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FOLLOW UP OF ABNORMAL CLINICAL AND IMAGING FINDINGS OF THE BREAST: FIVE SELF-STUDY MODULES FOR PRIMARY CARE CLINICIANS

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Breast Cancer Module I: Breast Anatomy, Physiology, and Pathology

Module I Objectives

Understanding breast anatomy, physiology and pathology is essential for follow-up of abnormal breast cancer screening findings.

At the completion of this module, the clinician will be able to:

- Identify the normal anatomy and physiology of the breast;
- Distinguish abnormal clinical and pathology findings of the breast; and
- Define the major types of benign and malignant breast lesions and their prognostic significance.

Breast Anatomy

The breast lies on top of the pectoralis major muscle. Fibrous stroma provides the background architecture of the breast. Cooper's ligaments are attached to both the fascia of the skin and the pectoralis major muscle. Carcinoma invading these ligaments may result in skin dimpling which could be subtle or obvious during visual inspection (Figure1).

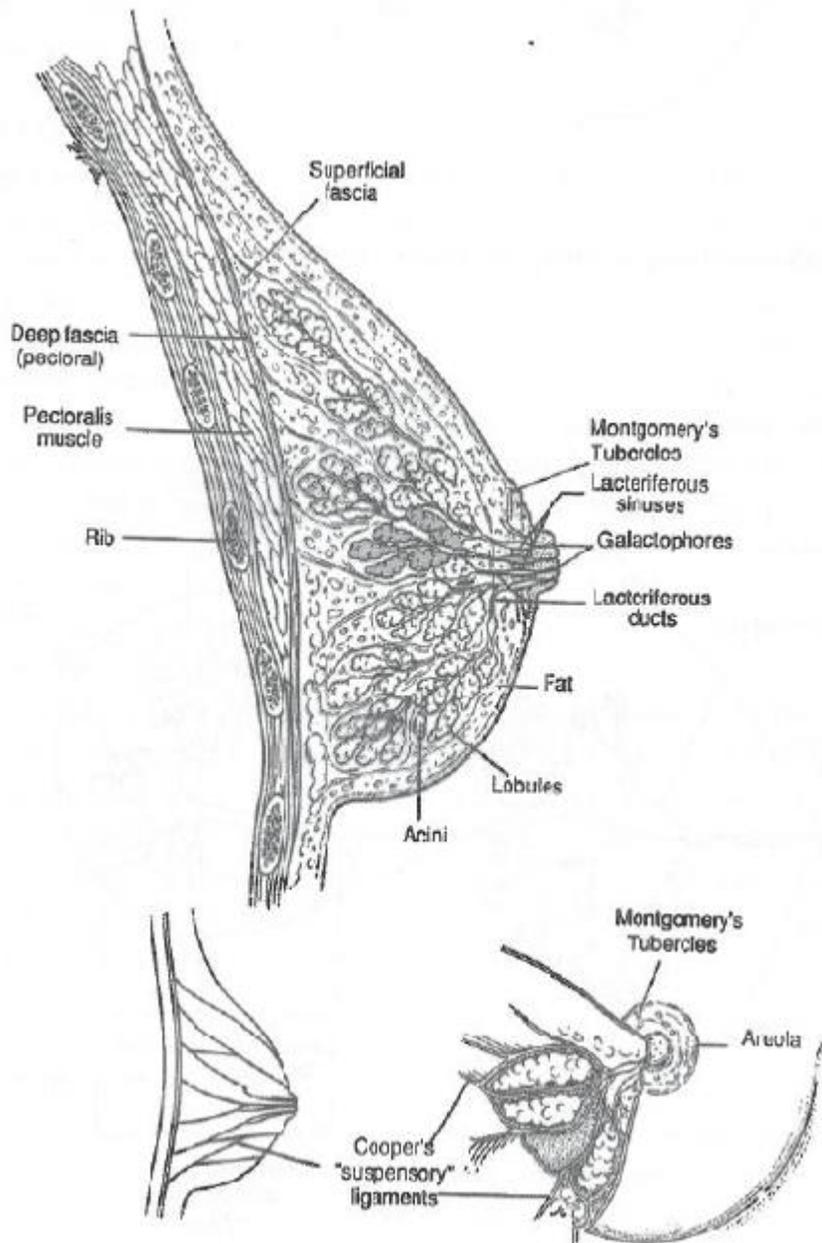


Figure 1. Carcinoma may result in skin dimpling.

Internal Anatomy

Where does breast cancer originate?

The breast is composed of glandular ducts and lobules, connective tissue, and fat, with most of the benign and malignant pathology arising in the duct and lobular network (**Figure 2**). Specifically, most breast cancer is thought to originate in the terminal ductal lobular unit (TDLU).

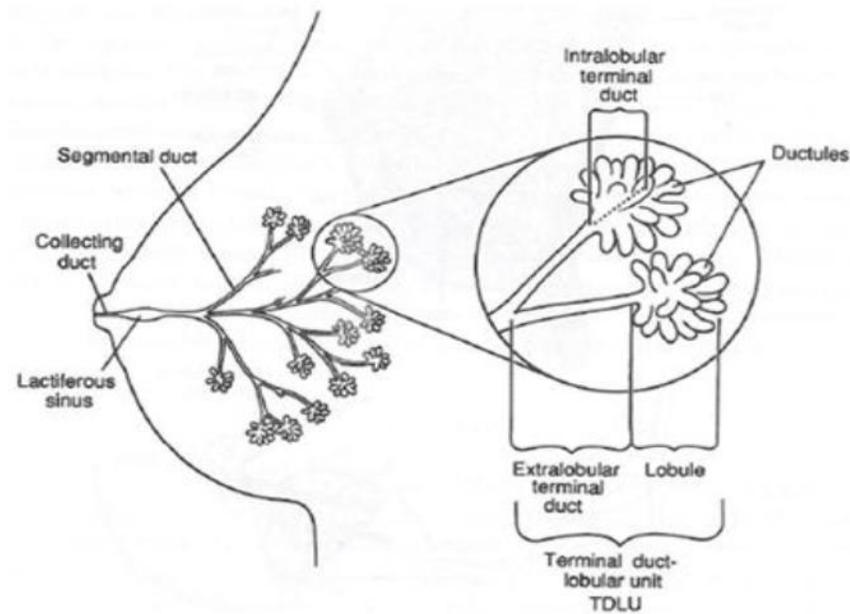


Figure 2. The breast is composed of glandular ducts and lobules, connective tissue, and fat. Republished with permission from Hindle, William H. *Breast Care: A Clinical Guidebook for Women's Primary Health Care Providers*. New York, NY: Springer-Verlag; 1999.

Half of this glandular tissue is located in the upper outer quadrant; therefore, nearly one half of all breast cancers occur in this area.

Glandular tissue and fat vary with a woman's age and weight. Lobes, lobules, and acini serve to produce and secrete milk—the primary function of the breast mammary glands. Ducts and lactiferous sinuses are tubular connections between the lobes and nipples to allow milk to exit the breast. The lactiferous sinuses (located beneath the nipple) may contribute to feeling granularity under the areola on physical examination. The parenchyma of the breast is composed of these ductal/glandular structures. Adipose tissue is present throughout the breast. A high ratio of ductal/glandular breast tissue to adipose and fibrous tissue makes detection of abnormalities during clinical breast examination (CBE) and mammography more difficult, especially in premenopausal women.

All women, regardless of breast size, have the same number of lobes, approximately 15-25. Six to 10 major ducts exit the nipple

Nipple and Areola

The nipple and areola are separate structures. The unique anatomy explains why 18% of malignant cancers are found in the subareolar region, a location not easily palpated unless using a technique that permits palpation to the chest wall (**Figure 3**) (see **Module II**).

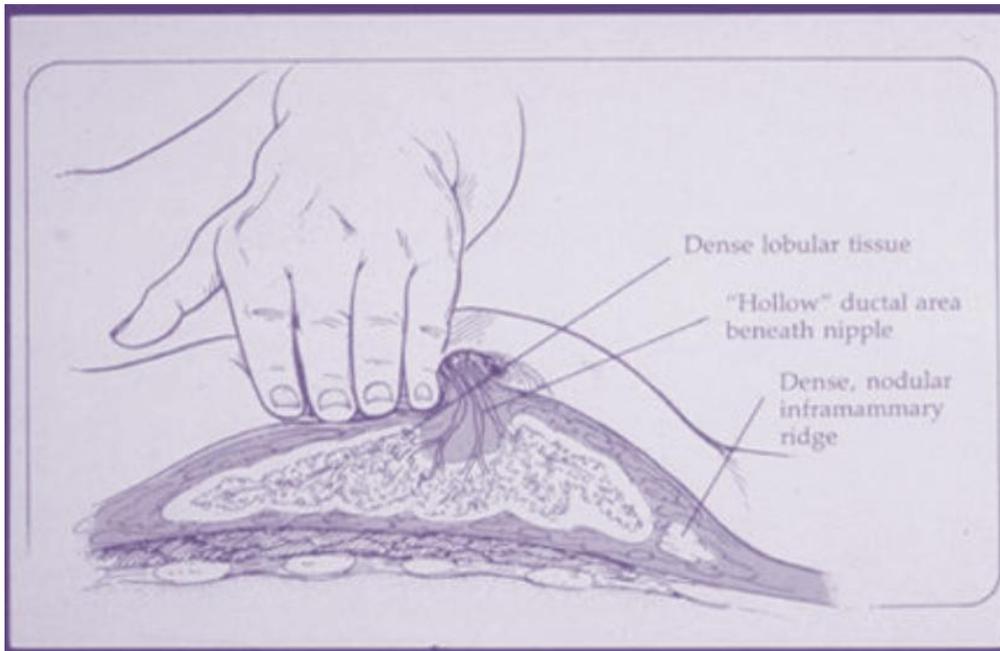
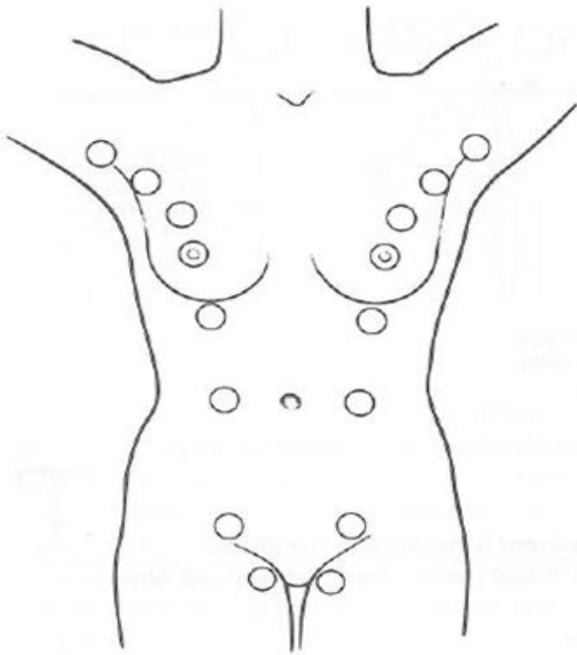


Figure 3. Subareolar region. Republished with permission from the professional education unit cancer detection section, California Department of Health Services. Supernumerary nipples

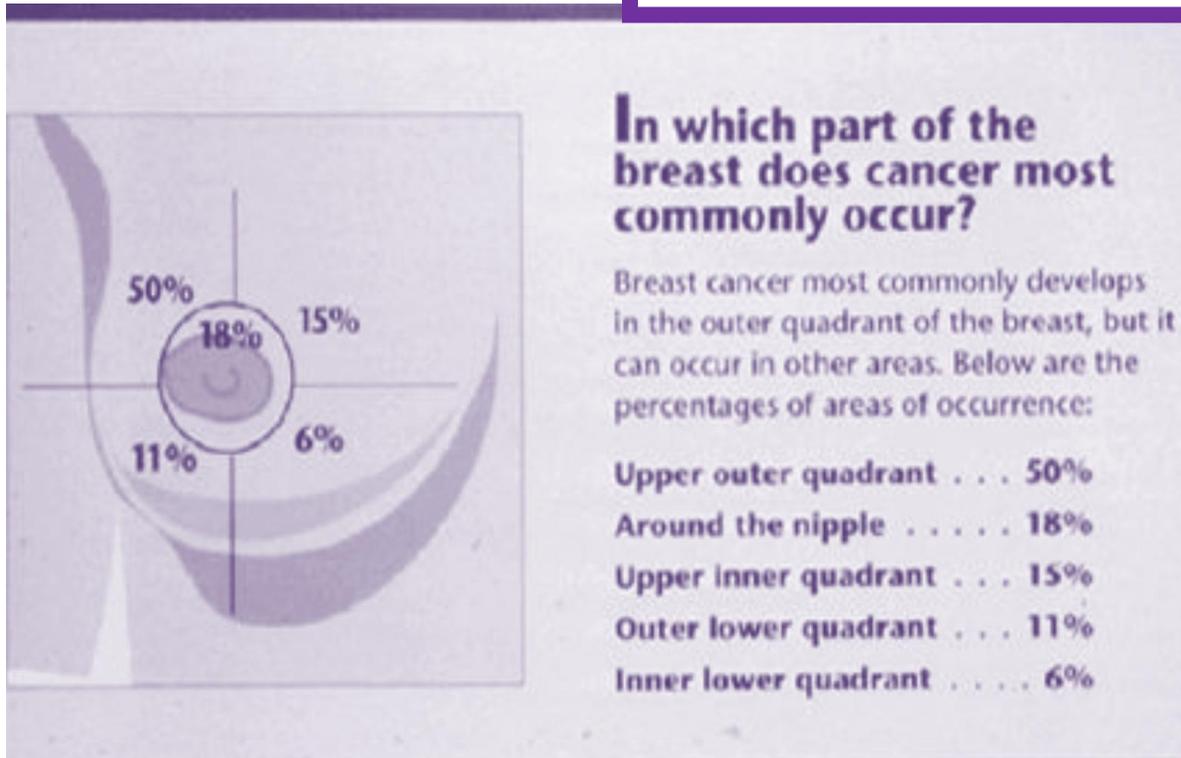
Supernumerary nipples and/or breasts and inverted nipples are congenital conditions that occur in about 10% of the population. Supernumerary nipples occur along the milkline and are sometimes mistaken for skin tags or moles (Figure 4). Neoplasms can occur in supernumerary breasts and should be screened and diagnosed in the same manner as usual breast cancer (CBE, imaging or minimally invasive biopsy^[2]).

Figure 4. Supernumerary nipples are sometimes mistaken for skin tags or moles. Graphic republished with permission from Hindle, William H. *Breast Care: A Clinical Guidebook for Women's Primary Health Care Providers*. New York, NY: Springer-Verlag; 1999.



Breast cancer can occur anywhere within the breast perimeter, including in supernumerary breast tissue anywhere along the milkline. Most breast cancers occur in the upper outer quadrant and subareolar region because that is where most of the tissue is located. (Figure 5).

Figure 5. Upper outer quadrant of the breast.



Microscopic Anatomy

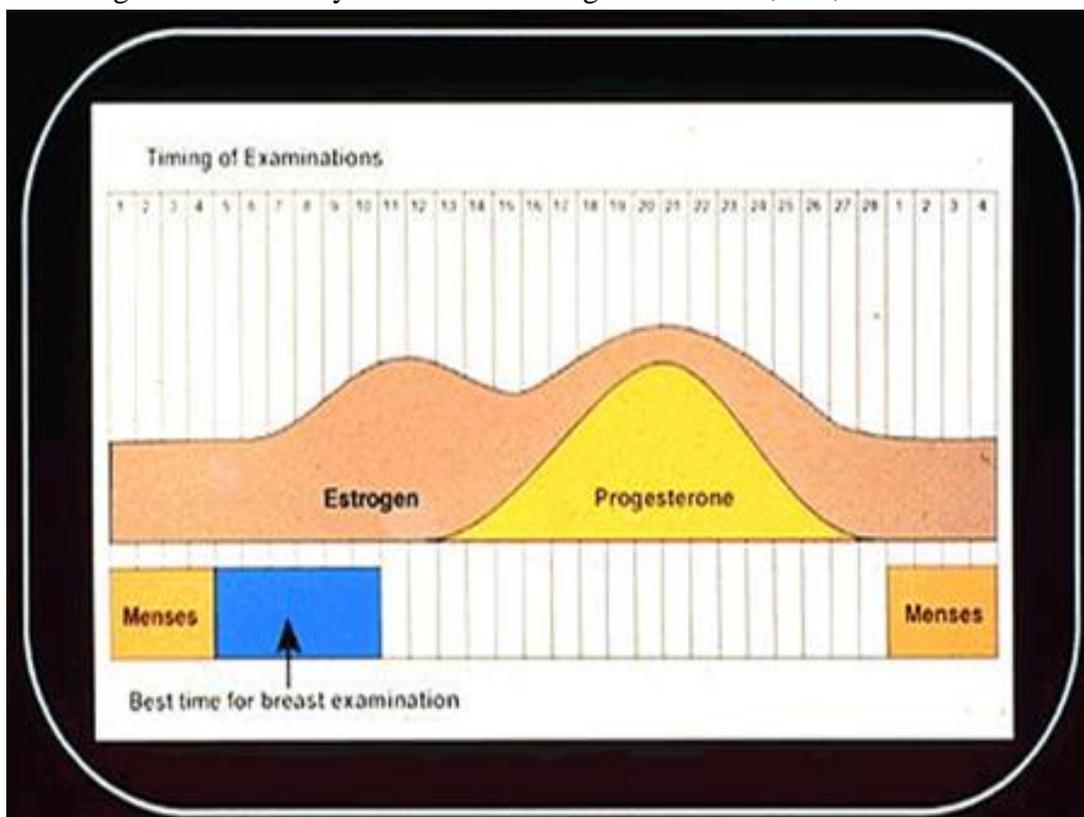
The distal terminus of the ductal network is the terminal ductal lobular unit (TDLU). Each of the lobes in the breast contains thousands of TDLUs, which form the functional secretory unit. The secretory units produce milk, which drains via the branching ducts to their terminus as the ampullae at the surface of the nipple. The TDLU is complex and consists of the extralobular and intralobular terminal ducts, and the blindly ending lobules (or ductules). An inner layer of secretory cells and an outer layer of myoepithelial cells which contain contractile fibers that eject the milk into the ducts during lactation surround this inner layer. Hence the lobules are referred to as acini during pregnancy and lactation.

Lymphatic Drainage and Blood Supply

Most of the lymphatic drainage of the breast is into the axilla, although the lower inner quadrants drain to the infraclavicular and sometimes to the medial substernal nodes. The lymphatic channels travel through the axilla, along the sternum, and above and below the clavicle. Arterial blood supply is abundant, while the venous drainage is variable. Most major venous pathways lead to the pulmonary capillary network (why lung metastases are common) or the vertebral veins (skeletal metastases). Obstruction of the lymphatic system in the dermis of the skin is a serious sign of inflammatory carcinoma of the breast. Later-stage presentation will give the skin an orange peel appearance called "peau d'orange."

Breast Physiology

All women experience changes in their breasts throughout the life cycle (**Table I-A**). Fluctuating hormone levels during the menstrual cycle can cause changes in the look, feel, and tenderness of the breasts (**Figure**



6).

Figure 6. Fluctuating hormone levels can cause changes in the look and feel of the breasts.

Table I-A. The Stages of Breast Development

Fetal development	Breast tissue begins to develop around the sixth week in utero.
Prepuberty	Breasts are in resting state with ducts present but nonfunctional
Puberty	Ducts elongate due to estrogen; breast bud appears and is sometimes mistaken for a mass and removed. Breast buds do not always develop simultaneously.
Young Adult	Effects of progesterone are influenced by initiation of ovulation; ducts elongate; side branches of ducts and lobular elements form
Maturity	Breasts become pendulous after many ovulatory cycles; lobular elements are well formed. Distinct morphologic changes occur with the menstrual cycle. During the first 5 menstrual days, there is minimal edema in the intralobular stroma and no mitoses or apoptosis is seen in the lobular epithelium. Intraluminal secretions are common. During the following 2 weeks, the follicular phase, the lobular acini increasingly develop a distinct double-cell layer appearance with increasing basal layer vacuolation. The stroma remains nonedematous until the third week, the midluteal phase. In the last few days prior to menstruation, the late luteal phase, there is extensive vacuolation and increased inflammation. Breast pain is more common during this part of the cycle. In premenopausal women, the breast is most sensitive to touch, or tender, about 7-14 days following ovulation. Thus, the best times for scheduling any type of clinical or mammographic breast exam are the days immediately following the start of menses (Days 5 to 10). Both require pressure and compression for better quality and may be more tolerable during these days when nodularity at its minimum.
Pregnancy	Distal ducts grow and branch; breasts enlarge to twice their normal weight; increase in mammary blood flow leads to vascular engorgement and areolar pigmentation; sometimes bloody nipple discharge occurs due to hypervascularity.
Lactation	Acini are dilated and engorged with colostrum and then milk.
Menopause	Lobules begin to recede, leaving mostly ducts, adipose tissue, and fibrous tissue; histologically, postmenopausal and prepubertal breasts are very similar. Hormone therapy may delay postmenopausal changes in the breast and mimic a more active physiologic or premenopausal state (i.e., cyclic tenderness due to increased nodularity, etc.).

Breast Pathology- Noninvasive

Almost all neoplastic breast pathology arises in the TDLU.[3] Subsequent risk of invasive breast cancer varies based on the histologic category of a benign breast lesion.^[4-9]

What is fibrocystic change and how can I confirm that what I'm palpating is normal for my patient?

Fibrocystic change, a benign condition of the breast, is actually a spectrum of a variety of morphologic changes in the TDLU (Table I-B).^[4-10] Some of these changes result from cellular proliferation (hyperplasia) and can cause palpable masses and/or mammographic lesions.

Table I-B. Types of Fibrocystic Change

Adenosis	A benign proliferation of glandular acini within a lobule, which may also be referred to as sclerosing adenosis when acini are deformed by sclerotic reaction. A subtype of adenosis is called blunt duct adenosis, in which there is dilatation of acini within the TDLU. Blunt duct adenosis can show calcifications within the acinar secretions.
Apocrine metaplasia	A change in which the cells of the TDLU resemble those of apocrine sweat glands; it is often associated with cysts of various sizes.
Cysts and duct ectasia	A dilation of medium to large ducts lined by flattened cells and filled with secretions and amorphous debris, which can include some calcifications ("milk of calcium"). These dilated spaces, when large, are referred to as cysts. Smaller dilated ducts are often referred to as duct ectasia, particularly when associated with periductal inflammation
Fibrosis	Replacement of the normal fatty stroma by increased fibrous tissue.
Epithelial hyperplasia	<p>A spectrum of complexity in the proliferation of benign cells lining the TDLU, both quantitatively and qualitatively:</p> <ul style="list-style-type: none"> • Mild hyperplasia contains only a few more cells beyond the normal 2-cell layer, and the cells do not have any significant nuclear changes. • Moderate or florid hyperplasia contains many more cells than the usual 2-cell layer and is found in 20% of breast biopsies. • Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) are 2 forms of epithelial hyperplasia that are referred to as "atypical" since they have many, but not all, of the histologic features of carcinoma in situ. As a "borderline" category, pathologists often have a hard time making this diagnosis and it may not be as reproducible among pathologists as other diagnostic categories.[10] ADH is associated with a significant risk for the development of invasive breast cancer.[4-9] However, the risk of developing breast cancer associated with ALH is less than that of ADH and more similar to proliferative fibrocystic change.[6-8] Since their risk for developing invasive cancer and histologic appearance are not significantly different, lobular carcinoma in situ and ALH are often referred to together as lobular neoplasia.

Fibroadenoma is a benign breast lesion but is not part of fibrocystic change (Figure 7). Fibroadenoma represents a focal hyperplasia of the stroma and the epithelial component of the TDLU and creates a distinctive round and well circumscribed mass on physical exam or mammogram. The stromal hyperplasia often compresses and stretches the hyperplastic glands, creating the fibroadenoma's characteristic histologic pattern. With age, the stroma will become more sclerotic and may undergo dystrophic calcification, and the epithelial hyperplasia may decrease. When a fibroadenoma contains cysts, sclerosing adenosis, epithelial calcifications, or papillary apocrine changes, it is referred to as a complex fibroadenoma and there is a slightly increased risk in the development of breast cancer^[11]

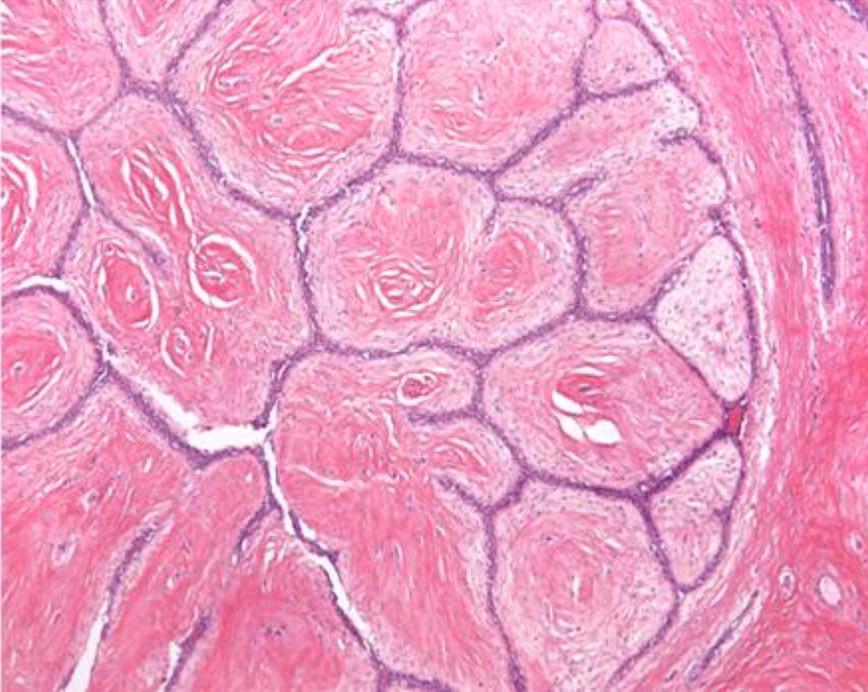


Figure 7. Fibroadenoma. Republished with permission from Dr. Lydia Howell.

Papillomas are frond- or finger-like hyperplastic epithelial growths with a fibrovascular core (Figure 8). Small calcifications can occur at the tip of the epithelial fronds. The epithelial hyperplasia may be of varying degrees. Papillomas can occur in large or small ducts and can be solitary or multiple. When multiple and small, the term "papillomatosis" is used and is considered to be part of the spectrum of fibrocystic change.

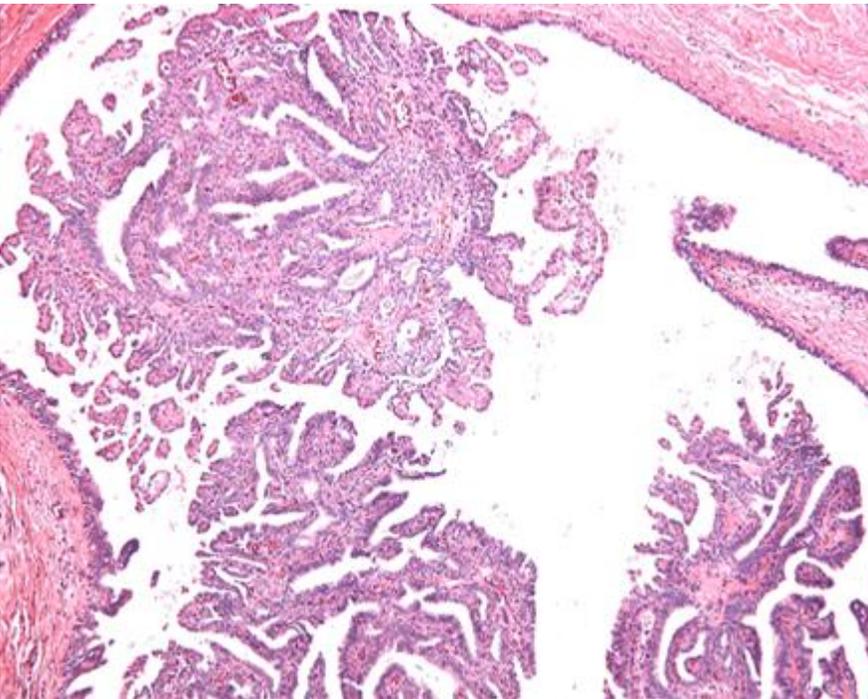


Figure 8. Papilloma. Republished with permission from Dr. Lydia Howell.

Carcinoma in situ has traditionally been classified into 2 major types: ductal and lobular. These terms denote a histologic pattern, since both types arise in the TDLU. Though ductal and lobular carcinomas were both originally thought to be precursors to invasive carcinoma, the risk for subsequently developing invasive carcinoma is quite different.

- Lobular carcinoma in situ (LCIS) is usually an incidental finding in breast tissue removed for another indication and is frequently multifocal (Figure 9). This lesion rarely causes clinical findings such as a mass. On palpation it feels more like a platform of dense tissue and may be seen as calcifications on mammography. It is characterized microscopically by distention of at least half of the acini in a lobular unit by a very round uniform population of small cells, which may have clear cytoplasm or nuclear vacuoles. The histologic differences and clinical implications of LCIS and atypical lobular hyperplasia (ALH) are not particularly distinctive. Thus, many pathologists prefer to refer to them together as lobular neoplasia. The risk of the development of breast cancer is considerably less than that of DCIS or even atypical ductal hyperplasia (ADH), and is more similar to florid epithelial hyperplasia in fibrocystic change.

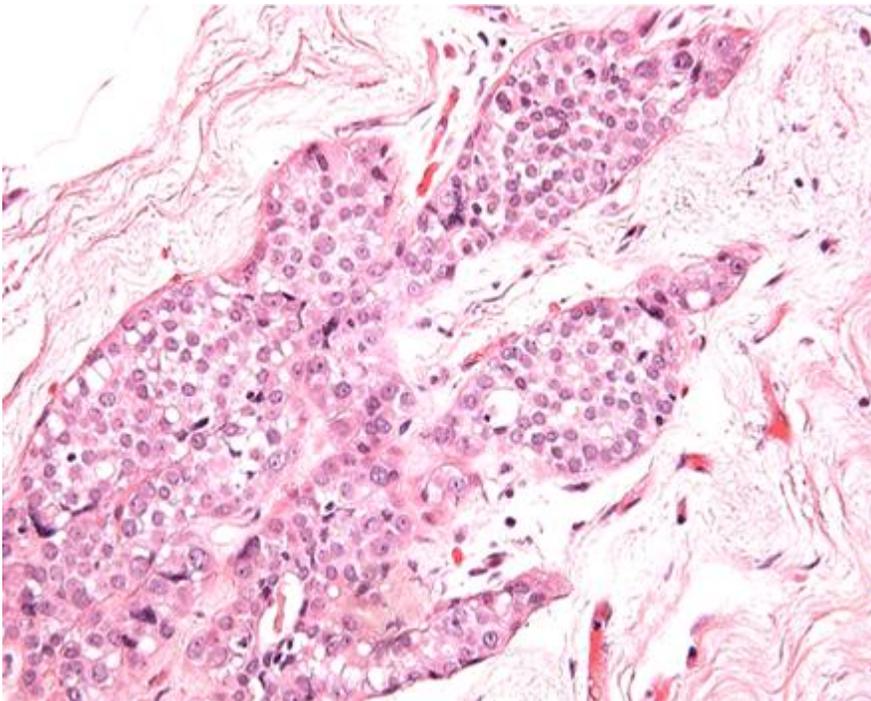


Figure 9. Lobular carcinoma in-situ (lobular neoplasia). Republished with permission from Dr. Lydia Howell.

Ductal carcinoma in situ (DCIS) is considered a precursor to invasive breast cancer because it is often noted in and around invasive cancers and because invasive cancer has been noted to develop when these lesions are incompletely excised (Figure 10). Of the invasive carcinomas that subsequently develop, invasive ductal carcinoma is the most common type. ^[6-9] However, it is not a single entity and the risk of progression to invasive carcinoma may vary considerably based on several pathologic features. Histologically, DCIS is characterized by a proliferation of neoplastic cells, which distend the TDLU but do not breach the basement membranes. Microscopic criteria important to the diagnosis of DCIS include architectural pattern, nuclear

grade, and necrosis, and these features should be listed in the pathology report. ^[11]

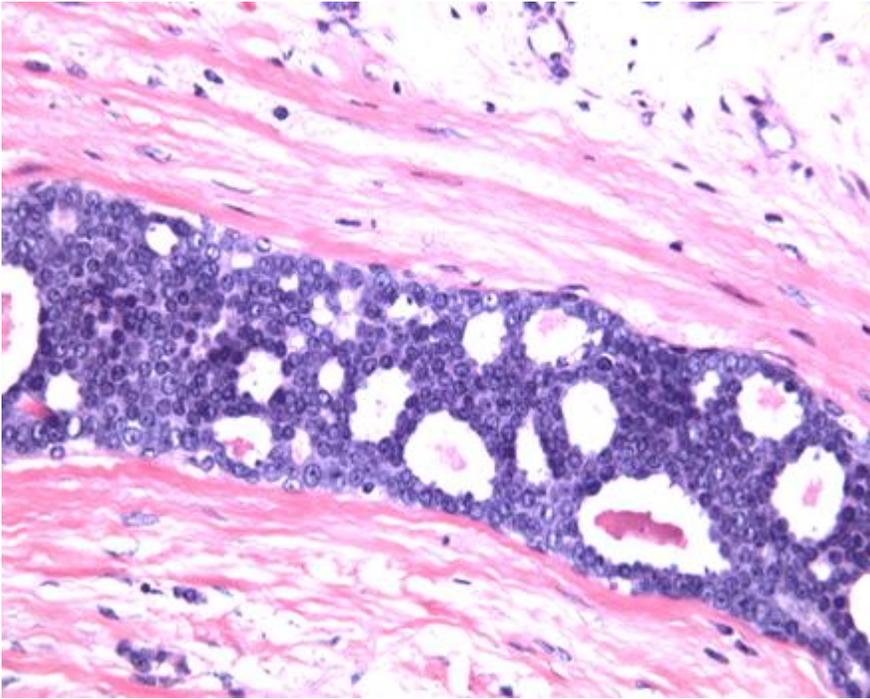


Figure 10. Ductal carcinoma in-situ, non-comedo (cribriform) type. Republished with permission from Dr. Lydia Howell.

Breast Pathology- Invasive

Infiltrating lobular carcinoma - This type is characterized histologically by a monotonous population of small cells that frequently contain a cytoplasmic vacuole and that classically infiltrate in a single-file pattern (Figure 11). The stroma is densely sclerotic, giving this tumor a rock-hard feeling on palpation and making the cells difficult to remove by FNA. This tumor has a better prognosis than infiltrating ductal carcinoma, an increased incidence of multifocality and bilaterality, and a distinctive pattern of metastases. Tumors that do not fulfill these classic criteria should be designated as "infiltrating carcinomas with lobular features" or as "lobular carcinoma variants" since they do not have the same prognostic implications.

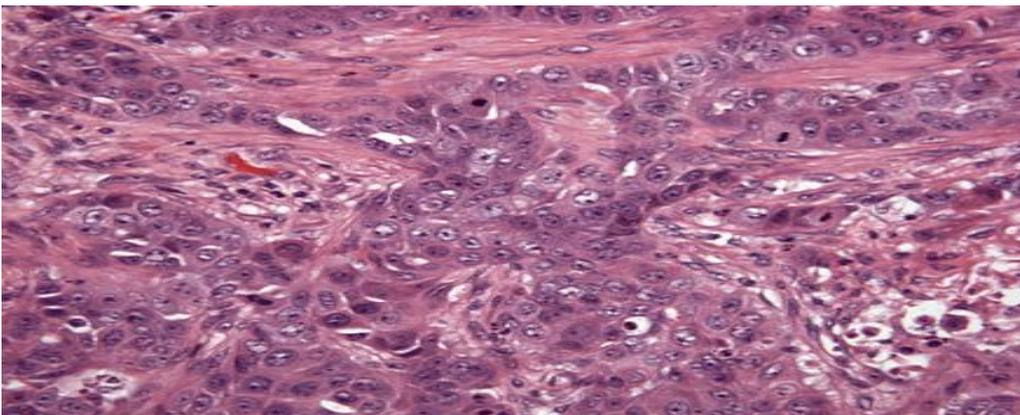


Figure 11. Infiltrating ductal carcinoma, no special type, grade 2. Republished with permission from Dr. Lydia Howell.

Infiltrating ductal carcinomas are the most common type of invasive breast cancer, accounting for 50% to 75% of cases, and is sometimes referred to as ductal carcinoma of no special type. There are many histologic and cytologic patterns within this category, and grading these features can give a clue to prognosis. In general, this form of breast cancer is composed of neoplastic cells that infiltrate the tissue in nests, sheets, cords, tubular structures, or as a combination of these patterns. The cells can vary in size but are usually at least twice the size of a normal ductal cell. The nuclei are enlarged and have conspicuous nucleoli. Nuclear pleomorphism and the number of mitoses may vary. The stroma is usually sclerotic. The tumor may invade vascular spaces.

Ductal carcinomas of special type are all relatively uncommon forms of breast cancer, all of which have a prognosis that is better than the more common infiltrating ductal carcinoma of no special type. Strict adherence to diagnostic criteria is required when classifying these lesions as a special type. Many tumors may show a mixed histologic pattern with both a special type and non-special type component; however, these should be designated as such in the pathology report since there are different clinical implications. For tumors with a mixed pattern, the prognosis is related to the worst part present. Ductal carcinomas of special type include: mucinous (colloid) carcinoma; tubular carcinoma; papillary carcinoma; medullary carcinoma; and infiltrating lobular carcinoma. ^[12]

Evaluation of Surgical Margins

Regardless of the type of carcinoma, the presence or absence of invasive carcinoma or DCIS at the surgical margins is a significant predictor of local recurrence following breast-conserving surgery. If the margins are not free of cancer cells, further surgery is usually required. This may consist of a wider excision or may require mastectomy. The pathology report should denote the specific margin that is involved and the distance of the tumor from the closest margin. ^[13]

Prognostic and Predictive Factors

There has been a profusion of articles describing a variety of new methods for determining prognosis in patients with breast cancer. There are several factors which are important in interpreting this information. Routine pathologic evaluation remains the most critical element in determining the prognosis of patients with breast cancer. Among the most potent prognostic factors available are lymph node status, tumor size and histologic grade, histologic tumor type and lymphatic vascular invasion (Category I in Table I-C below). ^[15-26]

- **A prognostic factor** is capable of providing information on clinical outcome at the time of diagnosis, independent of therapy. Such markers are usually indicators of growth, invasion, and metastatic potential. Prognostic factors influence disease outcome and are not affected by treatment.
- **A predictive factor** is capable of providing information on the likelihood of response to a given therapeutic modality. Such markers are either within the target of the treatment, or serve as modulators or epiphenomena related to expression and/or function of the target. Predictive differentially influence the outcome of 2 different adjuvant therapies, and therefore could be used to select between 2 different forms of adjuvant therapy. ^[14] The following are common prognostic and predictive factors used in the evaluation of

breast cancers, and they are categorized on the basis of the strength of published evidence by a consensus committee sponsored by the College of American Pathologists. ^[13]

Table I-C. Prognostic and Predictive Factors Useful in Clinical Patient Management

Category I	
Factors proven to be of prognostic import and useful in clinical patient management	
Tumor Size- predictor of tumor behavior with larger tumors associated with poorer prognoses.	Size is important in staging and a powerful predictor of tumor behavior. In general, the larger the tumor, the poorer the prognosis. The tumor should be measured in at least 2 dimensions, but the single largest dimension should be reported. Only the invasive component should be considered in the tumor size for staging purposes. Gross and microscopic size should be correlated. If there is a discrepancy between the two, microscopic size takes precedence ^[15,16]
Axillary lymph node status - the most important predictor of disease-free and overall survival in breast cancer, since it is an indicator of systemic rather than local disease	The presence or absence of metastases in axillary lymph nodes is the most important predictor of disease-free and overall survival in breast cancer since it is an indicator of systemic rather than local disease. The absolute number of nodes is also important. Patients with metastases in 4 or more lymph nodes have a worse prognosis than those who have fewer involved lymph nodes. Extension of tumor beyond the capsule of the lymph node should be included in the pathology report, but the significance is as yet unclear. Also uncertain is the significance of micrometastases (metastases < 2 mm in diameter) which increasingly detected with serial sectioning or through the use of immunohistochemistry for cytokeratins. For this reason, cytokeratin immunohistochemistry is not routinely recommended with sentinel or other lymph node biopsies. ^[15-20]
Histologic grade - denotes cell differentiation of a tumor. Can be performed on core biopsies, if there is sufficient tissue.	Grade is a method of denoting differentiation of the tumor. All invasive breast carcinomas, with the exception of medullary carcinoma, should be graded. Grading can and should be performed on core biopsies, if there is sufficient tissue. The most common grading system is the Scarff-Bloom-Richardson (Nottingham) system in which 3 features (the degree of tubule formation, the frequency of mitoses, and nuclear pleomorphism) are each assigned a score from 1-3. The scores for each feature are added together for a final sum ranging

	<p>from 3-9. A tumor with a sum of 3,4 or 5 is considered to be well-differentiated and assigned a Grade I, a sum of 6 or 7 considered to moderately differentiated or Grade II, and a poorly differentiated tumor will have a sum of 8 or 9 and given Grade III. Histologic grade relates to outcome within each stage grouping [15,16,21]</p>
<p>Histologic type - designation as infiltrating carcinoma or carcinoma of special type, with subsequent prognostic significance as noted above.</p>	<p>As mentioned earlier, designation as infiltrating ductal or lobular carcinoma or carcinoma of special type has prognostic significance. It should be reported routinely in pathology reports. [15,16]</p>
<p>Estrogen receptors (ER) and progesterone receptors (PR) - intracellular proteins that specifically bind hormones. ERs are found in 50% to 85% of all breast cancers and are more common in postmenopausal women. ER+ tumors have a better prognosis, including after recurrence. PRs are also usually present when ERS are present in large amounts and survival may be even better when a tumor is both ER+ and PR+.</p>	<p>Breast cancers were first noted to be responsive to hormonal manipulation over 100 years ago when it was observed that oophorectomy induced tumor regression. It was not until 75 years later that hormone-dependent tissues such as the breast were found to contain intracellular proteins, referred to as estrogen receptors, which specifically bind estrogen. When estrogen is bound, it becomes an activated complex which is then transported to the nucleus. In the nucleus, it binds to DNA and stimulates adjacent target genes for transcription of a variety of growth factors. Hormone receptors should be routinely evaluated in all breast cancers. ERs are found in 50-85% of all breast cancers and are more common in post-menopausal women. Progesterone receptors (PRs) also exist and are usually present when ERs are present in large amounts. Patients with ER+ tumors have a higher disease-free survival and overall survival than patients whose tumors are negative, including patients with metastatic disease. ER+ also indicates improved survival after recurrence. Survival may be even better when the tumor is both ER+ and PR+. PR+ is associated with a good prognosis as well, though it is felt that generally PR does not significantly improve the predictive value indicated by ER alone. ER+ and PR+ are also the only firmly established factors known to predict the efficacy of hormonal therapy. Immunohistochemistry has replaced the traditional ligand-binding assay as the preferred method. The name of the reagent kit, commercial supplier and tissue fixative should be included in the report. The percentage or proportion of cells expressing the antigen should also be reported. There is no data to indicate that an intensity score has any significance [15,16,22,23]</p>

Category II

Factors that had been extensively studied biologically and clinically, but whose import remains to be validated in statistically robust studies

HER-2/neu: This proto-oncogene encodes a transmembrane protein which functions as a cell-surface receptor which is involved with regulation of cell growth and proliferation. When mutated, it promotes neoplastic transformation. Mutations cause over-expression of the gene and is seen in approximately one third of breast cancers

HER2-Neu tumor positivity can also be used as a predictive marker for a variety of adjuvant therapies, including trastuzumab (Herceptin), an anti-HER2 humanized recombinant monoclonal antibody which targets the HER2 transmembrane receptor. Tumors over-expressing HER2-Neu have also been found to be less response to hormonal manipulation with Tamoxifen, resistant to adjuvant treatment with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) treatment regimens 14-P. Assay methods include both fluorescence in-situ hybridization (FISH) and immunohistochemistry, and it is uncertain which is superior. The report should indicate methods, primary reagent, name of reagent kit, and commercial supplier. An estimate of the percentage of immunopositive cancer cells and a score indicating staining intensity (usually 0 to 3+) should be reported. Only the invasive component of the tumor should be scored, and only those with membranous activity when immunohistochemistry is used. Tumors with 2+ staging should be reported. Only the invasive component of the tumor should be scored, and only those with membranous activity when immunohistochemistry is used. Tumors with 2+ staging should be tested with FISH for more definitive results. ^[15,16,22,24-26]

p53: This tumor suppressor gene is located on chromosome 17 and is involved in the maintenance of normal cell growth by suppressing cell replication and possibly inducing apoptosis. Genetic alterations of p53 lead to over-expression with increased accumulation of the mutated gene product which is detectable in the affected cells by immunocytochemical stains. Approximately one third of breast cancers demonstrate this change, but those that do are associated with high nuclear grade and have a considerably worse prognosis.

• p53 is a useful prognostic marker in node-negative breast cancer, and has been shown to correlate with decreased survival in patients with metastatic carcinoma. p53 is associated with high tumor grade and absence of estrogen receptors. It may also help indicate those patients most likely to respond to chemotherapy or radiotherapy. Despite these promising results, it is not routinely evaluated. Several methods can be used for detection, including immunohistochemistry and molecular methods, but none has been identified as preferable. ^[15,16,22]

<p>Lymphatic or vascular channel invasion: Identification of this feature predicts local failure and decreased overall survival.</p>	<p>Special stains are not required and this evaluation is performed on routine sections.^[15-20]</p>
<p>Proliferation markers, Ki67 and MIB-1: The proliferation rate of a tumor is believed to be a useful prognostic marker. A high proliferation rate tends to indicate a poorer prognosis</p>	<p>Ki67 is a monoclonal antibody (Mab) which recognizes a labile non-histone nuclear protein that is expressed during G1, S, and G2M phases of the cell cycle, and is absent in the G0 resting phase. Ki67 expression correlates with tumor grade and histologic type of breast carcinoma. There is an inverse relationship between Ki67 and ERs. Ki67 staining can only be performed on frozen sections. MIB-1 is a Mab to a different epitope of the same proliferation-related protein as Ki67. It has become a more popular choice since it can be used on formalin-fixed, paraffin embedded tissue, and because several studies have suggested that it may have greater predictive value than Ki67.</p>
<p>S-phase fraction (SPF): SPF is a calculation of proliferation rate obtained by DNA analysis through flow cytometry or image analysis. Flow cytometry is the faster method and is therefore employed more often. SPF has been shown to be useful in both node-negative and node-positive tumors. Combining SPF, lymph node status, and other prognostic studies can be a helpful means of prognostication</p>	<p>In patients with node-positive breast cancer, there are statistically significant differences in rates of relapse-free survival in patients whose tumors were aneuploid vs those that were diploid. In node-negative breast cancer, combining SPF with tumor grade or size provides additive prognostic information. Despite these useful correlations, standardization of laboratory methods, quality control, and optimal separation into different risk groups must be improved before this test can be used routinely^[15,16]</p>

<p>Category III All other factors not sufficiently studied to demonstrate their prognostic value</p>	
<p>DNA ploidy analysis: This is a measure of DNA content and is usually classified as diploid or aneuploid.</p>	<p>The degree of DNA content abnormality is reported as the DNA index which represents a ratio of the G0-G1 peaks for the tumor cells and normal reference cells. Multivariate analyses have shown that neither DNA index nor ploidy is an independent prognostic indicator, and there is no correlation with clinical outcome^[15,16]</p>
<p>Bcl-2: High bcl-2 expression is associated with an indolent type of breast cancer and with ER+, PR+, low proliferative fraction, lower lymph node</p>	<p>Though this molecule regulates programmed cell death (apoptosis), it is not associated with apoptosis status in the primary tumor. Bcl-2 has also been</p>

metastases, and better survival.

suggested as a potential marker for therapeutic response to hormonal and cytotoxic therapy.^[15,16]

Table I-D summarizes the NCI American Joint Committee on Cancer (AJCC) staging system. Therapeutic decisions are formulated in part according to staging categories but primarily according to tumor size, lymph node status, estrogen-receptor and progesterone-receptor levels in the tumor tissue, menopausal status, and the general health of the patient.

For more information on breast cancer staging, go to:

<http://www.cancer.gov/cancertopics/pdq/treatment/breast/HealthProfessional/page3>.

Table I-D. AJCC Staging System

Stage	Description	AJCC Stage Groupings
Stage 0 (carcinoma in situ)	There are 2 types of breast carcinoma in situ: <ul style="list-style-type: none"> • Ductal carcinoma in situ • Lobular carcinoma in situ 	Tis, N0, M0
Stage 1	The tumor is 2 cm or smaller and has not spread outside the breast.	T1*, N0, M0
Stage IIA	<ul style="list-style-type: none"> • No tumor is found in the breast, but cancer is found in the axillary lymph nodes (the lymph nodes under the arm); or • The tumor is 2 cm or smaller and has spread to the axillary lymph nodes; • The tumor is larger than 2 cm but not larger than 5 cm and has not spread to the axillary lymph nodes. 	T0, N1, M0 T1*, N1, M0 T2, N0, M0
Stage IIB	The tumor is either: <ul style="list-style-type: none"> • Larger than 2 cm but not larger than 5 cm and has spread to the axillary lymph • Larger than 5 cm but has not spread to the axillary lymph nodes. 	T2, N1, M0 T3, N0, M0
Stage IIIA	<ul style="list-style-type: none"> • No tumor is found in the breast, but cancer is found in axillary lymph nodes that are attached to each other or to other structures; or • The tumor is 5 cm or smaller and has spread to axillary lymph nodes that are attached to each other or to other structures; or • The tumor is larger than 5 cm and has spread to axillary lymph nodes that may be attached to each other or to other structures. 	T0, N2, M0 T1*, N2, M0 T2, N2, M0 T3, N1, M0 T3, N2, M0

Stage IIIB	<p>The cancer may be any size and:</p> <ul style="list-style-type: none"> • Has spread to tissues near the breast (the skin or chest wall, including the ribs and muscles in the chest); and • May have spread to lymph nodes within the breast or under the arm. 	<p>T4, N0, M0</p> <p>T4, N1, M0</p> <p>T4, N2, M0</p>
Stage IIIC	<ul style="list-style-type: none"> • Has spread to lymph nodes beneath the collarbone and near the neck; and • May have spread to lymph nodes within the breast or under the arm and to tissues near the breast. <p>Stage IIIC breast cancer is divided into operable and inoperable stage IIIC. In operable stage IIIC, the cancer:</p> <ul style="list-style-type: none"> • Is found in 10 or more of the lymph nodes under the arm; or Is found in the lymph nodes beneath the collarbone and near the neck on the same side of the body as the breast with cancer; or • Is found in lymph nodes within the breast itself and in lymph nodes under the arm. <p>In inoperable stage IIIC breast cancer, the cancer has spread to the lymph nodes above the collarbone and near the neck on the same side of the body as the breast with cancer.</p>	<p>Any T, N3, M0</p>
Stage IV	<p>The cancer has spread to other organs of the body, most often the bones, lungs, liver, or brain.</p>	<p>Any T, Any N, M1</p>

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Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no associated invasion of normal breast tissue

T1: Tumor ≤ 2 cm in greatest dimension

t2: tumor > 2 cm but ≤ 5 cm in greatest dimension

t3: tumor > 5 cm in greatest dimension

T4: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed (e.g., previously removed)

N0: No regional lymph node metastasis

N1: Metastasis to movable ipsilateral axillary lymph node(s)

N2: Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident lymph node metastasis

N3: Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or, metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

Distant metastasis (M)

MX: Presence of distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis References

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