Breast Cancer* covers a wide variety of molecular studies. Understanding the mechanisms of DNA alterations leading to carcinogenesis can provide crucial insights for resolving the development of malignant processes, such as growth, invasion, and metastasis. This chapter reviews hereditary and somatic genetic alterations, epigenetic misregulations, and miRNA signatures associated with breast cancer. This chapter also emphasizes the molecular profiles of breast cancer and critical signaling pathway alterations.

Human breast cancers depend on estrogen and/or progesterone for growth, and these effects are mediated through *estrogen receptors* (ERs) and *progesterone receptors* (PRs), respectively. The *human epidermal growth factor receptor 2* (HER2) gene encodes a member of the epidermal growth factor receptor family of receptor tyrosine kinases, and its amplification with resultant overexpression plays a major role in sustaining multiple pathways in cancer growth. ERs, PRs, and HER2 status are the most important molecular markers in the standard care of all primary and recurrent/metastatic breast cancer patients and play both predictive and prognostic roles. The responsiveness of a tumor to hormone therapy is an important parameter in breast cancer management in both the adjuvant and metastatic settings. Only breast cancers with HER2 amplification or overexpression respond to HER2-directed therapies. Tumor hormonal status is prognostic for patient outcome and potential sites of metastasis. Hormonal receptor-positive disease represents an indolent and slowly growing tumor with longer time to disease recurrence. HER2 is a poor prognostic factor in the absence of HER2-directed therapies. Assessment of the ER/PR/HER2 status is an essential factor in the evaluation of every newly diagnosed breast cancer, and the standardization of assay methods is crucial.

Invasive breast carcinomas comprise a heterogeneous group of lesions that differ in their molecular and pathologic features and clinical behavior. Some patients experience long periods of disease-free survival, whereas others experience the rapid development of recurrence and metastases that are fatal within a few years of the initial diagnosis. Numerous factors in individual tumors can be evaluated to stratify patients into subsets with varying risks of recurrence and response to different therapy modalities. The *Prognostic and Predictive Factors of Invasive Breast Cancer* chapter describes the current standard prognostic and predictive factors of invasive breast carcinoma and discusses emerging data on molecular markers that can be considered in clinical practice.

Adjuvant chemotherapy and endocrine treatment decrease the mortality of early breast cancer. However, not all early breast cancer patients benefit equally from adjuvant endocrine treatment and/or chemotherapy. High-risk patients are classically identified based on clinicopathological factors, such as age, tumor size, histopathological grade, nodal status, hormone and HER2 receptor positivity, and menopausal status. However, for patients with early breast cancer, the use of these standard clinicopathological factors might not thoroughly reveal the individual risk of disease recurrence and the benefits from adjuvant systemic chemotherapy.

Many patients with early breast cancer do not derive benefit from adjuvant systemic chemotherapy. Quantitative approaches for defining prognoses and individualizing treatments are required. In recent years, *molecular signatures of gene expression* have been correlated with breast cancer recurrence risk. Several tests for genomic expression have been developed and validated on specimens from previous phase III studies to improve the prognostication of early breast cancer patients and/or the prediction of adjuvant systemic treatment.

In clinical practice, although local recurrence or distant metastasis develops in some individuals who have been assessed as low risk despite treatment, some individuals with high-risk disease do not relapse despite systemic and local therapy. Therefore, oncologists must determine objective prognostic factors to identify early recurrence and metastasis in patients with breast cancer. Based on the presumption of residual disease, clinicians have recently attempted to identify micrometastases using *disseminated tumor cells* (DTCs) in the *bone marrow* and *circulating tumor cells* (CTCs) from the peripheral blood. DTCs are known as epithelial cells in the bone marrow, and they are also considered to be micrometastases in the bone marrow. DTCs are observed in approximately 30 % of early-stage breast cancer patients. Tumor cells that circulate in the peripheral blood of patients with cancer are referred to as CTCs. CTCs are cells that have entered the peripheral blood circulation after having detached from an existing primary tumor or its metastases. DTCs and CTCs can be used to predict progression-free and overall survival as well as response to treatment.

In the *Pathology of Breast Cancer* chapter, the classification is based on the recent WHO classification of breast carcinoma, and specific gross and microscopic features of in situ and invasive breast carcinomas are explained. Morphological groups, grading of DCIS, and the necessary information that should be included in a surgical pathology report are discussed. Recent information regarding columnar cell lesions and flat epithelial atypia of the breast are discussed along with their clinical importance. Common forms of invasive carcinomas, such as invasive ductal carcinoma and invasive lobular carcinoma, special types, and rarer forms, are also discussed along with their clinical consequences.

Intraoperative pathological examination may be performed for the rapid diagnosis of breast malignancy, the assessment of the surgical margins of breast-conserving excision specimens, and the pathological analysis of sentinel lymph nodes. The most commonly used methods for intraoperative pathological examination of breast lesions are cytological and frozen section examinations in addition to gross analysis. The pathological examinations of sentinel lymph nodes necessitate careful gross examination and serial and/or step sectioning. Immunostaining using antibodies against pancytokeratin can also be performed. Sentinel lymph node metastases should be clearly defined as macro- or micrometastases or isolated tumor cells. The differential diagnosis of subtypes of metastasis and mimickers is detailed.

Fibroepithelial tumors of the breast represent a heterogeneous group of biphasic tumors composed of a proliferation of epithelial and stromal components. Fibroadenomas and phyllodes tumors constitute the major entities. These tumors are among the most challenging diagnostic lesions for pathologists. It can be difficult to make a clear microscopic distinction between fibroadenomas and benign phyllodes tumors. No reliable morphological features or immunohistochemical markers that predict phyllodes tumors are available.

A variety of reactive and neoplastic lesions of the breast are characterized by spindle cell proliferation. The pathologist must be aware of the clinical, radiological, and morphological overlap between reactive and *neoplastic spindle cell lesions* of the breast. In addition, metaplastic (spindle cell) carcinoma is far more common than spindle cell sarcoma in the breast. Among the vascular lesions of the breast, angiosarcoma is more common and may appear very bland, simulating a hemangioma. Core biopsy samples must be evaluated very carefully to interpret spindle and vascular lesions. In general, excision is recommended due to morphological overlap, and clinicopathological correlation is necessary for a correct diagnosis.

In this edition, a new valuable tool, *liquid biopsy*, will be discussed. Liquid biopsy detects a group of "new-generation markers" that expand into the bloodstream from primary and metastatic tumor sites. These markers offer some advantages, such as real-time monitoring of

disease and detection of tumor heterogeneity. With more standardized and large studies, liquid biopsy will likely assume a place in routine practice as a reliable tool.

We would like to dedicate this book to postgraduate physicians in training to become breast cancer specialists. Some of the recommendations are controversial and the subject of ongoing trials. We hope this book stimulates today's young doctors to contribute to the research on which future books will be based.

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Breast Anatomy and Physiology

1

Kandace P. McGuire

Embryology/Development

During the 5th and/or 6th week of fetal development, the two bands of thickened ectoderm referred to as the ectodermal primitive milk streak develop between the groin and the axilla [1, 2]. This remains in the thorax to become the mammary ridge, whereas the remainder regresses in the human development [2].

The breast develops from an ingrowth of the ectoderm into the mesoderm to form a breast bud [1]. The glandular portion of the breast develops from the ectoderm. During the 12th week of development, 16–24 secondary buds will form off the primary bud [3].

Sequence of Development

The development of the breast, summarized in Table 1.1, follows a stepwise progression beginning at the 5th week post-conception and continuing until birth. In weeks 5 and 6, the primitive milk streak develops from a thickened band of ectoderm. Following development of the primitive milk streak in weeks 7 and 8, the mammary anlage will thicken, and the mesoderm will invaginate. Simultaneously, the breast buds begin to grow. This process continues until weeks 12 through 16, when mesenchymal cells begin to differentiate into the smooth muscle of the nipple and areola. Secondary breast buds will further develop and branch but remain solid structures during this time period.

At week 16, the tips of the buds become the secretory alveoli. The secondary mammary anlage differentiates into hair follicles and the sebaceous and sweat gland elements. Apocrine glands develop to form the Montgomery glands.

Table 1.1 Embryonic breast development by gestational week

Gestational week	Breast development
5–6	Primitive milk streak develops from the ectoderm
7–8	Thickening of the mammary anlage
	Invagination into the mesoderm
	Growth of breast buds
12–16	Mesenchymal cells differentiate into the smooth muscle of the nipple-areola
	Secondary breast buds develop and branch
16–20	Tips of breast buds become the secretory alveoli
	Secondary mammary anlage differentiates into hair follicles and sebaceous and sweat gland elements
	Apocrine glands develop into Montgomery glands
20–32	Breast buds canalize and become lactiferous/mammary ducts
32–40	Parenchymal differentiation; lobules/alveoli develop
	Proliferation of mesenchyme forms the nipple-areola complex
	Pigmentation of the nipple-areola complex

Beginning at week 20 of development and continuing until week 32, the breast buds will canalize to form lactiferous/mammary ducts. These ducts open into a shallow mammary pit, which will become the nipple-areola complex. In the final weeks before birth, weeks 32 through 40, parenchymal differentiation occurs. The lobules and alveoli complete the development. Finally, the nipple-areola complex develops via proliferation of the mesenchyme and becomes pigmented (Fig. 1.1) [2, 3].

Developmental Anomalies

The development of a normal breast requires perfect adherence to the sequence of development described above. Should development stray from this pattern, anomalies may occur. The three most common developmental anomalies of the female breast are (1) supernumerary breasts or nipples (polymastia/polythelia), (2) underdevelopment or lack of development of the breast, and (3) nipple inversion.

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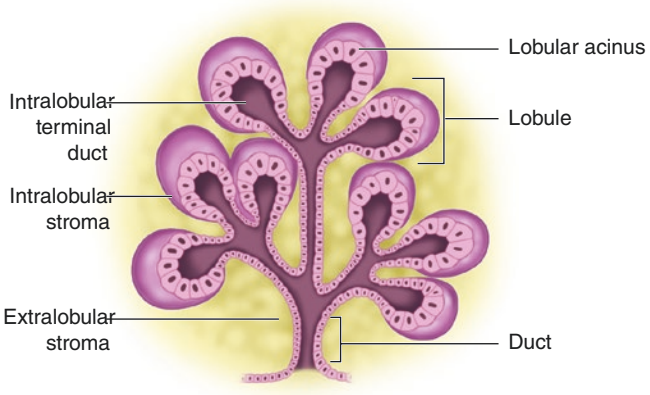

Fig. 1.1 Fully developed breast lobular unit. (From Townsend et al. [5]. Reproduced with permission from Elsevier)

Supernumerary breasts/nipples (polymastia/polythelia) can occur in both genders and are referred to as accessory if they occur along the milk line (former primitive milk streak). They are referred to as ectopic if they occur elsewhere [3].

Accessory nipples (polythelia) occur in 2.5% of the population and are much more common than accessory breasts (polymastia). Polythelia most commonly occurs in the thorax, while polymastia most commonly occurs in the axilla [2, 3].

Underdevelopment or hypoplasia of the breast can occur unilaterally or bilaterally and is usually clinically insignificant. However, severe unilateral hypoplasia of the breast can occur and is usually associated with hypoplasia of the pectoral muscle (lacking the lower third of the muscle) and deformity of the rib cage. This defect is termed *Poland's syndrome* because it was first recognized by Dr. Alfred Poland in 1841. Associated abnormalities of the hand (syndactyly and/or hypoplasia of the phalanges) may be present [2].

Amastia or lack of breast development is exceedingly rare. Athelia, a lack of development of the nipple-areola complex, can also occur, as can amazia, a lack of breast development in the presence of a nipple-areola complex [2, 3].

Failure of the mesenchyme of the nipple-areola to proliferate and elevate the mammary pit above the skin results in an inverted nipple. This failure can occur unilaterally or bilaterally and occurs in 4% of infants, both male and female [3].

Anatomy

Breast

The adult female breast lies between the second and sixth/seventh ribs. The base of the breast spans from the sternal border medially to the midaxillary line laterally and is encompassed by the superficial and deep fascia of the chest wall. Two-thirds of the breast lies anterior to the pectoralis major; the remainder lies anterior to the serratus anterior. A prolongation of the upper outer quadrant of the breast, referred to as the tail of Spence, extends into the axilla [3, 4].

Components of the Breast

Skin – the skin is the most superficial layer of the breast. The dermis merges with the superficial fascia [3].

Superficial fascia – this layer lies just beneath the skin. It is continuous with the superficial abdominal and cervical fascia. Along with the deep fascia, it envelopes the breast parenchyma [3].

Breast parenchyma – the parenchyma is composed of three principal tissue types: glandular epithelium, fibrous stroma, and supporting structures and fat.

Glandular epithelium comprises approximately 10–15% of the adult female breast. It is composed of 15–20 lobes, which are subsequently composed of several lobules. These lobules are referred to as terminal ductules or acini, the milk-producing glands. The major milk ducts are lined with two layers of cuboidal epithelium, while the minor ducts have a single layer. The ductal epithelium is entirely surrounded by myoepithelial cells that serve to propel milk forward through the ducts. These cells are surrounded by a continuous basement membrane. Invasion through this membrane distinguishes invasive cancer from in situ carcinoma. The ducts widen under the nipple-areola complex to form the lactiferous sinuses and then exit through 10–15 orifices in the nipple.

The fibrous stroma and supporting structures are most commonly referred to as the suspensory ligaments of Cooper. These ligaments are fibrous bands of connective tissue that travel through the breast and insert into the dermis. Tumor involvement and contraction of these bands are responsible for the puckering noted at the site of a palpable breast lump.

The remainder of the breast is composed of adipose tissue (fat). The proportion of fat to glandular tissue increases with age and is maximal in the postmenopausal breast (Fig. 1.2) [1, 4, 5].

Nipple-areola complex – As described above, each lobe of the breast leads to a ductal structure that then widens to form a large lactiferous duct (2–4 mm) that continues to form a sinus. The sinus is lined with stratified squamous epithelium. This sinus then narrows as it passes into the ampulla of the nipple (0.4–0.7 mm).

The areola comprises a combination of sebaceous, sweat, and accessory glands that form the Montgomery tubercles. Smooth muscle fibers are contained in the areola and extend into the nipple, and these fibers are responsible for nipple erection. Erection is stimulated by the sensory nerve endings and Meissner's corpuscles, which are located within the dermis of the nipple [1, 3].

Deep fascia – This layer is deep to the breast parenchyma and envelops the pectoralis major. It is continuous with the

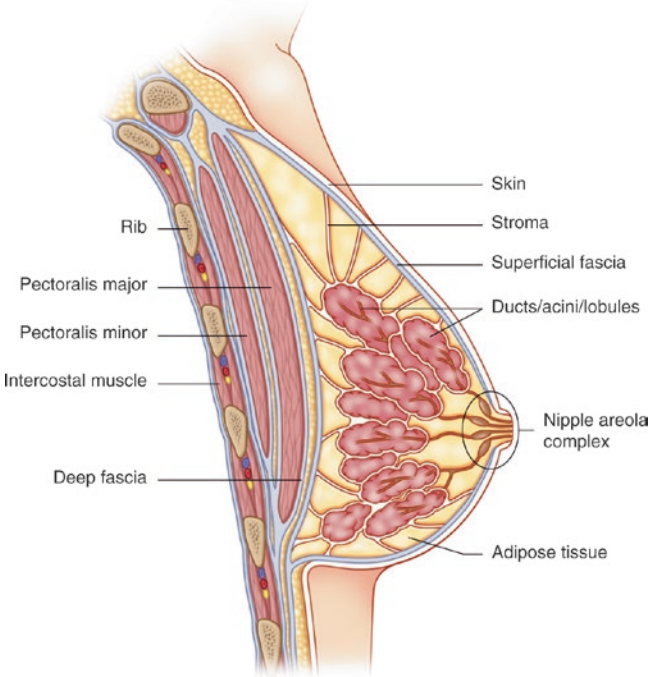

Fig. 1.2 Components of the breast

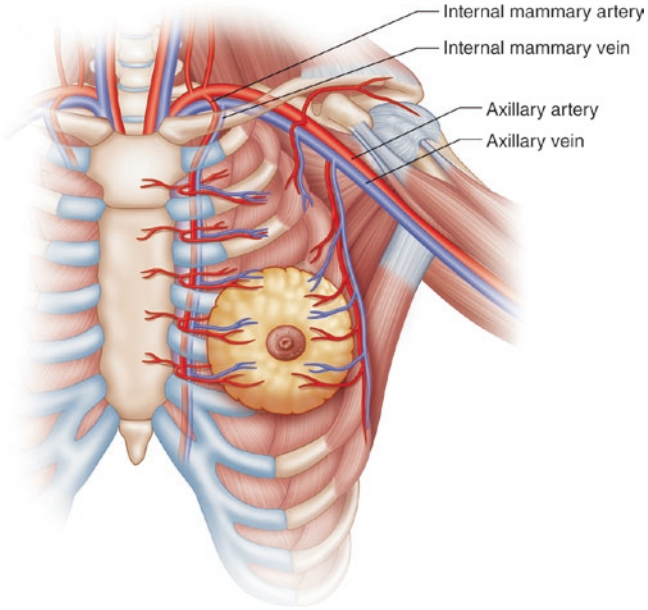

Fig. 1.3 Arterial supply and venous drainage of the breast

deep abdominal fascia caudally and spans from the sternum to the axilla laterally and to the clavicle cranially [3].

Neurovascular Structures

Arterial

The arterial blood supply to the breast comes primarily from three sources: (1) anterior perforators of the internal mammary artery (responsible for approximately 60% of the breast, mostly medial and central); (2) branches from the axillary artery, such as the highest and lateral thoracic, and the thoracoacromial artery (responsible for approximately 30% of the breast, mostly the upper outer quadrant); and (3) lateral branches of the intercostal arteries (Fig. 1.3) [1–3].

Venous

Venous drainage typically mimics the arterial supply. Thus, the primary venous drainage consists of: (1) internal mammary perforating branches, (2) tributaries of the axillary vein, and (3) branches of the intercostal veins (Fig. 1.3) [1].

Nervous

The sensory nerve supply to the breast is principally derived from the lateral cutaneous branches of the third through sixth intercostal nerves. Cranially, some sensory innervation is supplied by cutaneous branches of the cervical plexus. The nipple-areola complex is innervated by the fourth intercostal nerve [1, 3].

Lymphatic Structures

The superficial lymphatic plexus that drains the skin of the breast and the nipple-areola complex is often referred to as Sappey's plexus. Lymph flows from the skin to the subareolar plexus and then into the interconnected deep lymphatic plexus that drains the breast parenchyma via the lymphatic vessels associated with the lactiferous ducts. Approximately 97% of the lymphatics from the breast drain to the axilla; the remaining 3% drains to the internal mammary lymph nodes.

The internal mammary chain is located between the first and sixth intercostal spaces along the border of the sternum. The nodes are medial to the internal mammary vessels in the first two intercostal spaces and then become lateral to the vessels in spaces 3–6 (Fig. 1.4) [2, 4, 5]. The anatomy of the axilla and axillary lymph nodes will be discussed in the following section.

Axilla

The axilla is an important component of breast anatomy. Directly contiguous with the breast, the lymph nodes within the axilla provide a rich drainage basin for the breast. The borders of the axilla, which define the extent of axillary dissection, are as follows:

Lateral – the axillary fat pad and the bicipital groove of the humerus.

Medial – the serratus anterior and the second to sixth ribs.

Superior – the apex of the axilla bordered by the clavicle, the scapula, and the first rib.

The apex of the axilla can also be defined by the costoclavicular ligament, which is also called Halsted's ligament. The axillary vein is the superior extent of the modified

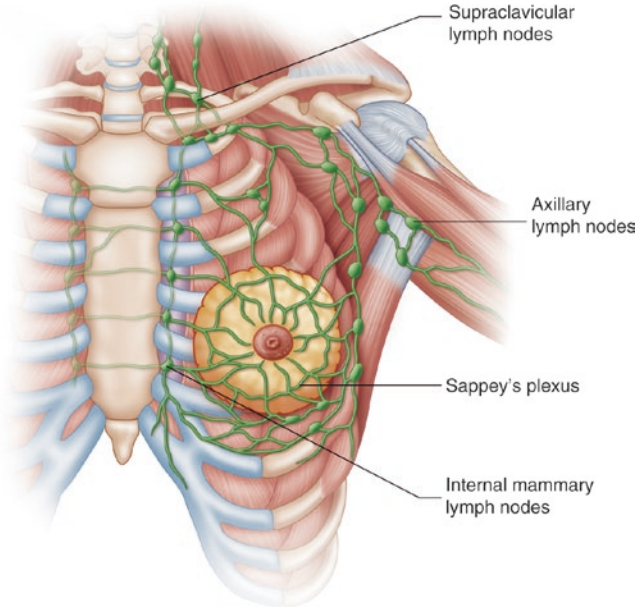

Fig. 1.4 Lymphatic drainage of the breast

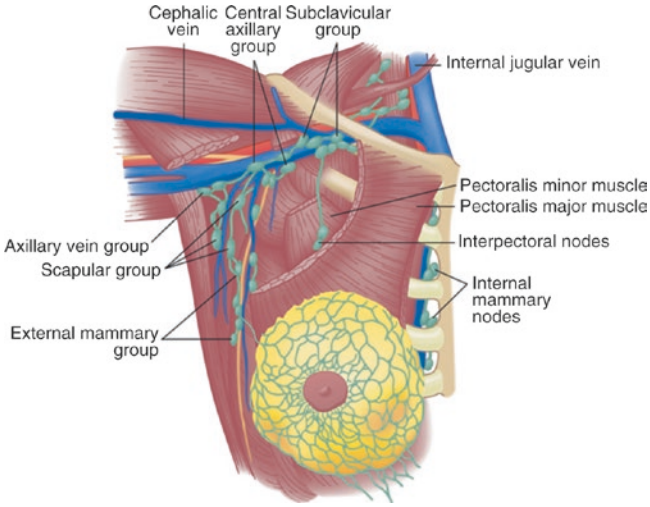

Fig. 1.5 Axillary lymph node groups. (From Townsend et al. [5]. Reproduced with permission from Elsevier)

radical axillary dissection. Medial to Halsted's ligament, the axillary vein becomes the subclavian vein.

Anterior – the pectoralis (major and minor) and subclavius muscles and the clavipectoral fascia. The clavipectoral fascia envelops the subclavius and pectoralis minor and is often referred to as the costocoracoid membrane. The lateral band of the clavipectoral fascia between the first rib and the coracoid process is called the costocoracoid ligament.

Posterior – the scapula, the subscapularis, the latissimus dorsi, and the teres major. The axillary fascia lying across the base of the axillary pyramid will envelop the pectoralis major and then the latissimus dorsi. It forms the dome of the axilla. Occasionally, there can be a muscular connection between this fascia and the clavipectoral fascia, which is referred to as the suspensory ligament of the axilla [3, 5, 6].

Axillary Lymph Nodes

There are several groups of lymph nodes within the axilla. These nodes can be grouped as the apical or subclavicular nodes, which are located medial to the pectoralis minor muscle, or the axillary vein lymph nodes, which run along the axillary vein between the pectoralis minor and the humerus. The interpectoral or Rotter's nodes lie between the pectoralis major and minor muscles. The central axillary nodes are found beneath the border of the pectoralis major muscle and below the pectoralis minor. The external mammary nodes lie over the axillary tail of Spence. Intramammary lymph nodes and paramammary lymph nodes can also be found in the fat layer over the upper, outer quadrant of the breast (Fig. 1.5).

For surgical dissection purposes, there are three lymph node levels of the axilla, which are all defined by their relationship to the pectoralis minor muscle. Level I nodes are found lateral to the edge of the pectoralis minor. This level includes external mammary, subscapular, and lateral axillary lymph nodes. Level II nodes are located posterior to the pectoral minor. This level includes the central axillary lymph nodes. Level III nodes are medial and superior to the pectoralis minor. This level includes the subclavicular or apical lymph nodes [2, 6].

Structures Within the Axilla

The *axillary lymph nodes* are divided into several different groups and levels as described above and are variable in number. The maximum number identified and removed during a radical mastectomy is approximately 50, including the level I, II, and III axillary lymph nodes.

The *axillary vein* defines the superior border of the axilla during axillary dissection. It lies posterior and caudal to the brachial plexus. The axillary vein is often paired or branches during its course through the axilla.

The *thoracodorsal nerve/neurovascular bundle* innervates the latissimus dorsi and should be preserved during axillary dissection. It runs posterior to the axillary vein and medial to the subscapular vein.

The *long thoracic nerve/neurovascular bundle* innervates the serratus anterior and should be preserved during axillary dissection. If sacrificed, it will lead to "winging" of the scapula. It runs longitudinally over the serratus anterior and can be found during dissection in the axillary fat pad approximately 7 or 8 cm deep to the lateral edge of the pectoralis minor. As the long thoracic nerve/neurovascular bundle continues caudally, it will become more anterior.

The *intercostobrachial nerves* provide sensory innervation to the medial portion of the upper arm. These nerves run parallel to the axillary vein between the chest wall and the

arm. One or more of these nerves run through the axillary fat pad and may be difficult to dissect away from lymph nodes. If sacrificed, either hypo- or hyperesthesia of the posterior axillary web and the medial/upper arm can result [4, 6].

Physiology

Physiological Breast Development

Breast development is stimulated by a variety of hormones that are upregulated during the beginning stages of puberty. Estrogen and progesterone are the main hormones responsible for breast growth and development during this time. Estrogen stimulates ductal development; progesterone stimulates lobular development and epithelial differentiation.

At the onset of puberty, the hypothalamic-pituitary axis becomes less sensitive to the negative feedback of estrogen. This desensitization leads to an increase in gonadotropin-releasing hormone (GnRH) from the hypothalamus. This increase in GnRH stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary, which in turn leads to an increase in estrogen and progesterone release, thus stimulating breast development, among other developmental changes.

During pregnancy and lactation, prolactin is primarily responsible for upregulating hormone receptors and stimulating epithelial development and lactogenesis in the breast [1].

Abnormal Breast Development/Gynecomastia

Gynecomastia refers to male breast hypertrophy and can be caused by numerous factors.

1. Physiological gynecomastia: This can occur in the neonatal, pubertal, and senescent periods. Neonatal hypertrophy occurs in response to maternal estrogen. Pubertal hypertrophy occurs due to a relative excess of estradiol to testosterone. Senescent hypertrophy occurs in response to falling testosterone levels associated with aging. The enlargement is usually unilateral in puberty but bilateral in senescence. This usually does not require surgery unless the enlargement is associated with a mass by physical exam or mammogram, fails to regress, or is cosmetically unacceptable.
2. Pathologic gynecomastia: There are a number of pathological causes of gynecomastia, including true hermaphroditism, testicular tumors, adrenal cortical neoplasms, lung or hepatocellular carcinoma, endocrine disorders, cirrhosis, and nutritional deficiencies (estrogen excess states). Hypogonadism, as observed in congenital syndromes such as Klinefelter (XXY) syndrome or ACTH deficiency, can also cause gynecomastia. Secondary testicular failure from trauma, radiation, or untreated cryptorchidism can also cause hypertrophy (androgen deficiency states). Renal failure and other systemic diseases can lead to gynecomastia, as can drugs that provide exogenous estrogen or stimulate estrogen synthesis (e.g., digoxin, estrogens, anabolic steroids, marijuana, and HCG) or that inhibit the activity or production of testosterone (e.g., cimetidine, ketoconazole, phenytoin, spironolactone, antineoplastic drugs, and diazepam). Some drugs, such as reserpine, theophylline, verapamil, tricyclic antidepressants, and furosemide, lead to gynecomastia through idiopathic mechanisms [3, 5].

Physiology of Puberty

As described above, pubertal development of the breast (thelarche) begins with the stimulation of estrogen and progesterone production via the hypothalamic-pituitary axis. At this time, the breast is composed primarily of dense fibrous stroma and scattered ducts lined with epithelium. Estrogen stimulates growth of the ductal epithelium. Buds form off the terminal ductules and will eventually become breast lobules. Periductal connective tissue grows and becomes more elastic. Some studies suggest that while estrogen promotes growth of ducts, estrogen and progesterone synergistically promote full ductular-lobular-alveolar development in the breast.

There are three distinct types of breast lobules in the human breast, and the proportion of each is related to a woman's parity and hormonal status. During puberty, the breast develops mostly type I (virginal) lobules, which consist of a cluster of 11 alveolar buds around a terminal duct. These lobules have a much higher rate of proliferation than type 2 or 3 lobules.

Physiology of the Menstrual Cycle

The postpubertal breast contains fat, stroma, lactiferous ducts, and lobular units. The menstrual cycle affects not only the uterus and uterine lining but also the breast. During the follicular phase (days 4–14), levels of estrogen increase, stimulating epithelial proliferation/sprouting and an increased mitotic rate. During the luteal phase (days 15–28), progesterone increases, while estrogen abates. At this time, mammary ducts dilate, and alveolar epithelial cells differentiate into secretory cells. Often, lipid droplets accumulate, and some intraluminal secretion occurs. During this time, estrogen also exerts a histamine-like effect on the breast parenchyma, resulting in increased blood flow and breast edema just prior to the onset of menses.

During this time, type I lobules continue to predominate. The increased rate of cellular proliferation in these lobules may partly explain the differences in breast cancer rates based on parity and age at first live birth.

Physiology of Pregnancy

During pregnancy, there is a decrease in fibrous stroma along with an increase in new acini/lobules. In the first trimester, ducts sprout and branch, and lobules develop as estrogen increases. Breast enlargement is significant, with dilatation of superficial veins and breast edema. The nipple-areola complex darkens and begins to enlarge. Type 3 lobules (with an average of 80 acini) begin to develop during this time and are referred to as alveoli.

In the second trimester, levels of progesterone increase, as does lobular formation. The alveoli begin to form colostrum, which is composed of desquamated eosinophilic cells, plasma cells, leukocytes, and epithelial cells.

In the third trimester, the alveoli continue to produce colostrum. At this time, epithelial differentiation is completed, resulting in the development of secretory cells that produce and secrete milk proteins. Oxytocin increases over the last trimester, resulting in the proliferation of myoepithelial cells surrounding the ductal structures, which propel the milk forward toward the nipple-areola complex.

Physiology of Lactation

After birth, there is a sudden decrease in the levels of estrogen, progesterone, and placental lactogen, coupled with an increase in prolactin, which induces the production and secretion of milk. Hormonal levels reach their lowest levels at about the fifth postpartum day, with a concomitant decrease in prolactin-inhibiting factor (PIF). This decrease results in the secretion of prolactin. Along with additional growth factors, prolactin secretion results in the accumulation of colostrum and, subsequently, milk in the alveoli and ducts. Stimulation of the nipple-areola complex stimulates the release of oxytocin and the contraction of the myoepithelial cells surrounding the ductal system. Upon cessation of breast-feeding (weaning), levels of prolactin and oxytocin fall. Retained secretions are removed via phagocytosis. Atrophy of the glandular, ductal, and stromal elements is observed. The secretory cells responsible for milk production undergo apoptosis. However, the type 3 lobules persist.

Physiology of Menopause

After menopause, the breast parenchyma regresses and is replaced by adipose tissue. This replacement occurs by involution of the ductal, glandular, and stromal elements/connective tissue of the breast. The ductal system remains but undergoes atresia, with collapse of the lobular units. Type 1 lobules again predominate, as in the nulliparous breast. The number of lymphatic channels through the breast parenchyma also decreases [2, 4, 5].

Surgical/Oncological Considerations

Tumor Location Within the Breast

The adult breast develops in a conical form, with epithelial/ductal tissue in each quadrant of the breast. The axillary tail of Spence, as discussed previously, is an extension of the upper outer quadrant of the breast over the axilla. Because of this extension, the upper outer quadrant contains significantly more epithelial tissue than the other quadrants. Thus, this quadrant is the most frequent site of breast neoplasms and harbors more than half of both benign and malignant tumors [3, 4, 7].

The location of the tumor within the breast can also affect the ability to perform breast conservation (segmental mastectomy). In general, segmental mastectomy can be performed with good cosmetic outcome when the tumor volume is less than 20% of the volume of the breast [8–10]. However, this percentage can vary with tumor location. Tumors in the upper outer quadrant are much easier to resect with good cosmetic outcome because there is a great amount of surrounding tissue in the region. Tumors that lie in the lower quadrants, particularly the lower inner quadrant, have little surrounding parenchyma, and excisions in these regions can lead to significant retraction and poor cosmetic outcome after surgery and radiation are performed. Partial breast reconstruction techniques, such as small latissimus dorsi flaps and local advancement flaps, can replace volume, particularly in the outer quadrants. However, these techniques require more extensive surgery, and the patient may be better served by mastectomy and whole breast reconstruction in this situation [11–13]. Depending on tumor location, volume loss can also be addressed by oncoplastic surgical techniques ranging from simple local advancement flaps to concurrent reduction mammoplasty [14–16].

Borders of Mastectomy

There are three different types of mastectomy, all with different extents of dissection:

1. Simple or total mastectomy – several skin incisions can be made, including peri-areolar (skin-sparing) or elliptical. Dissection is performed along the superficial fascial plane superiorly to the clavicle; medially to the sternal

edge; inferiorly to the inframammary fold, just cranial to the insertion of the rectus sheath; and laterally to the edge of pectoralis major muscle. The deep border of dissection is the deep fascial plane, just superficial to the pectoralis major muscle. This method of mastectomy removes nearly 100% of the breast epithelial/stromal tissue while preserving the axillary fat pad and axillary lymph nodes.

This approach is used most often in modern practice and is often combined with immediate reconstruction. When plastic surgery is involved, it is imperative that a multidisciplinary approach to surgery be used and that both oncological and plastic surgeons are involved in incision planning. This is particularly true in the case of nipple-sparing mastectomy, in which several incisions can be used [17–23]. An important anatomic consideration is the blood supply to the nipple and areola, which can vary greatly from patient to patient. Nipples that derive most of their blood supply from the underlying parenchyma are likely to suffer partial or complete necrosis after nipple-sparing mastectomy, whereas the viability of those that derive blood supply from the surrounding skin will be largely unaffected. Blood flow can be assessed either preoperatively or intraoperatively with imaging systems that detect fluorescent dye (usually indocyanine green) injected intravenously. The resulting perfusion patterns can help guide incision planning and also identify candidates for nipple-sparing surgery [24] (Fig. 1.6).

2. Modified radical mastectomy – this operation can be performed through the same incisions as a total or simple mastectomy. The elliptical incision can be extended superolaterally toward the axilla to facilitate axillary dissection. The superior, medial, inferior, and deep borders of the dissection are the same as in a total mastectomy. However, the modified radical mastectomy involves the removal of levels I and II axillary lymph nodes; thus, the

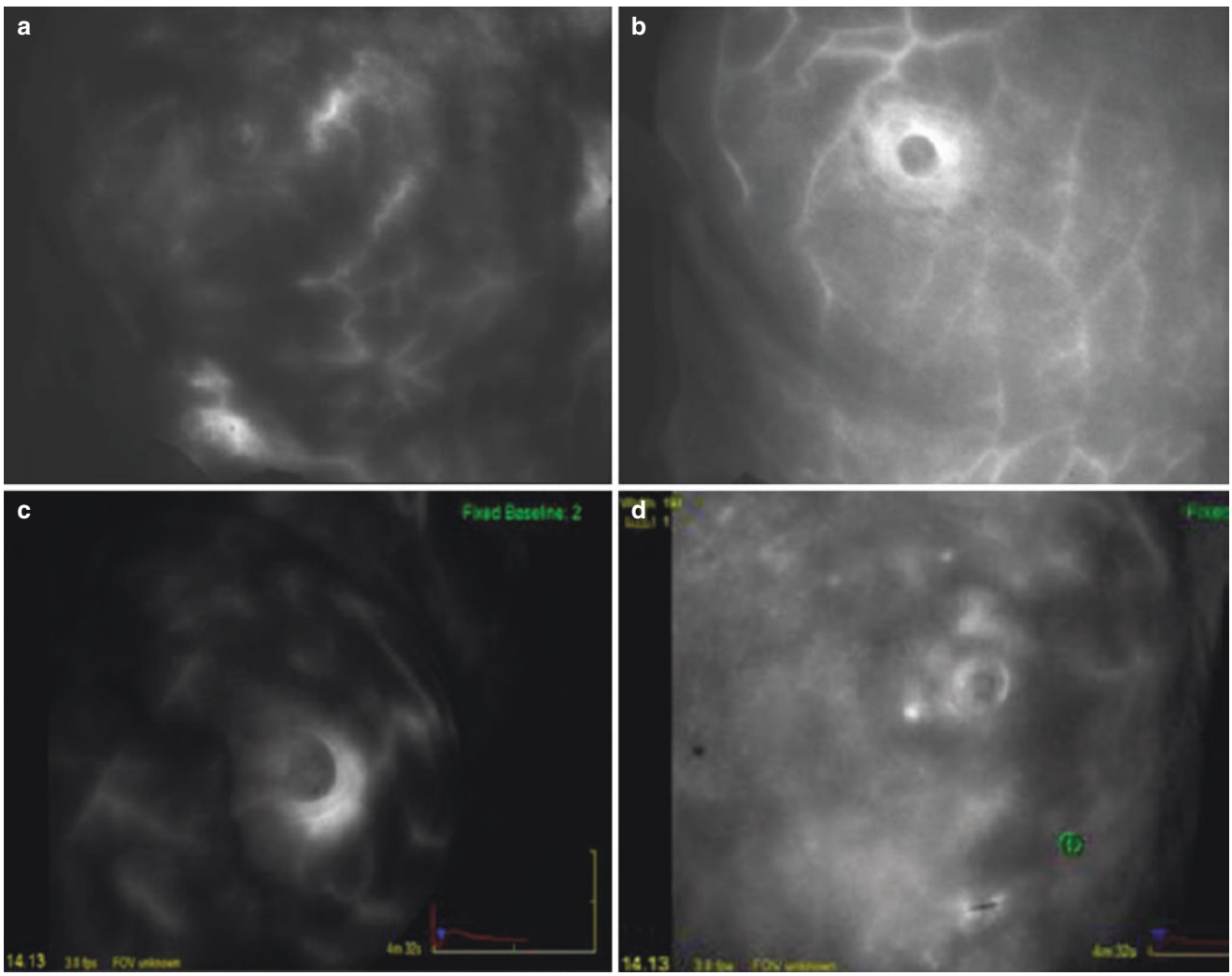

Fig. 1.6 Nipple perfusion patterns

lateral border of dissection is the latissimus dorsi extending superiorly to the axillary vein.

3. Halsted radical mastectomy – this operation is rarely performed and very rarely described in current surgical texts and atlases. The superior, medial, inferior, and lateral borders are the same as in a modified radical mastectomy. However, the deep dissection includes the pectoralis major and minor muscles. The axillary dissection includes levels I, II, and III of the axillary lymph nodes and is thus extended superior and medial to the axillary vein. This operation is performed only in the presence of locally advanced cancers that involve one or both pectoralis muscles [6].

Sentinel Node Biopsy

Sentinel lymph node biopsy was originally described as a method for detecting the lymphatic drainage of melanoma. It has been modified for use in breast cancer using the following method.

1. Isosulfan or methylene blue dye and/or technetium-99 are injected preoperatively into the superficial lymphatic plexus, either into the subareolar plexus or around the tumor.
2. This injection *can* be followed by lymphoscintigraphy to identify the area into which the radioactive dye has drained. Lymphoscintigraphy requires allowing the technetium 1 h or more to travel through the breast lymphatics into the axillary and/or internal mammary lymph nodes. As noted above, 97% of the breast drains to the axillary region; thus, this step is not necessary. It can be helpful in inner quadrant tumors, which more commonly drain to the internal mammary chain, and in patients with previous breast surgery, which might interfere with the normal lymphatic drainage of the breast.
3. Once in the operating room, the radioactive-sensitive probe can be used to localize the area in the axilla with the highest concentration of technetium colloid.
4. An incision is made in this area through the skin, the subcutaneous tissue, and the clavipectoral fascia. Once the axillary fat pad is identified, the probe can be used to localize the lymph node(s) with the highest concentration of radioactive dye. Those lymph node(s) that are both "hot" (radioactive) and "blue" (have taken up the blue dye) should be removed and sent for pathologic analysis (frozen, touch prep, or permanent). If these "sentinel" lymph nodes show evidence of malignancy, then a full axillary dissection as described for modified radical mastectomy is performed at that time or during a separate operation.

This method is based upon the anatomy of the breast lymphatic system. As described previously in this chapter, the lymph flows from the skin to the subareolar plexus and then into the interconnected deep lymphatic plexus that drains the breast parenchyma via the lymphatic vessels associated with the lactiferous ducts. Therefore, any lymphatic drainage from the breast must travel through both the superficial and deep lymphatic plexuses before leaving the breast, and an injection into the superficial lymphatic plexus will identify the main route of drainage for the breast. This drainage is standard and reproducible. Once the channels reach the axilla, they drain first to the "sentinel" lymph node(s) in either levels I or II of the axilla before draining to the remainder of the axilla. If no cancer is found in the sentinel node, there is a >95% likelihood that no other cancer exists in the axilla [2, 4, 5, 25].

Sentinel lymph node biopsy has several advantages over axillary dissection in appropriately selected patients, and in fact, axillary dissection has become increasingly rare. Several landmark trials have established the efficacy of sentinel lymph node biopsy in the setting of breast cancer. The great advantage of sentinel lymph node biopsy is the reduction in risk of postoperative arm (and to some extent breast) lymphedema. The rich lymphatic network experiences less disruption. In early studies, most notably NSABP B-32 and ACOSOG Z0010, the lymphedema rates after sentinel lymph node biopsy varied from 8% to 12%, whereas axillary dissection resulted in lymphedema rates of 14–42% [26, 27]. However, for patients who require axillary dissection, techniques can identify the lymphatics that primarily drain the arm (outside of the level III lymph nodes, which are excluded in modern axillary dissection if they are not clinically involved due to the low incidence of involved nodes in this region and the high incidence of arm lymphedema after radical mastectomy) [28, 29]. The best-described technique is axillary reverse lymphatic mapping (ARM). This technique involves injecting a small amount of blue dye in the subcutaneous tissue of the volar surface of the upper arm prior to lymphatic surgery. The axillary lymph nodes that drain the arm can be identified and frequently preserved. This can result in a lymphedema rate of 2.4% after ALND in which the identified arm lymphatics are preserved, much lower than previous reports [30–33].

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Benign Diseases of the Breast

2

Edward R. Sauter

Physical Examination of the Breast

Physical examination of the breast can be performed within the context of a clinical examination or by the individual. The former setting is often termed a clinical breast examination (CBE) and the latter a breast self-examination (BSE). Before the era of routine standardized breast imaging, physical examination was generally the primary method of diagnosing breast cancers. Breast imaging lacked standardization until the creation of the BI-RADS system in 1993 [1].

CBE is currently used as a screening test that can identify areas with breast cancer. While CBE is less sensitive than mammography, it is nonetheless the primary mode of detection for the 15% of breast cancers that are missed by mammography [2].

BSE was promoted to allow women to identify their own cancers at an early stage. Although BSE was anticipated to work for many reasons, randomized trials of BSE with increasingly sophisticated procedures for retraining and sustaining BSE practice have demonstrated that although there is increased identification of benign breast abnormalities, there is no increased identification of cancer and no improvement in breast cancer specific survival [2].

Examination of the Breast

The purpose of a CBE is to detect changes in the consistency of the breast tissue. Other tests are needed if an area of asymmetry is found [2]. CBE includes visual inspection of the breast first with the patient sitting and then supine. With the patient sitting, the position and contour of the breast are observed with changes in posture and arm position. Unexpected changes in breast contour should be further evaluated by breast palpation. Supine is the optimal patient position for breast palpation. Alterations in breast consistency should be further evaluated with imaging studies and/or biopsy. For women with pathological nipple discharge (PND) (discussed in more detail below), CBE can be used to localize the source of the discharge. In the absence of PND, CBE seeks changes in the visual appearance of the breasts and/or signs of local metastases, e.g., to regional lymph nodes. Signs of advanced cancer are rarely encountered during CBE of a truly asymptomatic patient.

Although a patient's personal and family history influences the probability that cancer will be found, history is not relevant to the CBE or when interpreting the CBE results because the majority of breast cancers occur in women without known risk factors. Models composed of silicone or other materials are widely used to teach both CBE and BSE skills, although their benefits in early cancer detection are largely unproven.

Signs and Symptoms of Breast Disease

Many of the features that students are taught to identify on CBE, such as skin dimpling, peau d'orange, hardness, and fixed mass, were first described before mammography and applied to advanced breast cancers, but these features are generally not applicable to the earlier stage cancers that are typically encountered in current practice [2]. Other findings can occur with early stage disease, such as PND, breast asymmetry, and masses. Breast inflammation is most often benign but can be an indicator of cancer. The most important consideration in any breast abnormality is to exclude carcinoma. Inflammatory carcinoma can present as erythema with or without pain in the breast. Biopsy of the skin and any associated underlying mass should be performed. The breast is also often

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inflamed in response to radiation therapy to treat breast cancer. In this chapter, we will focus on breast symptoms that are often, although not always, related to benign disease, including mastalgia, nipple discharge, breast inflammation, and breast masses.

Pathological Nipple Discharge

CBE does not seek to determine if nipple discharge can be elicited. Nipple discharge is of interest only if it is spontaneous. Fluid can be elicited by many women from their breast with massage. This fluid is not spontaneous nipple discharge (SND), which is of concern because of its potential implications related to disease, but rather intraductal fluid that is present in the breasts of all women and is often termed nipple aspirate fluid (NAF) because a modified breast pump is sometimes used to collect it [3]. However, if a woman reports noticing fluid on her bra that she did not elicit, particularly from one but not the other breast, this symptom should be further investigated, and pressure applied to the breast sequentially in a circular pattern can help localize the source of the spontaneous discharge.

SND is common, accounting for nearly 7% of all breast symptoms. SND is most often physiological, particularly if bilateral and from multiple breast ducts. Carcinoma prevalence in women with SND varies primarily according to the criteria used to assess whether the discharge is physiological or pathological. The criteria usually include whether the discharge is from one or both breasts and from one or multiple nipple ducts and the characteristics of the discharge (bloody vs. nonbloody; clear or serous vs. white, yellow, or green). Additional criteria include the presence of an associated mass or an imaging abnormality. Because the criteria distinguishing pathological from physiological discharge vary from publication to publication, the published incidence of carcinoma among women with SND also varies [4].

PND is more likely when the discharge is unilateral and from one milk duct. The most common diagnosis in women with PND is papilloma. Among breast lesions, papilloma is unique in its frequent presentation as PND. NAF originates in the breast ducts similarly to SND but is less voluminous and can be obtained from essentially all nonlactating women after a learning period [4]. In contrast to NAF cytology, in which false positives are rare, PND cytology in patients with papillomas is occasionally falsely interpreted as containing malignant cells [5] because exfoliated cells from papillomas can appear quite abnormal when not viewed in the context of histological architecture. Although older studies reported that bloody nipple discharge was more commonly associated with cancer than nonbloody discharge, more recent studies challenge this belief [4].

Breast Inflammation

The breast is most fundamentally an appendage of the skin. Many systemic inflammatory conditions are present on the skin of the breast, including sarcoidosis, vasculitides, diabetes, and infections [6]. Sarcoidosis of the breast occurs in less than 1% of individuals with sarcoid and usually presents as a breast mass, less often with skin dimpling and peau d'orange changes [7]. Primary sarcoidosis of the breast without systemic manifestations can occur but is uncommon. Giant cell (temporal) arteritis can manifest in the breast, typically presenting as painful breast masses. Systemic symptoms related to giant cell arteritis are usually present. Other vasculitides such as polyarteritis nodosa and Wegener's granulomatosis involving the breast have also been reported [7]. Diabetic mastopathy is most often observed in premenopausal women with type I diabetes and classically presents as a hard painless mass in one or both breasts [8]. Diagnosis requires biopsy, and treatment is mass excision. IgG4-related autoimmune syndrome can present in the breast, commonly as a tender breast mass [6].

Mastalgia (breast pain) accounts for two thirds of all physician visits for breast symptoms but is not a risk factor for breast cancer [9]. The pain may be cyclical. Cyclic pain is most often related to the menstrual cycle, is bilateral and diffuse, and occurs during the luteal phase as rising progesterone levels increase the water content in the breast [9]. Noncyclic pain may be in one or both breasts and has been associated with a variety of medications, including oral contraceptives, female hormones, psychotropics, and cardiovascular medications. Larger breasted women may develop ligamentous pain if an adequate support bra is not worn. If the clinical workup, including history of diffuse pain, CBE, and mammography (in women over 40), suggests a benign etiology, treatment is generally supportive, most often starting with confirming that the woman is wearing a supportive, well fitted brassiere. Acetaminophen or a nonsteroidal anti-inflammatory medication is often effective [9].

Fat necrosis generally presents as a painful mass in the breast. There may be multiple masses, with or without skin retraction. Fibrosis and calcification are common. Women with large breasts are at highest risk [7], and necrosis usually occurs following trauma. The trauma can include cyst aspiration, breast massage, mammography, radiation therapy, biopsy, implant removal, and reduction mammoplasty. A biopsy is often needed to exclude malignancy.

Mastitis occurs most commonly in women of childbearing age. It can occur during pregnancy and lactation and in women who are not pregnant or lactating [6], although in the latter group, most women report having given birth within 5 years of mastitis onset. The normal bacterial flora of breast tissue resembles that of the skin,

and coagulase negative *Staphlococcus* and *Propionibacterium* species are the predominant organisms [6]. Mastitis is associated with pain, breast swelling, mass(es), and inflammation that resemble an abscess. Ipsilateral axillary lymph nodes are enlarged in approximately one sixth of patients [7]. Mastitis frequently leads to surgical interventions to biopsy the lesion(s) to exclude malignancy and drainage procedures to treat the inflammatory process. The interventions can lead to breast scarring and/or shrinkage. Resolution occurs in only approximately half of benign conditions. The various forms of benign inflammatory processes (periductal mastitis, Zuska's disease, comedomastitis, duct ectasia, mastitis obliterans, lactiferous fistula, and idiopathic granulomatous lobular mastitis) may be part of a common disease process termed mammary duct associated inflammatory disease sequence (MDAIDS) [7]. Smoking is linked to MDAIDS, and severe disease occurs almost exclusively in heavy smokers. Therefore, smoking cessation is a very important part of the treatment process [7]. These conditions may result from lactiferous duct obstruction, resulting in duct distention, inflammation, and ultimately rupture. SND may be observed. Treatment requires excision of the affected ductal system. Simple incision and drainage are associated with a high rate of mastitis recurrence and breast scarring.

Breast Masses and Breast Imaging

Approximately 70–80% of the breast lesions detected by physical examination or imaging and biopsied [10] are benign. Most solid or complex cystic breast lesions should undergo biopsy. Possible exceptions are lesions in young women that are highly consistent with a fibroadenoma, as long as the lesion does not enlarge over time, and lesions that have been present for years and remain unchanged. Microcalcifications are biopsied based on whether they are considered suspicious by imaging criteria.

False positive imaging can occur not only with breast cancer screening but also in the workup of other malignancies. Patients who undergo 18F-fluorodeoxyglucose (FDG) PET or PET CT for staging of cancers other than breast are occasionally found to have 18F-FDG-avid breast lesions. When biopsied, these lesions are most often benign. Among the reasons for this increased uptake include acute and chronic inflammation, physiological lactation, and benign breast masses, including silicone granuloma, fat necrosis, fibroadenoma, and postsurgical changes [11]. To decrease the number of false positive biopsies, Adejolu et al. [11] recommend correlative imaging, including mammography, sonography, or MRI.

Changes During Pregnancy or Lactation

Normal pregnancy related breast changes include growth and enlargement, tenderness and hypersensitivity, darkening of the skin of the nipple and areola, and enlargement of superficial veins near the skin surface. The nipple and areola enlarge. The breasts are more prone to leaking during pregnancy.

Most pregnancy induced conditions of the breast that are not considered normal are nonetheless benign. These benign conditions include lactating adenoma, galactocele, gigantomastia, and benign nipple discharge [12]. Cancer must be excluded by a thorough workup, including breast biopsy if indicated. During lactation, the most common problems are inflammation and infection. Organisms from the infant are the usual source of breast infections during lactation. Continuing breastfeeding with an infection in the breast is recommended because it is not known to harm the infant, and keeping the breast empty of milk promotes infection resolution by draining the material that is facilitating bacterial growth.

Pregnancy associated masses are usually discovered during patient self examination. Ultrasound is the imaging modality of choice to further delineate the lesion and is often useful if a biopsy is indicated. Lactation should be suppressed prior to biopsy in nursing women to reduce the risk of abscess and milk fistula formation [13]. Fine needle aspiration is less reliable during pregnancy and lactation due to the hyperproliferative features in the tissue of the pregnant, lactating, or involuting breast [14].

During pregnancy and lactation, the breast can be affected by a variety of benign disorders, including inflammatory and infectious diseases, juvenile papillomatosis, and benign tumors. Fibroadenomas may manifest with growth or infarction. Galactocele is the most commonly observed breast lesion during lactation [15]. It manifests as either a cystic mass with a fat-fluid level or as a pseudohamartoma. The tumors and diseases that affect the breasts during pregnancy and lactation are also observed in nonpregnant women but may have a different appearance. The sensitivity of mammography in pregnant and lactating women is decreased due to increased parenchymal density. Instead, ultrasonography is the most appropriate radiological method for evaluating breast masses in this setting and is particularly useful in the diagnosis and treatment of abscesses.

Three percent of breast carcinomas occur in women aged 35 or younger. Breast cancer is the leading cause of cancer related death for women 15–29 years of age [16]. Studies of how reproductive factors influence the development of breast cancer are increasing our understanding of why carcinoma presents at an advanced stage among women who are pregnant or lactating. Specifically, concurrent or recent pregnancy is associated with increased tumor aggressiveness and

poorer survival. More than 15% of women younger than age 40 who develop breast cancer do so during pregnancy or lactation [17]. Pregnancy associated breast cancer (PABC) is classically defined as breast cancer diagnosed during pregnancy or within the first 12 months postpartum. The average age of women with PABC is 32–38 years [18]. The incidence of PABC may increase as more women choose to postpone childbearing until their mid to late 30s. Pregnancy related Burkitt's lymphoma characteristically manifests with bilateral and diffuse involvement of the breasts [15].

Pathology of Benign Breast Disease

Fibroadenomas and disorders related to breast growth are the most common breast diseases in adolescent women. The assessment of breast disorders in adolescents generally involves CBE and, when needed, ultrasonography. Fibroadenomas can be treated conservatively unless they continue to grow. When the diagnosis is secure and surgical removal is selected, enucleation is the procedure of choice. Breast abscess is mainly due to duct ectasia [19]. Phyllodes tumors (PTs) of the breast are biphasic neoplasms in which interactions between the epithelium and stroma are critical for tumor development and progression. Intratumoral genetic heterogeneity is common in PTs and may account for the reported lack of correlation between histological grading and clinical behavior [20].

Desmoids are benign, slow growing fibroblastic neoplasms that are characterized by an infiltrative and locally aggressive growth pattern and frequent recurrence but no metastatic potential. Breast desmoids are rare and often misdiagnosed because they can mimic other breast lesions, including carcinoma. Desmoid tumors should be considered in the differential diagnosis of patients presenting with hard breast lumps [21].

Diabetic mastopathy is a proliferation of fibrous tissue in the breast that mimics a tumor. No imaging modality is entirely reliable in differentiating diabetic mastopathy from malignancy, and core biopsy is essential for accurate diagnosis when mammography and/or ultrasonography are indicative of potential malignancy [22]. Breast calcium deposits in the media of arterioles are more frequently detected in the mammograms of diabetic subjects and must be differentiated from suspicious breast microcalcifications.

Pseudoangiomatous stromal hyperplasia (PASH) is a benign, proliferative mesenchymal lesion of the breast that typically affects women of reproductive age [23]. PASH is frequently an incidental histological finding in breast biopsies. Rarely, it can present as a firm, painless breast mass. When presenting as a mass, it is well circumscribed, firm, and rubbery. Histologically, it demonstrates dense collagenous stroma. The most important differential diagnosis is angiosarcoma. When incidentally found, no treatment is required. When PASH forms a tumor mass, it is treated by local surgical excision with clear margins.

Papillary lesions of the breast are common and morphologically varied, ranging from benign to atypical to malignant. Cytologic assessment is very challenging and often inconsistent with the histologic assessment of the same lesion [24]. Completely excised papillary lesions have an excellent prognosis, whereas incompletely excised lesions may recur or persist as carcinoma. Complete excision is therefore recommended for all papillary lesions [24].

Ectopic breast tissue in axillary lymph nodes is a benign condition that must be differentiated from primary or metastatic carcinoma. Rarely, proliferative conditions such as an intraductal papilloma can occur in ectopic breast tissue [25].

The growing use of breast image detected biopsies has led to increased diagnosis of benign breast disease (BBD). As a group, BBD is a known risk factor for breast cancer among both Caucasian and African American women [26]. When separated into individual pathological entities, BBD ranges from diagnoses with no increased cancer risk to those with a consistently documented increased cancer risk. The lesions of highest risk, which are sometimes referred to as "borderline" lesions, contain atypical changes and include atypical hyperplasia and lobular carcinoma *in situ*. Some also classify ductal carcinoma *in situ* as a borderline lesion, although others do not. These "borderline" lesions can be difficult to diagnose, particularly because biopsy sample size is often limited [27]. Borderline lesions are associated with an increased risk of neighboring malignancy, particularly when the biopsy sample is small. Some of the most challenging scenarios include the differentiation between atypical ductal hyperplasia and low grade ductal carcinoma *in situ*, lobular neoplasia versus solid low grade ductal carcinoma *in situ*, correctly classifying papillary lesions with atypia, and classifying the spectrum of columnar cell changes [27]. Consensus criteria and uniform terminology for the diagnosis of these lesions do not exist.

Management of Palpable Breast Masses

In general, palpable breast masses are evaluated by CBE and imaging. Although imaging is not initially required, it does provide a more accurate assessment of mass size and shape and the involvement of the mass with surrounding structures. Most palpable breast masses should undergo biopsy, regardless of whether the lesion appears suspicious on breast imaging, because some cancers appear benign based on imaging criteria. Exceptions include simple cysts and tumors that are consistent with fibroadenoma in a young woman and do not continue to enlarge. Palpable intramammary lymph nodes are generally benign but rarely contain tumor spread from a