BREAST

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Breast

- Modified sweat gland
- The major function is the nutritional support of the infant.
- Social determinants flow from this fact.
- Normal anatomy:
- Two major structures
- Ducts and lobules
- Two types of epithelial cells
- Luminal and myoepithelial
- Two types of stroma
- Interlobular and intralobular

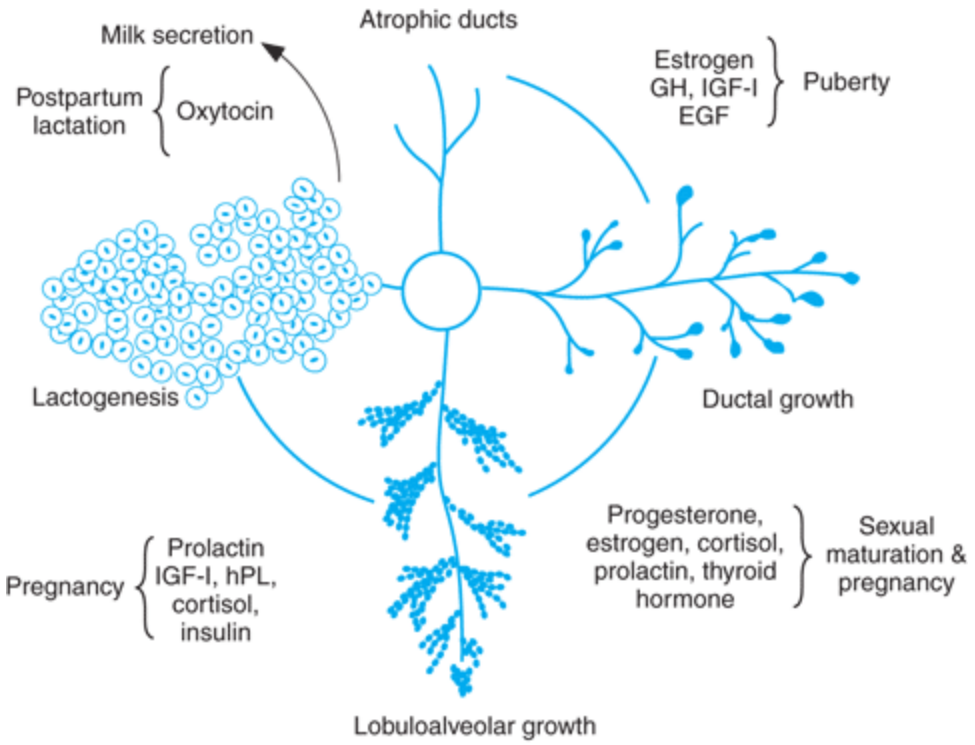
Breast

- Six to 10 major duct orifices open onto the skin surface at the nipple.
- The superficial portions are lined by keratinizing squamous cells that abruptly change to the double-layered epithelium, comprised of luminal and myoepithelial cells, of the remainder of the duct/lobular system.
- Successive branching of the large ducts eventually leads to the terminal duct lobular unit.
- In adult women, the terminal duct branches into a grapelike cluster of small acini to form a lobule

Breast

- Mammary glands develop under the influence of estrogen.
- Apart from gonadotropin secretion, IGF-1 needed for epithelial proliferation.
- Lactiferous duct branching occurs under the influence of placental lactogen
- As does differentiation of surrounding mesenchyme into fat and connective tissue.

Breast development



Source: Molina PE: *Endocrine Physiology*, 2nd Edition:
http://www.accessmedicine.com

Fig. 9-12 Accessed 05/01/2010

Breast

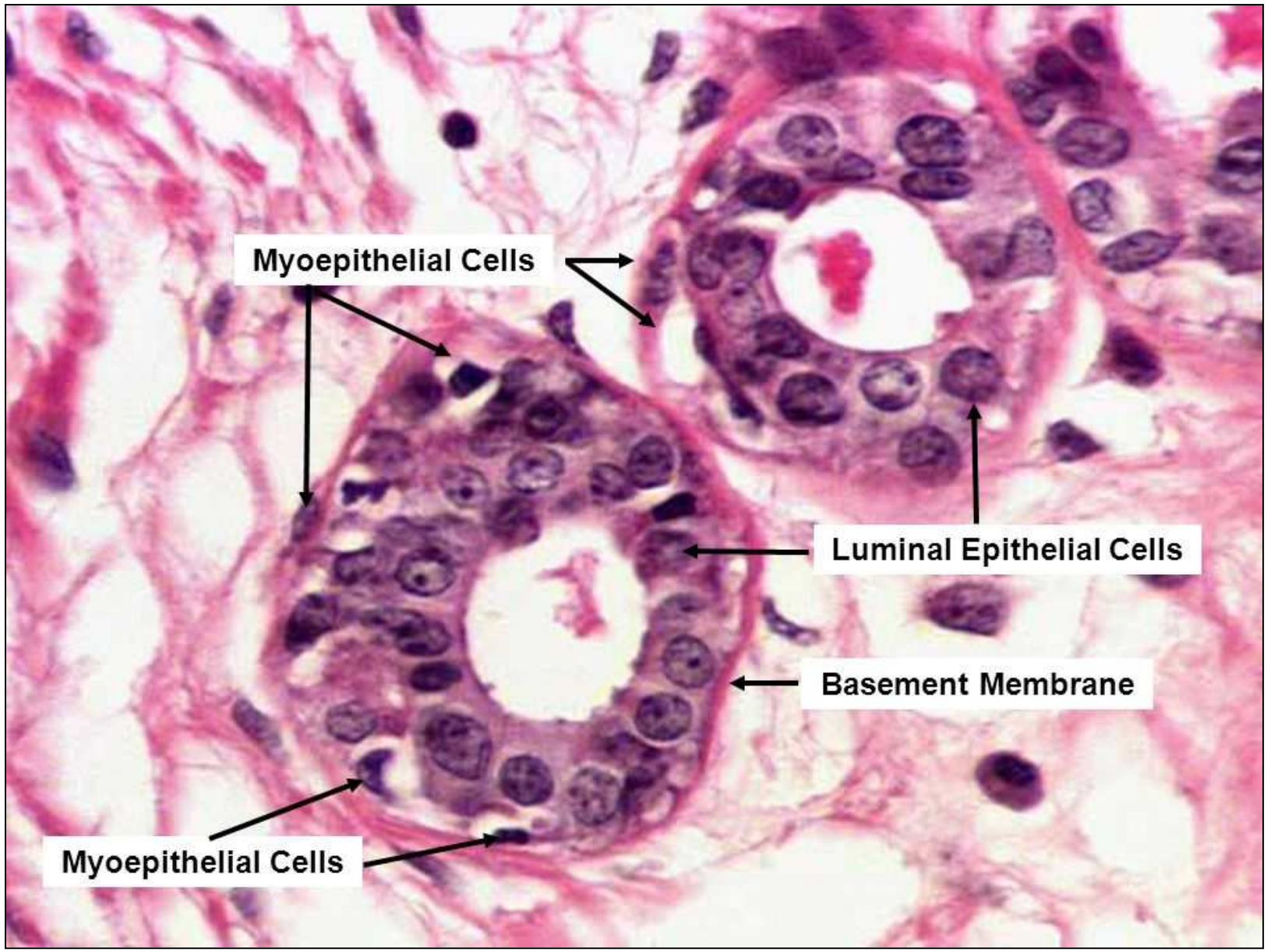
- In the pre-pubertal female breast and in the male breast, the large duct system ends in terminal ducts.
- In the first half of the menstrual cycle the lobules are relatively quiescent.

Breast

- After ovulation
- Under the influence of estrogen and rising progesterone levels
- Cell proliferation increases
- The number of acini per lobule increases.
- The intralobular stroma becomes markedly edematous.
- Upon menstruation
- Hormone levels fall
- The lobules regress and the edema disappears.

Breast

- The ducts and the acini are lined by two layers of epithelium:
- Luminal cell layer
- Single inner cell layer of cells with larger open nuclei, small nucleoli, and more abundant cytoplasm lining the ducts and acini
- Responsible for milk production.
- Myoepithelial cell layer
- Outer cell layer of dark, compact nuclei and scant cytoplasm lining ducts and acini
- Contractile function propels milk towards the nipple.


Myoepithelial Cells
Luminal Epithelial Cells
Basement Membrane
Myoepithelial Cells

Breast

- Lobules increase progressively in number and size in pregnancy.
- Driven by estrogen and progesterone produced by the corpus luteum (early first trimester), fetus, and placenta (later in pregnancy)
- By the end of the pregnancy the breast is composed almost entirely of lobules separated by relatively scant stroma.
- After parturition, the lobules produce colostrum (which is high in protein).
- The lobules switch to the production of milk (which is higher in fat and calories) over the next 10 days as progesterone levels drop.

Breast

- Upon the cessation of lactation, epithelial cells undergo apoptosis and lobules regress.
- Full regression does not occur
- Pregnancy causes a permanent increase in the size and number of lobules.
- After the third decade, long before menopause, lobules and their specialized stroma start to involute.
- The interlobular stroma is no longer radiodense.

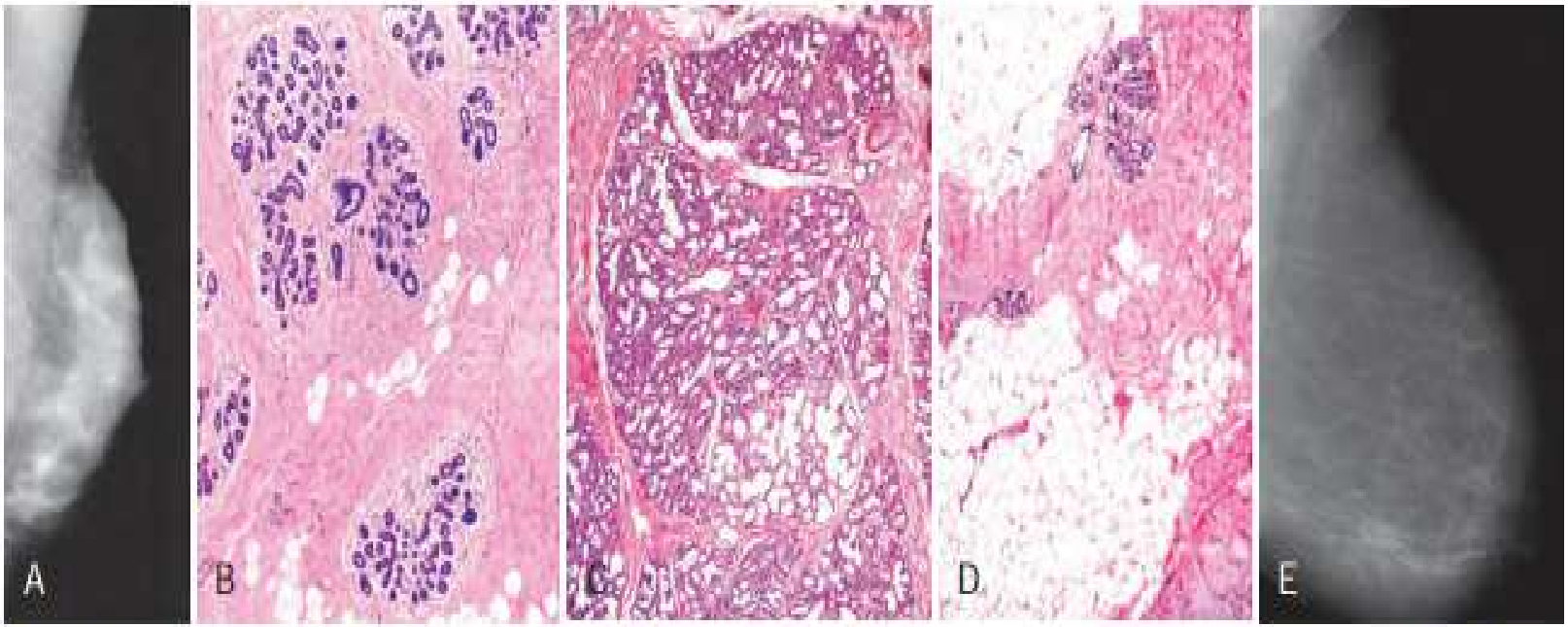


Figure 23-2 Life cycle changes. **A,** Mammograms in young women are typically radiodense or white in appearance, making mass-forming lesions or calcifications (which are also radiodense) difficult to detect. **B,** The density of a young woman's breast stems from the predominance of fibrous interlobular stroma and the paucity of adipose tissue. Before pregnancy the lobules are small and are invested by loose cellular intralobular stroma. **C,** During pregnancy, branching of terminal ducts produces more numerous, larger lobules. Luminal cells within lobules undergo lactational change, a precursor to milk formation. **D,** With increasing age the lobules decrease in size and number, and the interlobular stroma is replaced by adipose tissue. **E,** Mammograms become more radiolucent with age as a result of the increase in adipose tissue, which facilitates the detection of radiodense mass-forming lesions and calcifications. (**A, E,** Courtesy of Dr. Darrell Smith, Brigham and Women's Hospital, Boston, MA.)

Breast variants

- The failure of the nipple to evert during development is common and may be unilateral.
- Congenitally inverted nipples are usually of little significance since they correct spontaneously during pregnancy, or can sometimes be everted by simple traction.
- Only 25% of nipples have a terminal duct lobular unit.
- It is located at the base of the nipple and not within nipple.

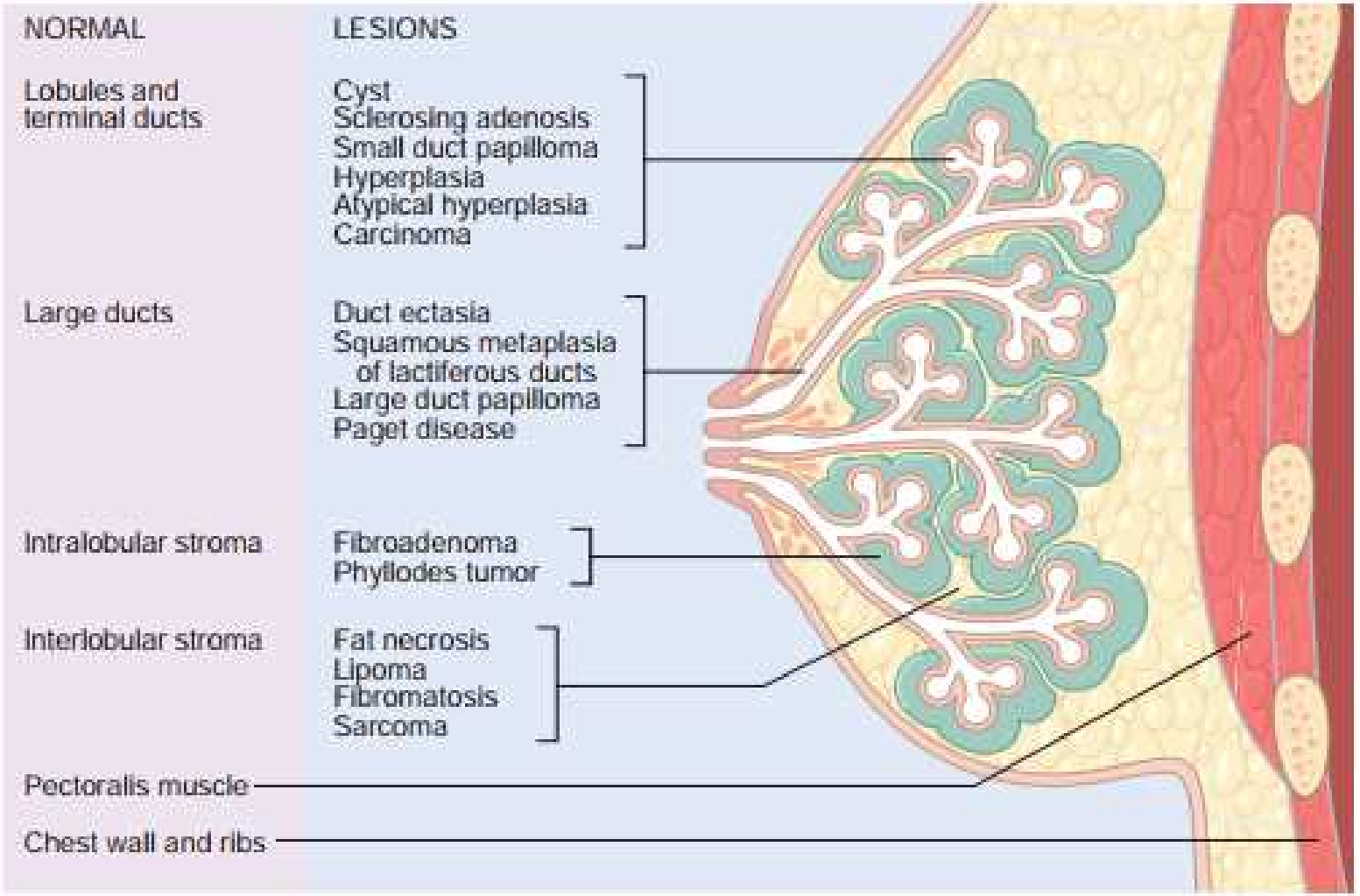


Figure 23-1 Anatomic origins of common breast lesions.

Heterotopic breast tissue

- In some women the normal ductal system extends into the subcutaneous tissue of the chest wall or the axillary fossa (the “axillary tail of Spence”)
- The milk line extends from the axilla to the perineum.
- Supernumerary nipples or breasts result from the persistence of epidermal thickenings along the milk line
- The disorders that affect the normally situated breast rarely arise in these heterotopic, hormone-responsive foci.
- Come to attention as a result of painful premenstrual enlargements.

Squamous metaplasia of lactiferous ducts

- Also known as recurrent subareolar abscess, periductal mastitis, and Zuska disease.
- Present with a painful erythematous subareolar mass that clinically appears to be a bacterial abscess.
- In recurrent cases, a characteristic fistula tract often tunnels under the smooth muscle of the nipple and opens onto the skin at the edge of the areola.
- Women may have an inverted nipple.
- 90% of those afflicted are smokers.

Squamous metaplasia of lactiferous ducts

- The key feature is keratinizing squamous metaplasia of the nipple ducts
- Keratin shed from these cells plugs the ductal system, causing dilation and eventually rupture of the duct.
- An intense chronic granulomatous inflammatory response develops once keratin spills into the surrounding periductal tissue.
- Secondary infection may follow.

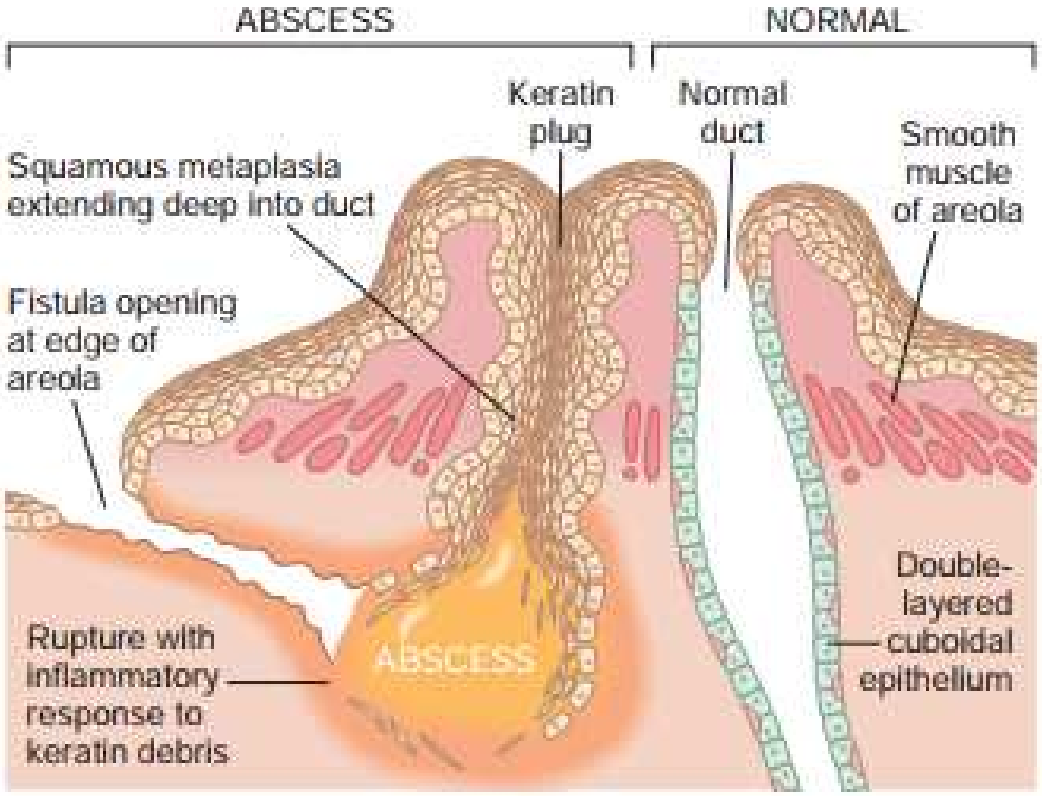


Figure 23-4 Squamous metaplasia of lactiferous ducts. When squamous metaplasia extends deep into a nipple duct, keratin becomes trapped and accumulates. If the duct ruptures, the ensuing intense inflammatory response to keratin results in an erythematous painful mass. A fistula tract may burrow beneath the smooth muscle of the nipple to open at the edge of the areola.

Duct ectasia

- Presents as a palpable periareolar mass
- Often associated with thick, white nipple secretions
- Occasionally, skin retraction.
- Pain and erythema are uncommon.
- 40-50 years of age
- Usually in multiparous women
- Not associated with cigarette smoking.

Duct ectasia

- Ectatic dilated ducts are filled with inspissated secretions and numerous lipid-laden macrophages.
- When ruptured, a marked periductal and interstitial chronic inflammatory reaction ensues.
- Lymphocytes, macrophages, and plasma cells comprise the inflammatory infiltrate.
- Granulomas may form around cholesterol deposits and secretions.
- Subsequent fibrosis produces an irregular mass with skin and nipple retraction.
- May mimic carcinoma clinically.

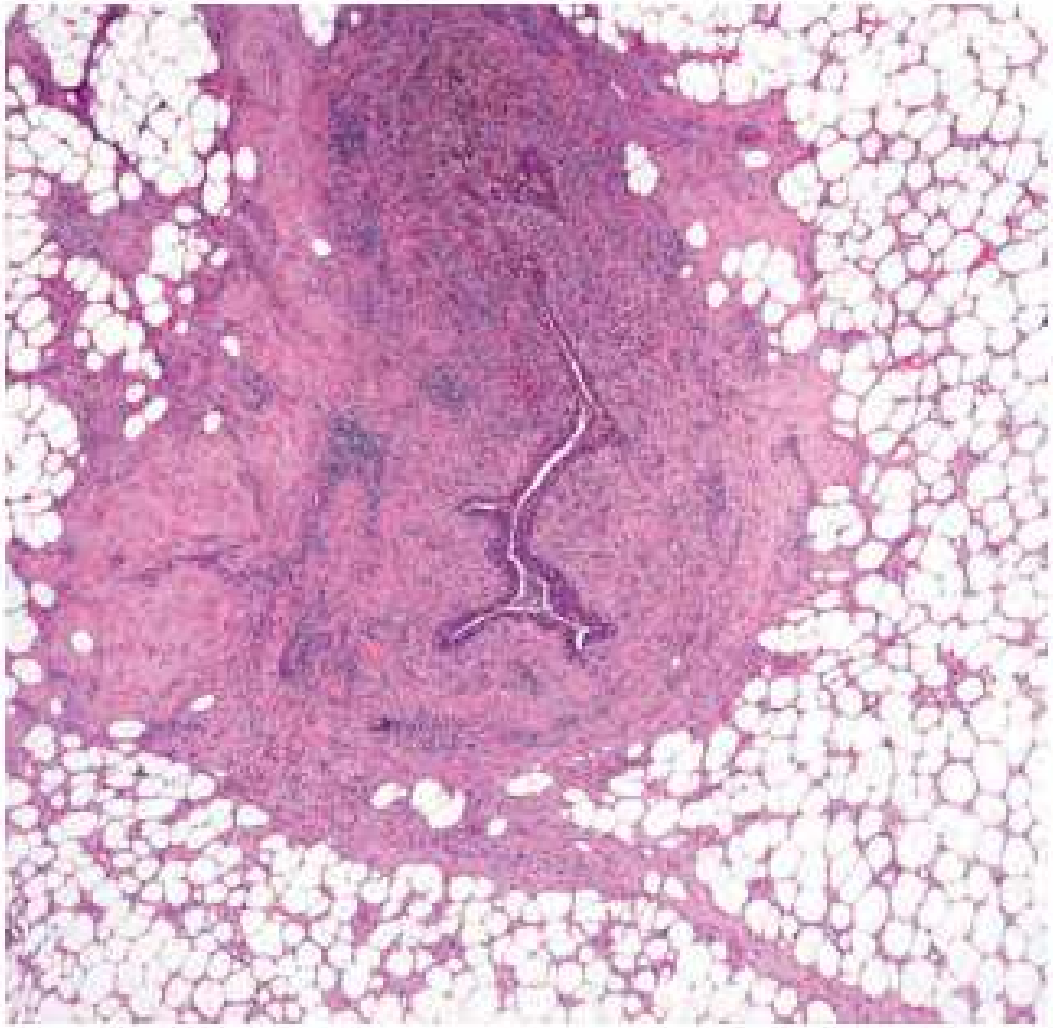


Figure 23-5 Duct ectasia. Chronic inflammation and fibrosis surround an ectatic duct filled with inspissated debris. The fibrotic response can produce a firm irregular mass that mimics invasive carcinoma on palpation or mammogram.

Fat necrosis

- Acute lesions may be hemorrhagic and contain central areas of liquefactive fat necrosis with neutrophils and macrophages.
- Over the next few days proliferating fibroblasts and chronic inflammatory cells surround the injured area.
- Subsequently,giant cells, calcifications, and hemosiderin make their appearance
- Eventually the focus is replaced by scar tissue or is encircled and walled off by fibrous tissue.
- Ill-defined, firm, graywhite nodules containing small chalky-white foci are seen grossly.
- May mimic carcinoma clinically.

Uncommon disorders

- Lymphocytic mastopathy or sclerosing lymphocytic lobulitis
- Atrophic ducts and lobules have thickened basement membranes and are surrounded by a prominent lymphocytic infiltrate.
- Common in women with type 1 diabetes mellitus or autoimmune thyroid disease

Uncommon disorders

- Granulomatoous mastitis
- Uncommon disease
- Only occurs in parous women.
- The granulomas are closely associated with lobules.
- A similar histologic pattern is seen in cystic neutrophilic granulomatous mastitis caused by Corynebacteria

Gynecomastia

- Enlargement of the male breast is the only benign lesion seen with any frequency in the male breast.
- It presents as a button-like subareolar enlargement and may be unilateral or bilateral.
- Microscopically, there is an increase in dense collagenous connective tissue associated with epithelial hyperplasia of the duct lining with characteristic tapering micropapillae.
- Lobule formation is almost never observed.

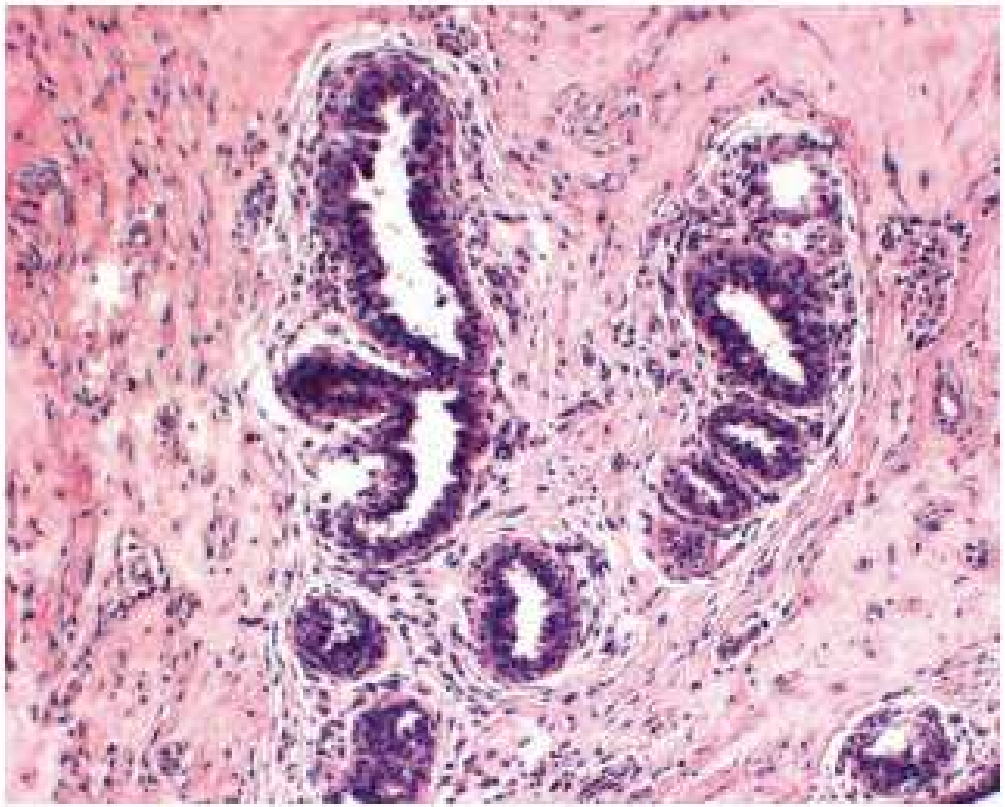


Figure 23-11 Gynecomastia. Breast enlargement in males is due to an increase in the number of ducts accompanied by loose cellular stroma. Lobule formation is absent.

Screening for breast cancer

- Screen all women beginning at age 50.
- Repeat every three years if negative.
- May cease screening at age 75.
- Screening not recommended if life expectancy is less than 10 years.
- Mammography not a good screen in pregnant woman.

Screening for breast cancer

- Begin screening earlier (as well as BRCA testing) if:
- First degree relative with breast or ovarian cancer
- Or breast cancer at young age
- Or triple negative breast cancer
- African or Korean ancestry
- MRI gives excellent detail.

Clinical presentations

- The most common symptoms reported by women with disorders of the breast are:
- Pain
- A palpable mass
- “Lumpiness” (without a discrete mass)
- Nipple discharge.

Pain

- Mastalgia or mastodynia
- Diffuse cyclic pain may be due to premenstrual edema.
- Noncyclic pain is usually localized to one area of the breast.
- Ruptured cysts, physical injury, and infections
- Often no specific lesion is identified
- About 10% of breast cancers present with pain.

Palpable masses

- “Lumpiness” is the normal nodularity of breast tissue.
- The most common palpable lesions are cysts, fibroadenomas, and invasive carcinomas.
- Benign palpable masses are most common in premenopausal women.
- Only 10% of breast masses in women younger than age 40 are malignant as compared with 60% of masses in women older than age 50.
- Approximately 50% of carcinomas are located in the upper outer quadrant, 10% in each of the remaining quadrants, and about 20% in the central or subareolar region.

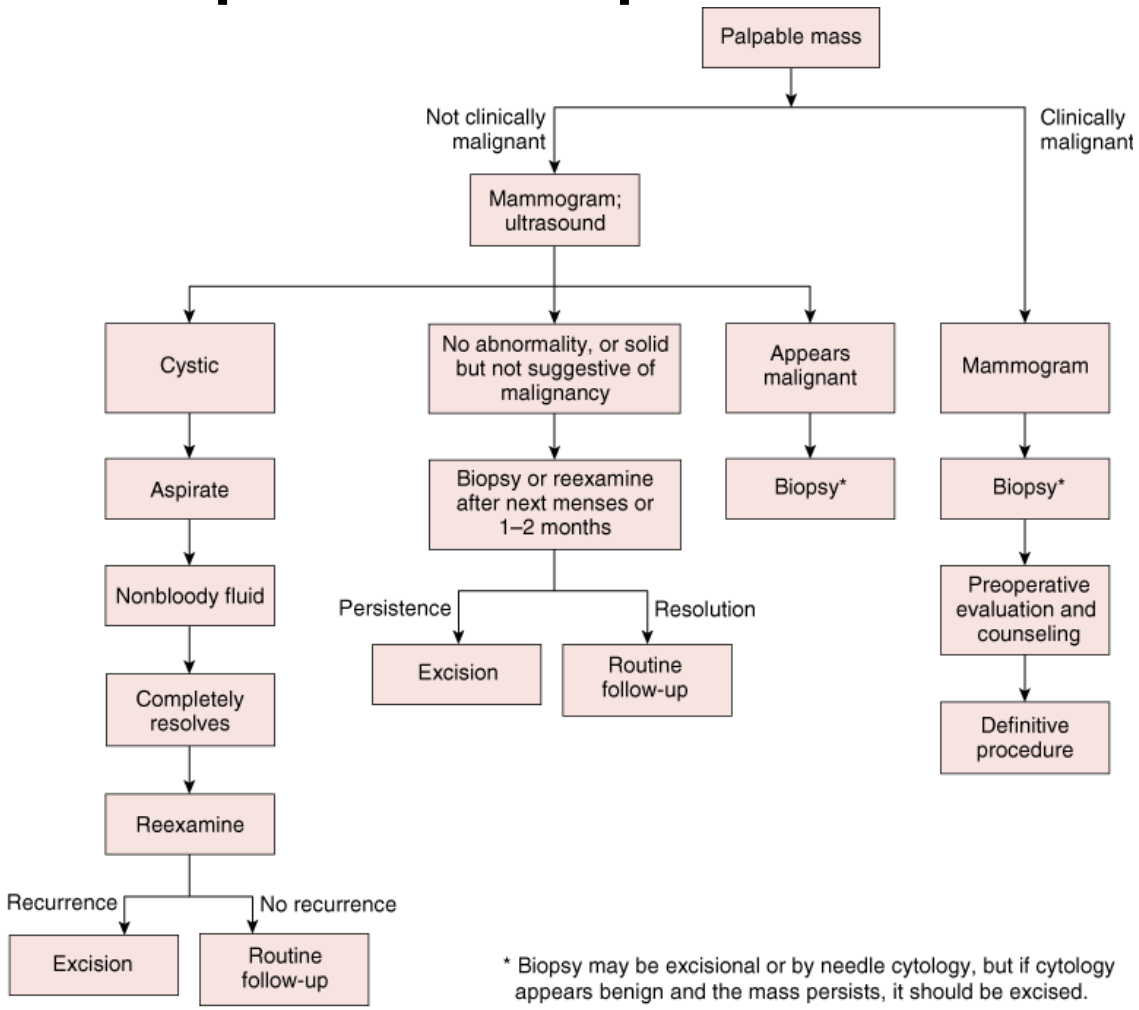
Nipple discharge

- A small discharge is often produced by the manipulation of normal breasts.
- Repeated nipple stimulation can also induce lactation.
- Milky discharges (galactorrhea) are associated with elevated prolactin levels (e.g., by a pituitary adenoma), hypothyroidism,or endocrine anovulatory syndromes
- Also occur in patients taking oral contraceptives, tricyclic antidepressants, methyldopa, or phenothiazines.
- Galactorrhea is not associated with malignancy.

Nipple discharge

- Bloody or serous discharges are most commonly due to large duct papillomas and cysts.
- During pregnancy, a bloody discharge can result from the rapid growth and remodeling of the breast.
- Nipple discharge is associated with carcinoma in 7% of women younger than age 60 but in 30% of older women.
- Of concern when is spontaneous and unilateral.

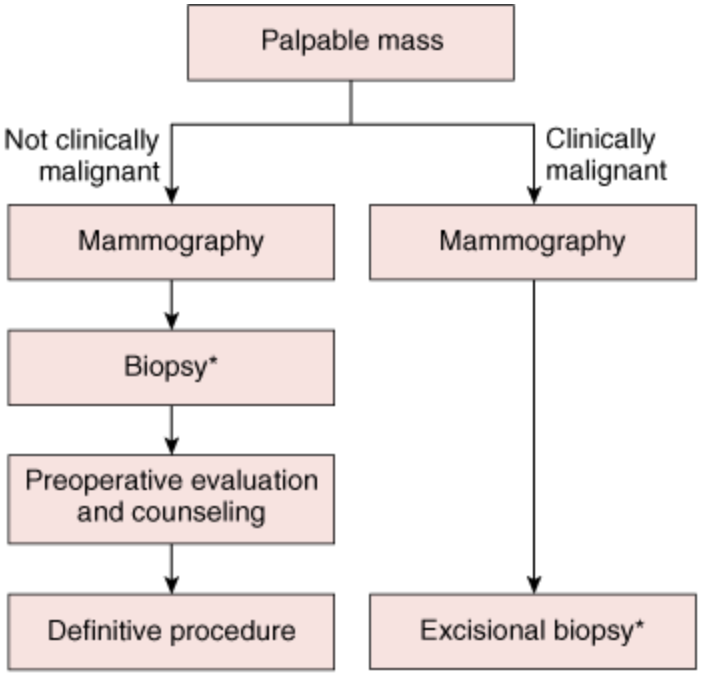
Evaluation of breast masses in premenopausal women



(Adapted, with permission, from Giuliano AE: Breast disease. In: *Practical Gynecologic Oncology,* 3rd ed. Berek JS, Hacker NF [editors], Lippincott Williams & Wilkins, 2000.)

Fig. 17-4 Accessed 08/01/2010

Evaluation of breast masses in postmenopausal women



* Biopsy may be excisional or by needle cytology, but if cytology appears benign and the mass persists, it should be excised.

(Adapted, with permission, from Giuliano AE: Breast disease. In: *Practical Gynecologic Oncology,* 3rd ed. Berek JS, Hacker NF [editors], Lippincott Williams & Wilkins, 2000.)

Fig. 17-5 Accessed 08/01/2010

Mammography

- Breast cancer prevalence is low before the age of 50.
- Its utility increases with the age of the population (fewer false positives).
- The principal mammographic signs of breast carcinoma are densities and calcifications.
- Rounded densities are most commonly benign lesions such as fibroadenomas or cysts.
- Invasive carcinomas generally form irregular masses

Mammography

- Calcifications are often associated with benign lesions such as clusters of apocrine cysts, hyalinized fibroadenomas, and sclerosing adenosis.
- Calcifications associated with malignancy are usually small, irregular, numerous, and clustered.
- Ductal carcinoma in situ is often discovered because of calcifications noted on mammogram.
- Ultrasonography distinguishes between solid and cystic lesions and defines more precisely the borders of solid lesions and may demonstrate increased tumor vascularity and blood flow.

Inflammatory disease

- The breast is erythematous and painful.
- Fever is often present.
- Caused by infections, autoimmune disease, or foreign body reaction to extravasated keratin or secretions.
- Acute mastitis generally occurs during first month of breast feeding.
- Superficial fissures in the nipples as portal of entry.
- Staph. aureus or Strep. as usual organisms
- At the outset only one duct system or sector of the breast is involved.
- Oral probiotics beneficial.

Nonproliferative Breast Changes (Fibrocystic Changes)

- There are three principal morphologic changes:
- (1) Cysts. Small cysts form by the dilation of lobules and in turn may coalesce to form larger cysts.
- Unopened cysts contain turbid, semi-translucent fluid of a brown or blue color (blue dome cysts)
- Cysts are lined either by a flattened atrophic epithelium or by metaplastic apocrine cells.
- Apocrine cells have abundant granular, eosinophilic cytoplasm and round nuclei
- Calcifications are common.

Nonproliferative Breast Changes (Fibrocystic Changes)

- More common in Europeans than in Asians or Native Americans
- Common in those with polycystic ovary disease
- Usually involves the upper outer quadrant of breast.
- May be bilateral.
- More tender at menstruation.
- Cyst size may vary with cycle.
- Histologically there is proliferation and cystic dilatation of ducts (duct restriction or obstruction) admixed with proliferation of breast lobules.

Nonproliferative Breast Changes (Fibrocystic Changes)

- 50% in women 25-45 years old
- Noted in older women on estrogen replacement therapy as well in the obese
- Exaggerated response to estrogen stimulation
- Mapping the cyst on the breast surface and measuring its fluctuation during the menstrual cycle confirms its benign nature.
- Needle aspiration of the cyst fluid is for cytologic examination as well as to collapse the cyst.

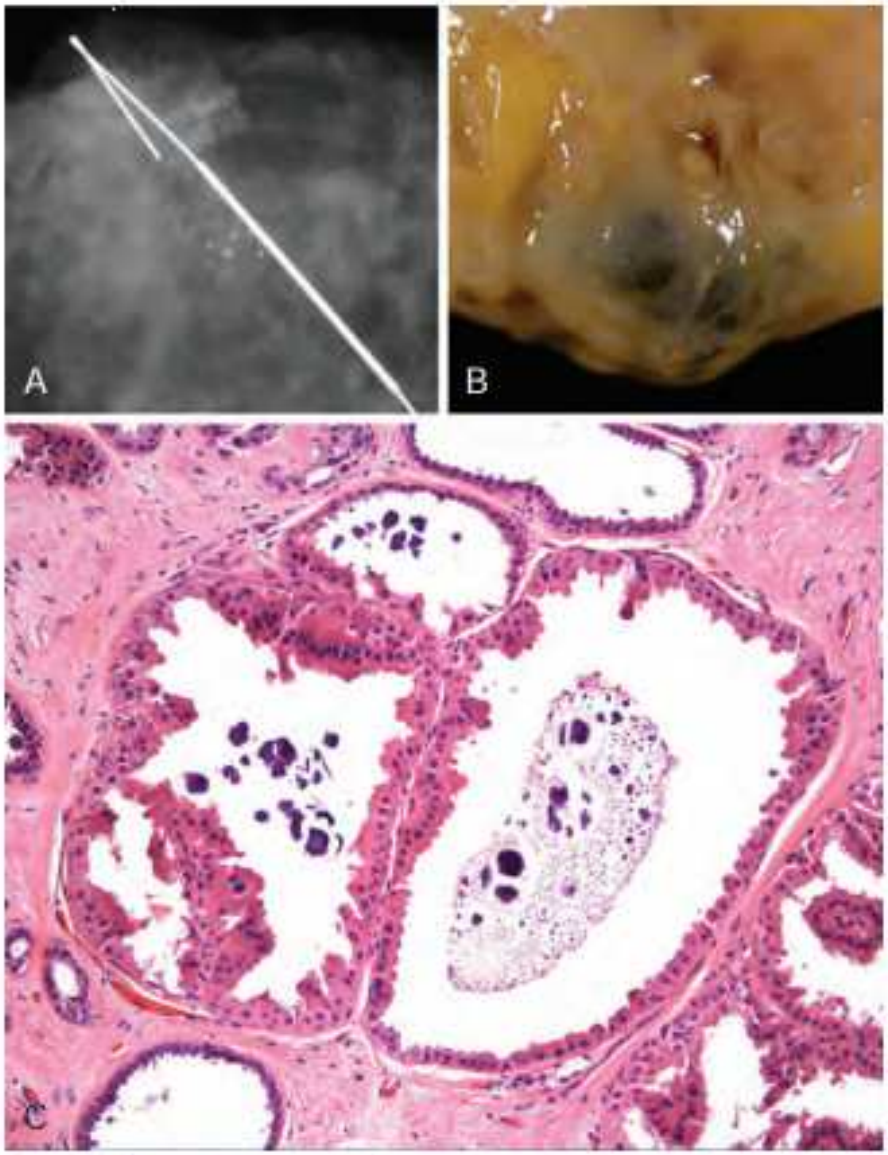


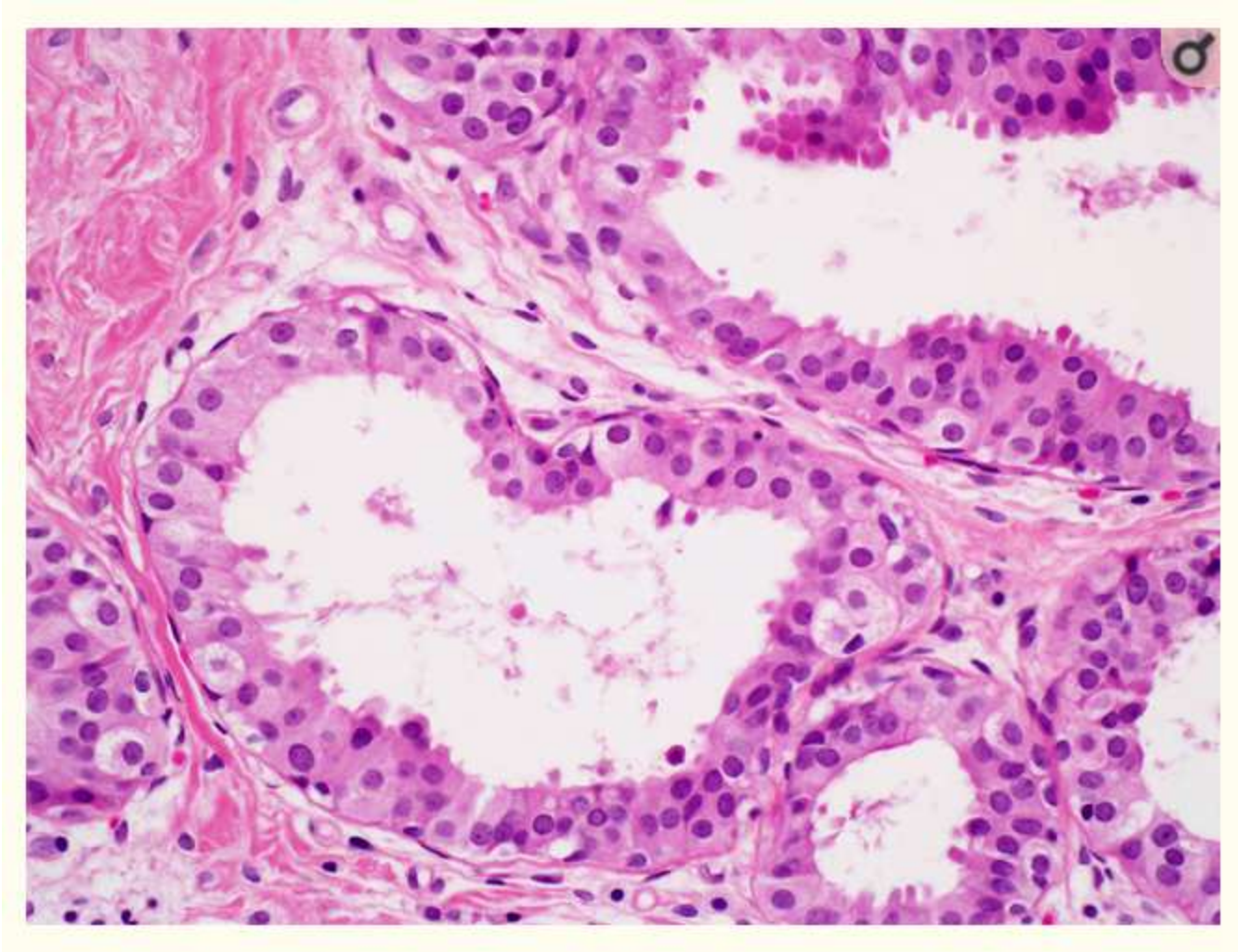
Figure 23-6 Apocrine cysts. **A,** Clustered, rounded calcifications are seen in a specimen radiograph. **B,** Gross appearance of typical cysts filled with dark, turbid fluid contents. **C,** Cysts are lined by apocrine cells with round nuclei and abundant granular cytoplasm. Note the luminal calcifications, which form on secretory debris.

Nonproliferative Breast Changes (Fibrocystic Changes)

- (2) Fibrosis. Cysts frequently rupture, releasing secretory material into the adjacent stroma.
- The resulting chronic inflammation and fibrosis contribute to the palpable nodularity of the breast.
- (3) Adenosis. There is an increase in the number of acini per lobule.
- It is a normal feature of pregnancy.
- In non-pregnant women, adenosis can occur as a focal change.
- Calcifications are occasionally present within the lumens.

Adenosis

- The acini are lined by monotypic columnar cells, which may appear benign or show nuclear atypia ("flat epithelial atypia") without architectural change.
- Flat epithelial atypia is a clonal proliferation associated with LOH 16q.
- This lesion is thought to be the earliest recognizable precursor of low-grade breast cancers



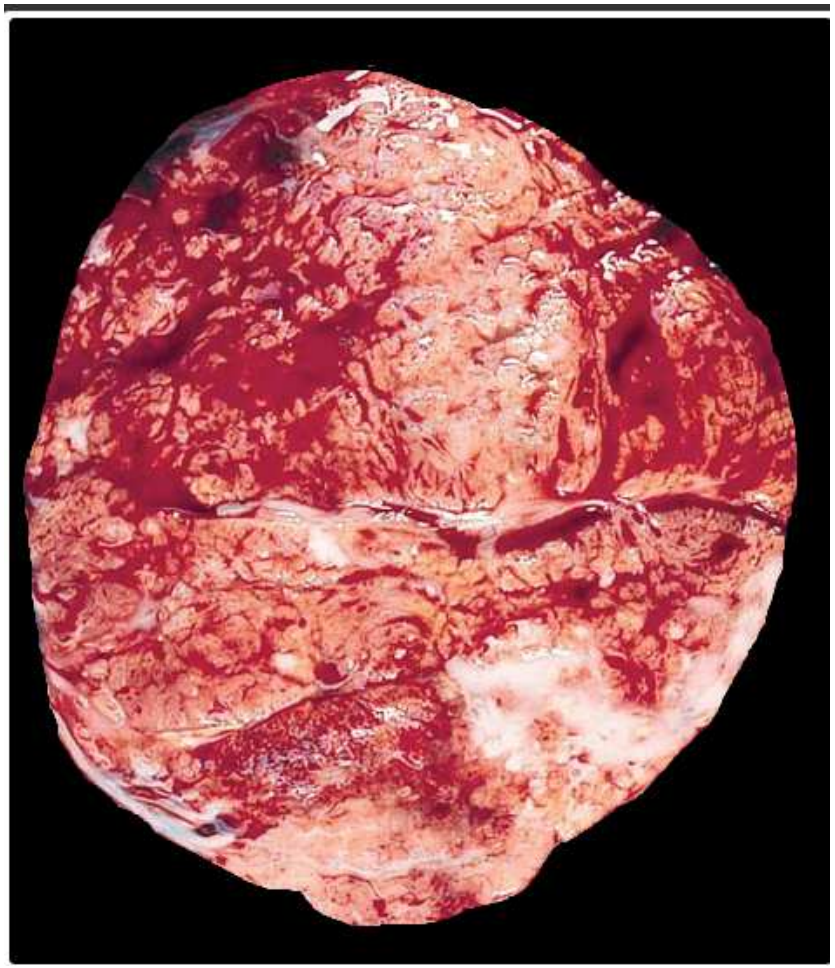
Flat epithelial atypia H&E x400

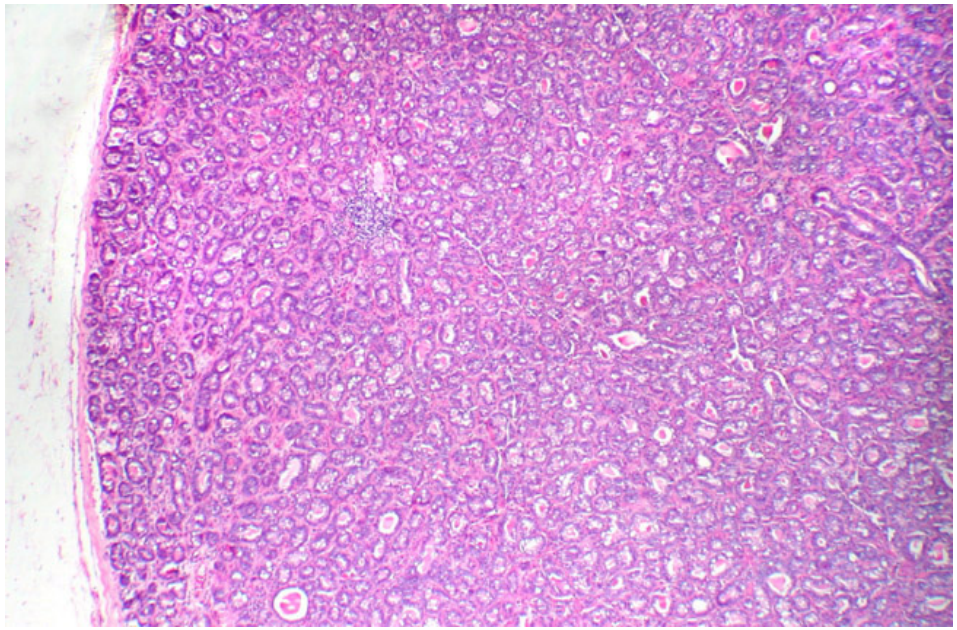
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4424157/
Accessed 06/10/2020

Adenosis

- Lactational adenomas
- Most prevalent mass in a pregnant or lactating woman.
- They resemble a tubular adenoma but with lactational changes.
- An exaggerated local response to gestational hormones.

Lactating adenoma





Left: Discrete fleshy mass.
Right: orderly arrangement of glands.

https://www.pathologyoutlines.com/topic/breastlactatingadenoma.html
Contributed by Dr. Mark Wick

http://breast.pathology-digitalatlases.org/XXIII-25.htm
Accessed 02/20/2020

Proliferative breast disease (without atypia)

- Epithelial Hyperplasia.
- Increased numbers of both luminal and myoepithelial cell types fill and distend ducts and lobules.
- Irregular lumens can often be discerned at the periphery of the cellular masses
- Epithelial hyperplasia is usually an incidental finding.

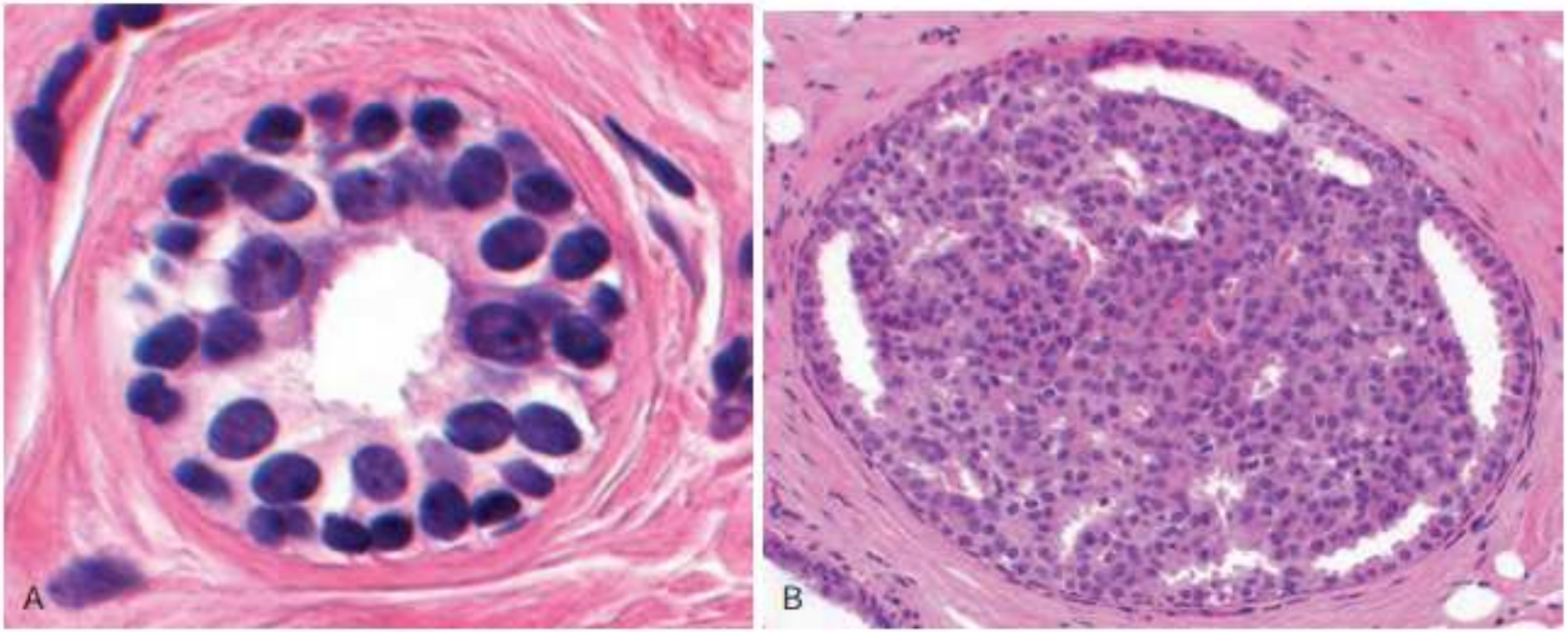


Figure 23-7 **A,** A normal duct or acinus with a single basally located myoepithelial cell layer (cells with dark, compact nuclei and scant cytoplasm) and a single luminal cell layer (cells with larger open nuclei, small nucleoli, and more abundant cytoplasm). **B,** Epithelial hyperplasia. The lumen is filled by a heterogeneous, mixed population of luminal and myoepithelial cell types. Irregular slitlike fenestrations are prominent at the periphery.

Proliferative breast disease (without atypia)

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Sclerosing adenosis

- There are enlarged and distorted lobules, containing duplicated and crowded acini, with prominent myoepithelium and stromal fibrosis.
- Stromal fibrosis may completely compress the lumens to create the appearance of solid cords or double strands of cells lying within dense stroma
- Closely mimics invasive carcinoma

Sclerosing adenosis

- Occurs more in those with a family history of breast cancer.
- Presence of sclerosing adenosis with other proliferative disease in the breast does not change overall risk.
- However, if alone, there is higher risk of progression to cancer.

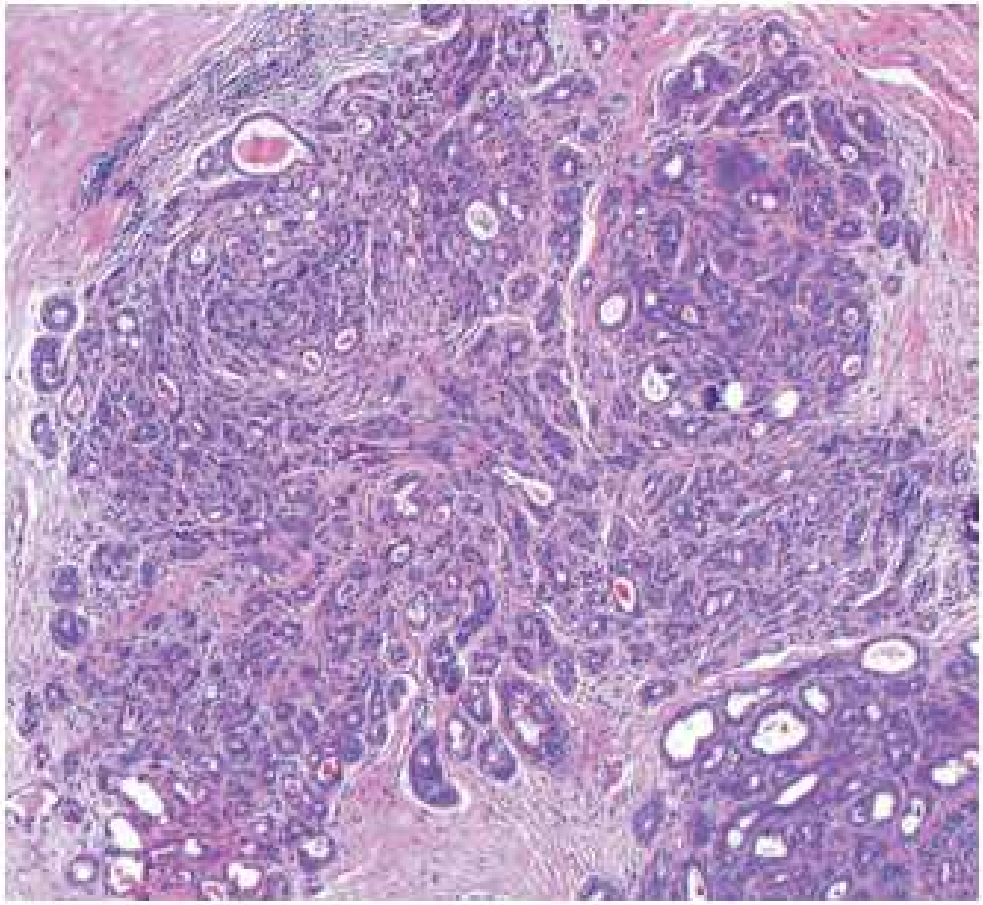


Figure 23-8 Sclerosing adenosis. The involved terminal duct lobular unit is enlarged, and the acini are compressed and distorted by dense stroma. Calcifications are present within some of the lumens. Unlike carcinomas, the acini are arranged in a swirling pattern, and the outer border is well circumscribed.

Complex sclerosing lesion

- These lesions have components of sclerosing adenosis, papillomas, and epithelial hyperplasia.
- The radial sclerosing lesion (“radial scar”), has an irregular shape and can closely mimic invasive carcinoma mammographically, grossly, and histologically
- A central nidus of entrapped glands in a hyalinized stroma is surrounded by long radiating projections into stroma.
- Not associated with prior trauma or surgery.

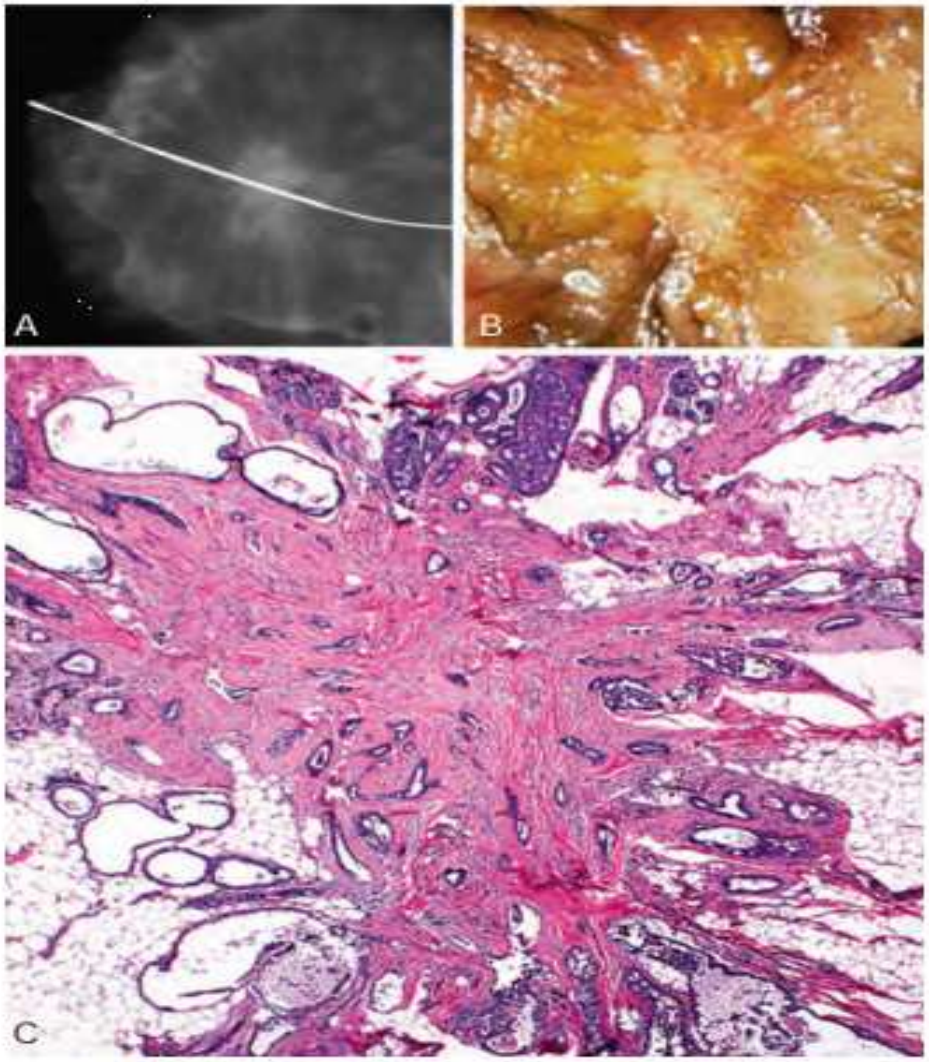


Figure 23-9 Radial sclerosing lesion. **A,** The radiograph shows an irregular central mass with long radiodense projections. **B,** Grossly the mass appears solid and has irregular borders, but it is not as firm as an invasive carcinoma. **C,** The mass consists of a central nidus of small tubules entrapped in a densely fibrotic stroma and numerous projections containing epithelium with varying degrees of cyst formation and hyperplasia.

Papillomas

- Grow within a dilated duct and are composed of multiple branching fibrovascular cores
- Epithelial hyperplasia and apocrine metaplasia are frequently present.
- Large duct papillomas are situated in the lactiferous sinuses of the nipple and are usually solitary.
- Small duct papillomas are commonly multiple and located deeper within the ductal system.
- 80% present with nipple discharge.

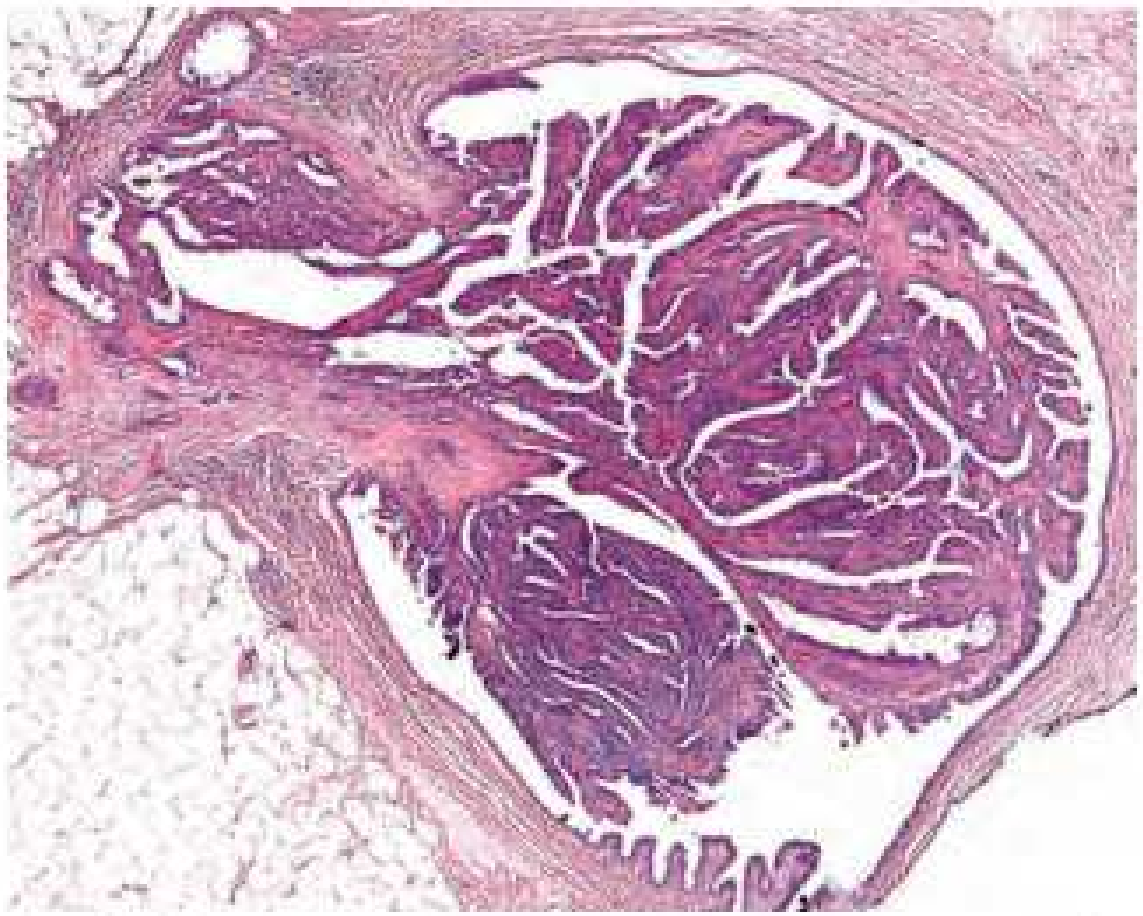


Figure 23-10 Intraductal papilloma. A central fibrovascular core extends from the wall of a duct. The papillae arborize within the lumen and are lined by myoepithelial and luminal cells.

Proliferative breast disease with atypia

- Atypical ductal hyperplasia is recognized by its histologic resemblance to ductal carcinoma in situ (DCIS).
- It consists of a relatively monomorphic proliferation of regularly spaced cells,sometimes with cribriform spaces.
- It is distinguished from DCIS in that it only partially fills involved ducts
- There is an increased risk of breast cancer; however, fewer than 20% of women will progress to cancer

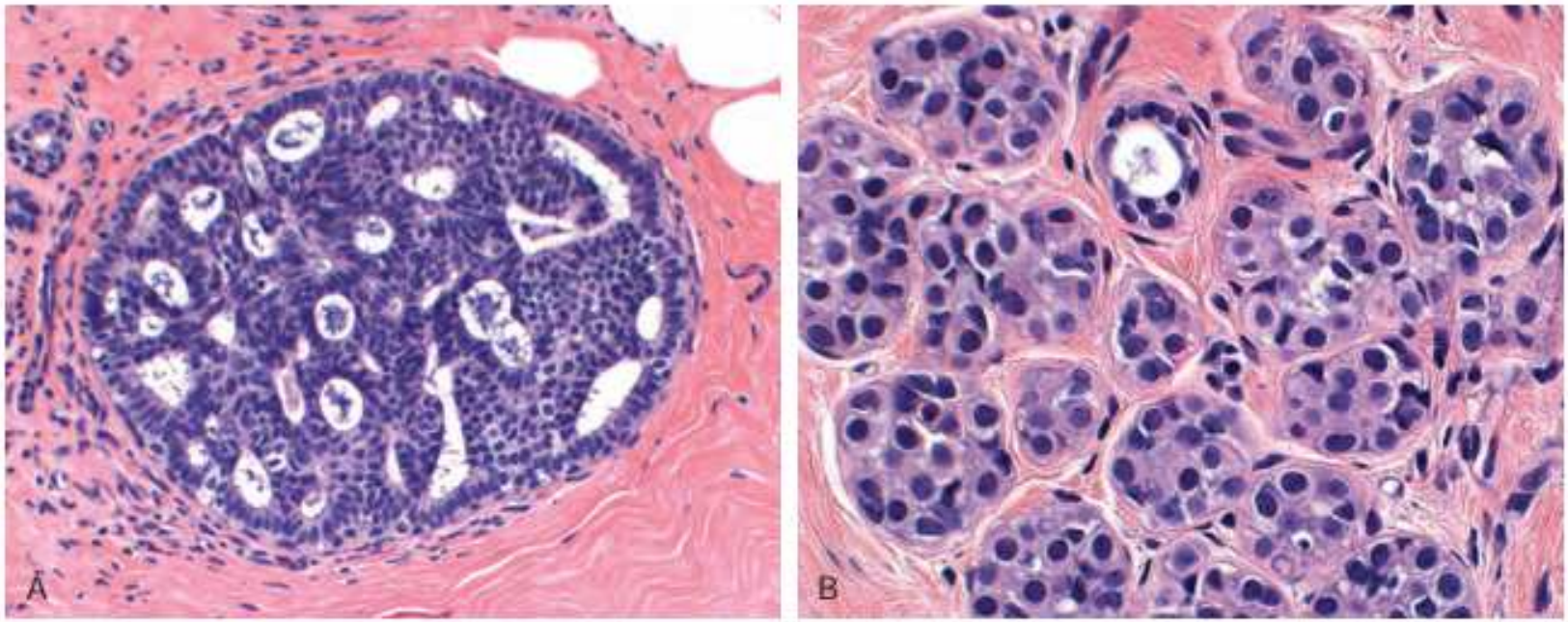


Figure 23-12 **A,** Atypical ductal hyperplasia. A duct is filled with a mixed population of cells consisting of oriented columnar cells at the periphery and more rounded cells within the central portion. Although some of the spaces are round and regular, the peripheral spaces are irregular and slitlike. These features are highly atypical, but fall short of a diagnosis of ductal carcinoma in situ. **B,** Atypical lobular hyperplasia. A population of monomorphic small, round, loosely cohesive cells partially fills a lobule. Although the cells are morphologically identical to the cells of lobular carcinoma in situ, the extent of involvement is not sufficient for this diagnosis.

Proliferative breast disease with atypia

- Atypical lobular hyperplasia consists of cells identical to those of lobular carcinoma in situ, but the cells do not fill or distend more than 50% of the acini within a lobule.
- In atypical lobular hyperplasia, atypical lobular cells may lie between the ductal basement membrane and overlying normal luminal cells.
- Cells lack E-cadherin (LOH 16q).
- FGFR1 amplification (8p11.2-12) common.

Table 23-1 Epithelial Breast Lesions and the Risk of Developing Invasive Carcinoma

Pathologic Lesion	Relative Risk (Absolute Lifetime Risk)*
Nonproliferative Breast Changes (Fibrocystic changes)	1 (3%)
Duct ectasia Cysts Apocrine change Mild hyperplasia Adenosis Fibroadenoma without complex features	
Proliferative Disease Without Atypia	1.5 to 2 (5%-7%)
Moderate or florid hyperplasia Sclerosing adenosis Papilloma Complex sclerosing lesion (radial scar) Fibroadenoma with complex features	
Proliferative Disease with Atypia	4 to 5 (13%-17%)
Atypical ductal hyperplasia (ADH) Atypical lobular hyperplasia (ALH)	
Carcinoma in Situ	8 to 10 (25%-30%)
Lobular carcinoma in situ (LCIS) Ductal carcinoma in situ (DCIS)	

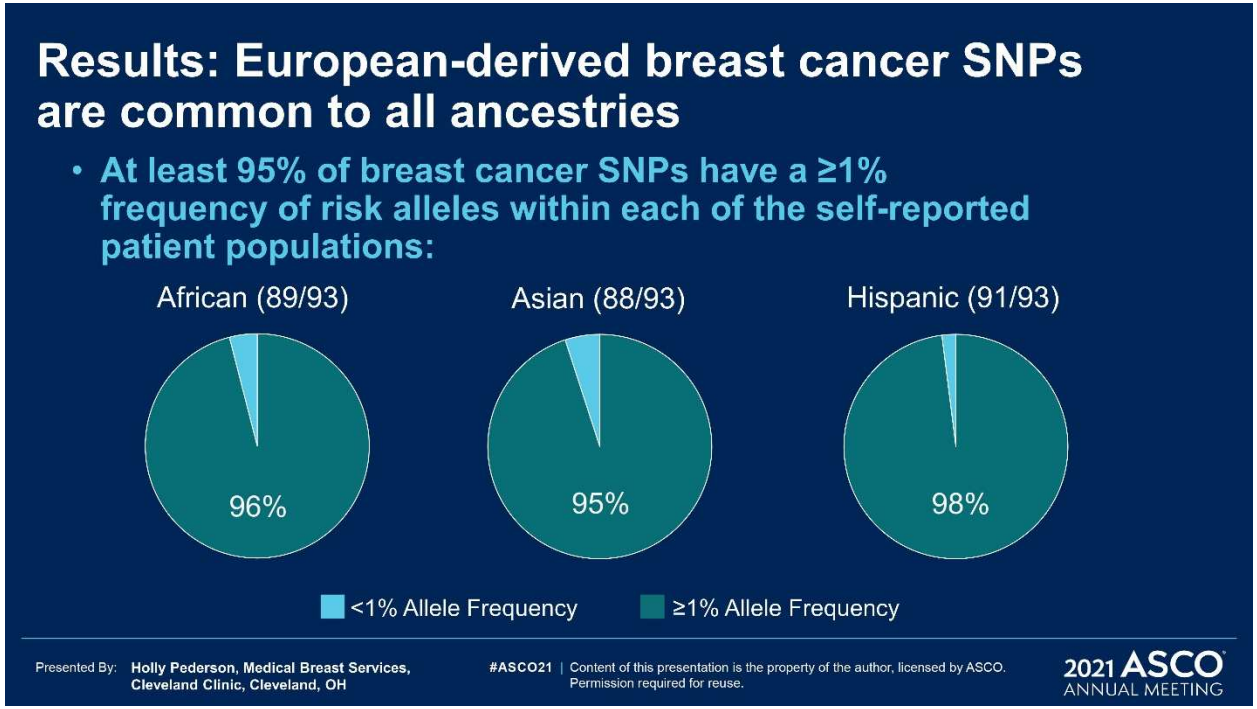
*Relative risk is the risk compared to women without any risk factors. Absolute lifetime risk is the percentage of patients expected to develop invasive carcinoma if untreated.

Breast cancer

- Second most common non-skin malignant lesion (after lung).
- Breast cancer is rare in women younger than age 25, but the incidence increases rapidly after age 30.
- ER-positive cancers continue to increase with age whereas the incidence of ER-negative cancers and HER2-positive cancers remains relatively constant.
- Ductal carcinoma in situ is rarely palpable and is usually detected on mammography.
- The incidence of carcinoma in the developed countries is 4-7 times that of lesser developed countries.

Breast cancer

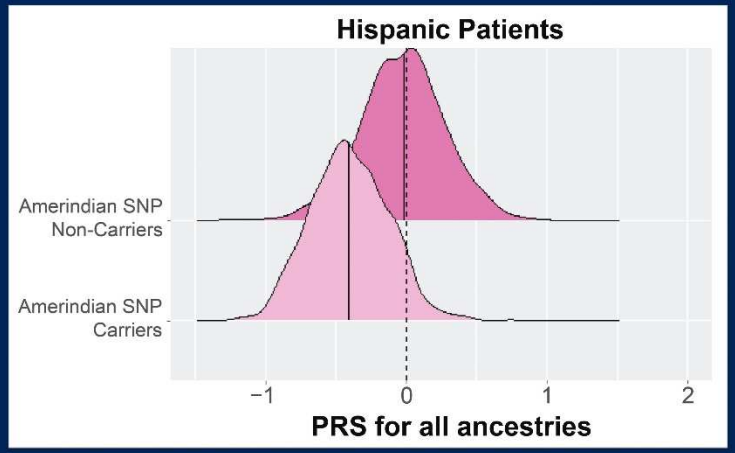
- Women of African ancestry have poorer survival
- Comparison of women with ER+, HER2- breast cancers when grouped by age, stage, BRCA1, BRCA2, CDK 4/6 abnormalities, socio-economic status, and therapy administered strongly suggests other genetic differences account for response to therapy as well as to survival
- Women of Native American ancestry have better survival



TP53 mutations found in 44.5% of Asians, 38.4% of whites, and 61.1% of blacks. The difference is significant.

Protective effect of the Amerindian SNP

Looking more closely at self-reported Hispanic patients, we see that the PRS is centered around zero for patients who do not carry the protective Amerindian SNP and shifted toward lower risk for carriers.



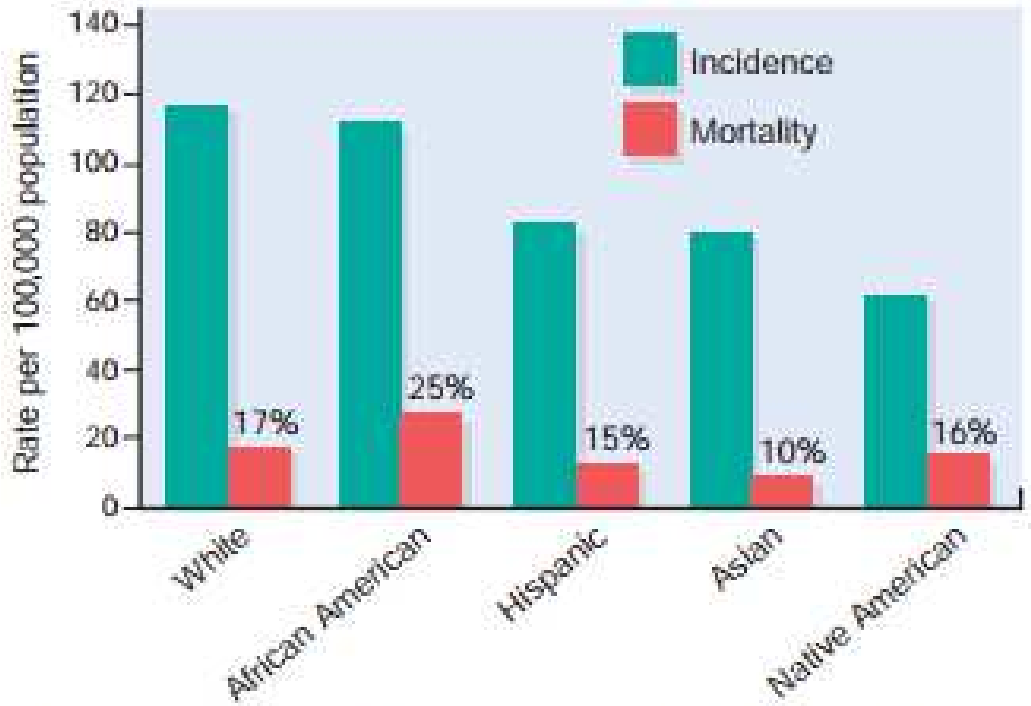
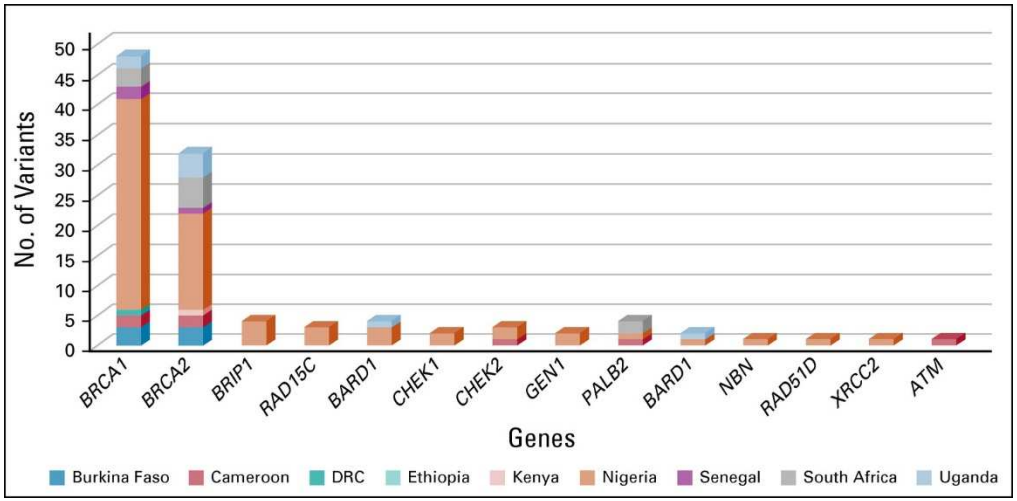


Figure 23-15 Breast cancer incidence and mortality in different ethnic groups (Data from North American Association of Central Cancer Registries). White women have the highest incidence of breast cancer, while African American women have the highest mortality rate. Likely contributors to these differences include socioeconomic factors (better access to care in white women) and biologic factors, particularly the higher incidence of aggressive, high grade, ER-negative tumors in younger African American women.



Genetic Susceptibility to Breast Cancer in Sub-Saharan African Populations
Mahtaab Hayat, Wenlong Carl Chen, Jean-Tristan Brandenburg, Chantal Babb de Villiers, Michèle Ramsay, and Christopher G. Mathew
JCO Global Oncology 2021 :7, 1462-1471

Risk factors

- Germline mutations.
- First-degree relatives with breast cancer
- Variation in the frequency of breast cancer genes across ethnic groups may explain racial and ethnic differences
- Age
- Age at menarche.
- Menarche at ages younger than 11 years increases risk by 20% compared to menarche at ages greater than 14.
- Late menopause also increases risk.

Risk factors

- Age at first live birth.
- A full-term pregnancy before the age of 20 halves the risk compared to nulliparous women or women who are older than the age of 35 at the time of their first birth.
- Menopausal estrogen exposure
- Obese women under the age of 40 have a decreased risk as a result of anovulatory cycles and lower progesterone levels.
- Postmenopausal obese women are at increased risk, which is attributed to the synthesis of estrogens in fat depots.

Risk factors

- Type 2 Diabetes Mellitus
- Metformin use associated with fewer hormone positive cancers
- Metformin reduces circulating insulin levels, reducing signaling through PI3K and RAS pathways, and directly on Complex 1 in the mitochondrion, leading to LKB1 mediation of MAPK activation with downstream inhibition of mTOR.
- Metformin use may increase risk of triple negative breast cancer

Risk factors

- Increased breast density
- Radiation exposure
- Tobacco
- Atypical hyperplasia
- The longer women breast feed, the greater the reduction in risk.
- Lactation suppresses ovulation and may trigger terminal differentiation of luminal cells.

Table 23-2 Most Common "Single Gene" Mutations Associated with Hereditary Susceptibility to Breast Cancer

Gene (Location) Syndrome (Incidence)*	% of "Single Gene" Hereditary Cancers†	Breast Cancer Risk by Age 70‡	Changes in Sporadic Breast Cancer	Other Associated Cancers	Functions	Comments
BRCA1 (17q21) Familial breast and ovarian cancer (1 in 860)	52% (~2% of all breast cancers)	40%- 90%	Mutations rare; inactivated in 50% of some subtypes (e.g., medullary and metaplastic) by methylation	Ovarian, male breast cancer (but lower than *BRCA2*), prostate, pancreas, fallopian tube	Tumor suppressor, transcriptional regulation, repair of double-stranded DNA breaks	Breast carcinomas are commonly poorly differentiated and triple negative (basal-like), and have *TP53* mutations
BRCA2 (13q12-13) Familial breast and ovarian cancer (1 in 740)	32% (~1% of all breast cancers)	30%-90%	Mutations and loss of expression rare	Ovarian, male breast cancer, prostate, pancreas, stomach, melanoma, gallbladder, bile duct, pharynx	Tumor suppressor, transcriptional regulation, repair of double-stranded DNA breaks	Biallelic germline mutations cause a rare form of Fanconi anemia
TP53 (17p13.1) Li-Fraumeni (1 in 20,000)	3% (~1% of all breast cancers)	>90%	Mutations in 20%, LOH in 30%-42%; most frequent in triple negative cancers	Sarcoma, leukemia, brain tumors, adrenocortical carcinoma, others	Tumor suppressor with critical roles in cell cycle control, DNA replication, DNA repair, and apoptosis	*TP53* is the most commonly mutated gene in sporadic breast cancers 53% ER- and HER2-positive
CHEK2 (22q12.1) (1 in 100)	5% (~1% of all breast cancers)	10%-20%	Mutations in 5%	Prostate, thyroid, kidney, colon	Cell cycle checkpoint kinase, recognition and repair of DNA damage, activates BRCA1 and p53 by phosphorylation	May increase risk for breast cancer after radiation exposure 70%-80% ER-positive

*Frequency of heterozygotes in the U.S. population; the incidence of gene mutations is higher in some ethnic populations (e.g., *BRCA1* and *BRCA2* mutations occur at high frequencies in Ashkenazi Jews).
†Defined as familial breast cancers showing a pattern of inheritance consistent with a major effect of a single gene.
‡Risk varies with specific mutations and is likely modified by other genes. *LOH*, loss of heterozygosity.

Familial cancers

- Approximately 12% of breast cancers occur due to inheritance of an identifiable susceptibility gene or genes.
- Mutations in BRCA1 and BRCA2 are responsible for 80% to 90% of “single gene” familial breast cancers and about 3% of all breast cancers.
- Germline mutations in TP53 (Li-Fraumeni syndrome) and mutations in CHEK2 together account for about 8% of breast cancers caused by single genes.
- PTEN (Cowden syndrome), STK11 (Peutz-Jeghers syndrome), and ATM (ataxia telangiectasia) are mutated in less than 1% of all familial breast cancers.

BRCA

- BRCA1-associated breast cancers are commonly poorly differentiated, have “medullary features” (a syncytial growth pattern with pushing margins and a lymphocytic response
- Biologically very similar to ER- and PR-negative/HER2-negative breast cancers identified as “basal-like” by gene expression profiling as well as to serous ovarian carcinomas.
- BRCA2-associated breast carcinomas also tend to be relatively poorly differentiated, but are more likely ER-positive/HER2-negative
- One in 40 Ashkenazi women carry the gene(s).

Gene loop

- BRCA1 mutation from paternal line associated with earlier presentation of breast cancer than if from maternal line
- ATM senses DNA damage and with p53 and CHEK2 induces cell cycle arrest.
- CHEK2 activates BRCA
- BRCA1, BRCA2 repair double stranded DNA breaks.
- p53 activates PTEN which blocks PIP3/AKT

BRCA

- BRCA1 and 2 involved in homologous recombination in repair of double stranded DNA breaks.
- Interact with RAD51.
- BRCA1 has high affinity for branched DNA structures.
- It promotes non-homologous end-joining as well as nucleotide excision repair pathways.
- BRCA1 mutated cells are deficient in the transcription-coupled repair of oxidative damage (due to estrogen metabolites).

BRCA

- BRCA1 is phosphorylated in response to DNA damage and may transduce damage signals from checkpoint kinases to effector proteins. (CHEK 2 activates BRCA1).
- Binds to BRCA2.
- Interacts as well with the estrogen receptor and is involved in X chromosome inactivation.
- BRCA2 binds directly to DNA.
- 30% of breast cancers have gain of function mutations of PI3K/AKT

BRCA

- BRCA1 mutated cells are deficient in the transcription-coupled repair of oxidative damage.
- Estrogen metabolism is abnormal in breast cancer.
- Increased levels of metabolites such as estrogen-3,4-quinones react with DNA to form depurinating adducts that spontaneously dissociate from DNA to form abasic sites and generate mutations that must be corrected by the error-prone base excision repair.
- Inhibition of poly-ADP-ribose polymerase (PARP) disables base excision repair.

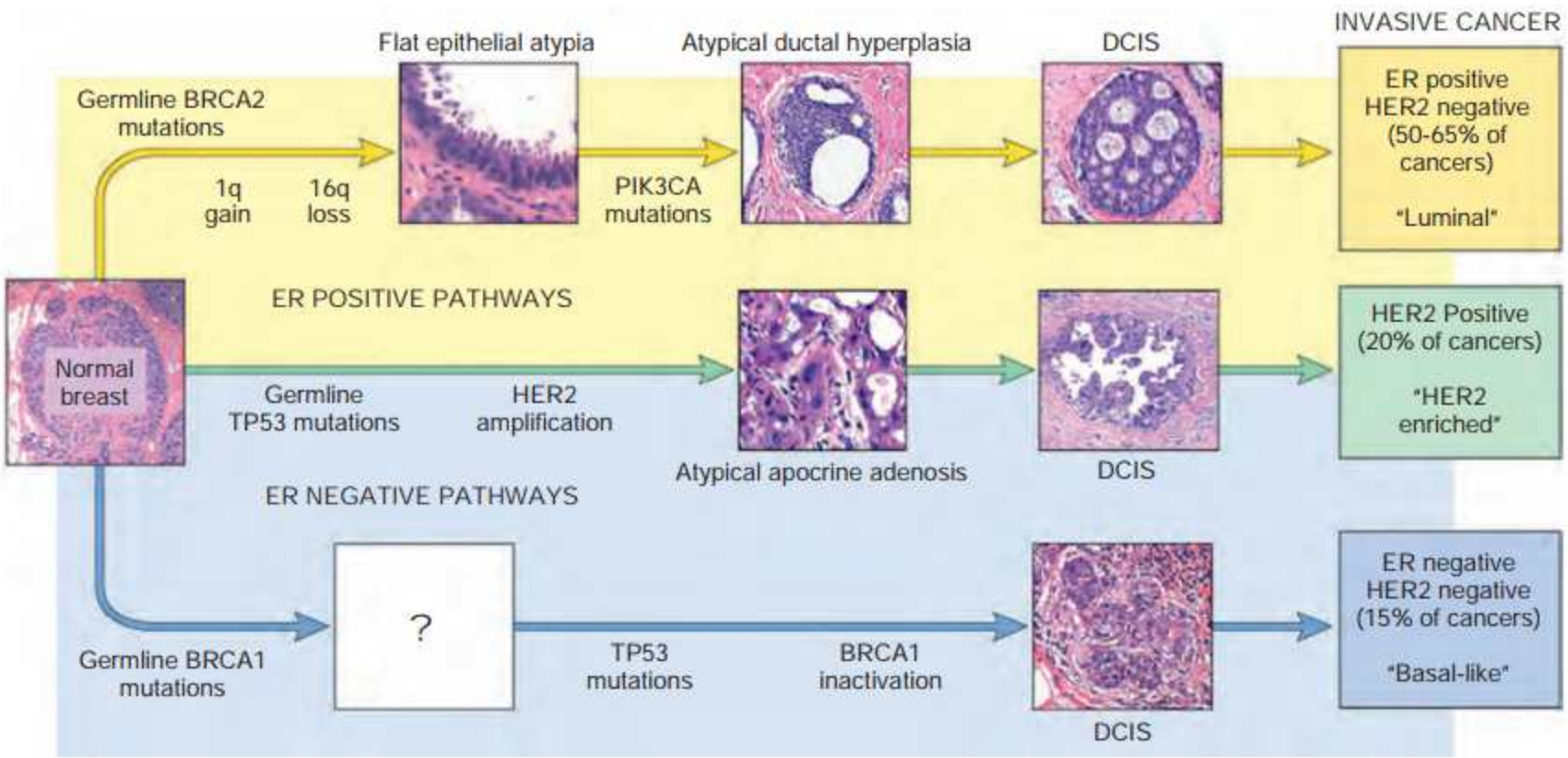


Figure 23-16 Major pathways of breast cancer development. Three main pathways have been identified. The most common pathway *(yellow arrow)* leads to ER-positive carcinomas. Recognizable precursor lesions include flat epithelial atypia and atypical hyperplasia. A less common pathway *(blue arrow)* leads to carcinomas that are negative for ER and HER2. The box with the question mark indicates that no precursor lesions have been identified—perhaps because lesions progress quickly to carcinoma. The third pathway *(green arrow)* consists of HER2-positive cancers, which may be ER-positive or ER-negative. Amplification of the *HER2* gene is also present in a subset of atypical apocrine lesions, which may represent a precursor lesion. Each molecular subtype has a characteristic gene expression profile termed luminal, HER2 enriched, and basal-like, respectively. See text for other details.

Breast cancer development

- ER-positive, HER2-negative cancers arise via the dominant pathway of breast cancer development, constituting 50% to 65% of cases.
- This is the most common subtype of breast cancer in individuals who inherit germline mutations in BRCA2.
- They are often associated with gains of chromosome 1q, losses of chromosome 16q, and activating mutations in PIK3CA, a gene that encodes phosphoinositide-3 kinase (PI3K).

Breast cancer development

- ER-positive cancers are termed “luminal,” as these cancers most closely resemble normal breast luminal cells in terms of their mRNA expression pattern, which is dominated by genes that are regulated by estrogen.

Breast cancer development

- HER2-positive cancers arise through a pathway that is strongly associated with amplifications of the HER2 gene on chromosome 17q.
- They constitute approximately 20% of all breast cancers and may be either ER-positive or ER-negative.
- HER2-positive cancers are the most common subtype of breast cancer in patients with germline mutations in TP53 (Li-Fraumeni syndrome).

Breast cancer development

- ER-negative, HER2-negative cancers arise through a distinct pathway that is independent of ER-mediated changes in gene expression and HER2 gene amplifications.
- These tumors comprise about 15% of breast cancers.
- Are the most common tumor type observed in patients with germline BRCA1 mutations.
- These tumors have a “basal-like” pattern of mRNA expression that includes many genes that are expressed in normal myoepithelial cells.

Breast cancer

- Almost all (>95%) of breast malignancies are adenocarcinomas that first arise in the duct/lobular system as carcinoma in situ
- At the time of clinical detection the majority (at least 70%) will have breached the basement membrane and invaded the stroma.

Atypical breast lesions

- Managed by close follow-up.
- Lobular carcinoma in situ is regarded as a marker for the risk of developing invasive cancer.
- 56% risk reduction in those receiving tamoxifen therapy.
- There is an 86% reduction in the risk of developing breast cancer for those women with ductal abnormalities who receive 5 years of tamoxifen therapy.

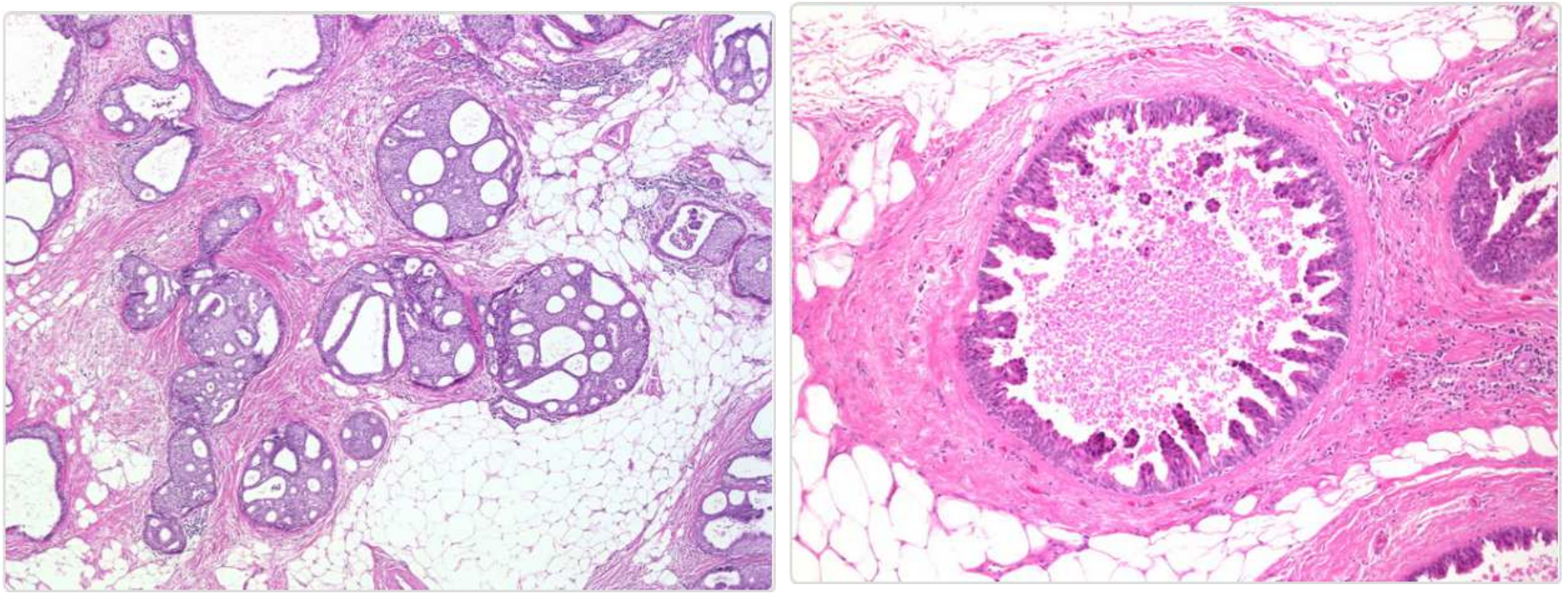
Ductal carcinoma in situ

- Two major architectural subtypes:
- Noncomedo
- Comedo
- Some cases of DCIS have a single growth pattern, but most are comprised of a mixture of patterns.
- Nuclear grade and necrosis are better predictors of local recurrence and progression to invasion than is architectural type.
- Up to 10% of DCIS involve both breasts

Ductal carcinoma in situ

- Noncomedo
- Lacks either high-grade nuclei or central necrosis.
- The cribriform pattern has rounded (cookie cutter–like or roman arch) spaces within the ducts
- Solid pattern not likely to have calcifications
- The micropapillary pattern produces bulbous protrusions without a fibrovascular core, often arranged in complex intraductal patterns.
- DCIS may produce true papillae with fibrovascular cores that lack a myoepithelial cell layer.
- Calcifications may also be seen with focal necrosis or intraluminal secretions.

Ductal carcinoma in situ



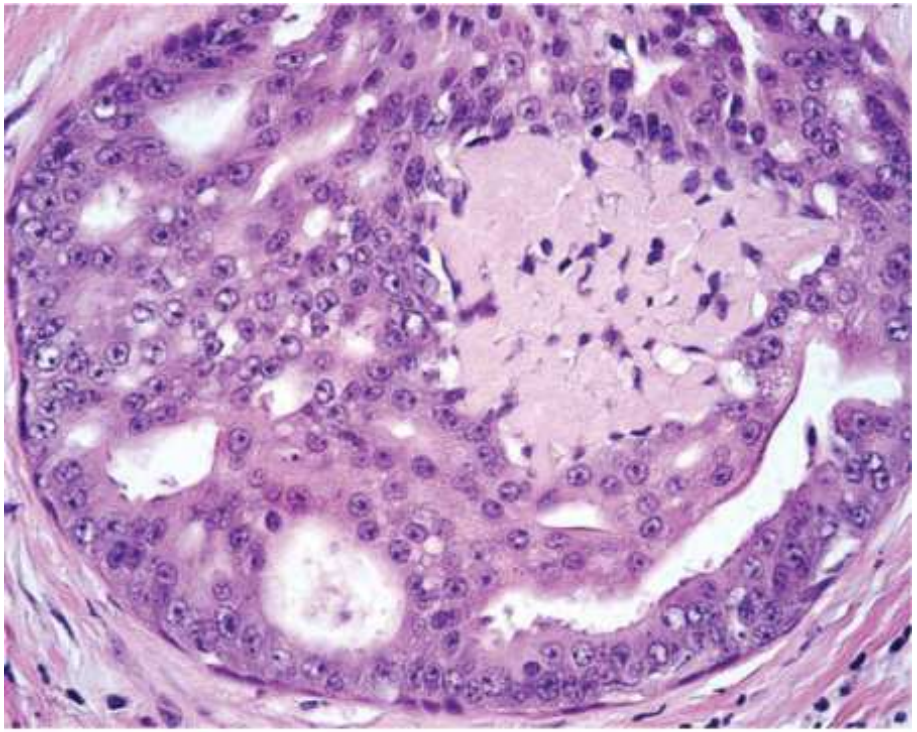
Left: In the cribriform DCIS, round fenestrations are found within the glands. The more regular these spaces are in size, shape and distribution, the more likely the lesion to be malignant. Right: In the micropapillary variant there are slender elongated epithelial fronds projecting into the glandular lumen. These projections are solid and lack true fibrovascular cores.

http://webpathology.com/image.asp?case=289&n=5 and n=1 Accessed 02/20/2020

Ductal carcinoma in situ

- Comedo DCIS may occasionally produce vague nodularity, but more often it is detected on mammography as clustered or linear and branching areas of calcification
- Tumor cells have pleomorphic, highgrade nuclei
- Areas of central necrosis
- Microinvasion is defined by a focus of tumor cells less than 0.1cm in diameter invading the stroma.
- It is most commonly seen with comedo carcinoma.

Ductal carcinoma in situ



Comedo

Fig. 12-11 Accessed 08/01/2010

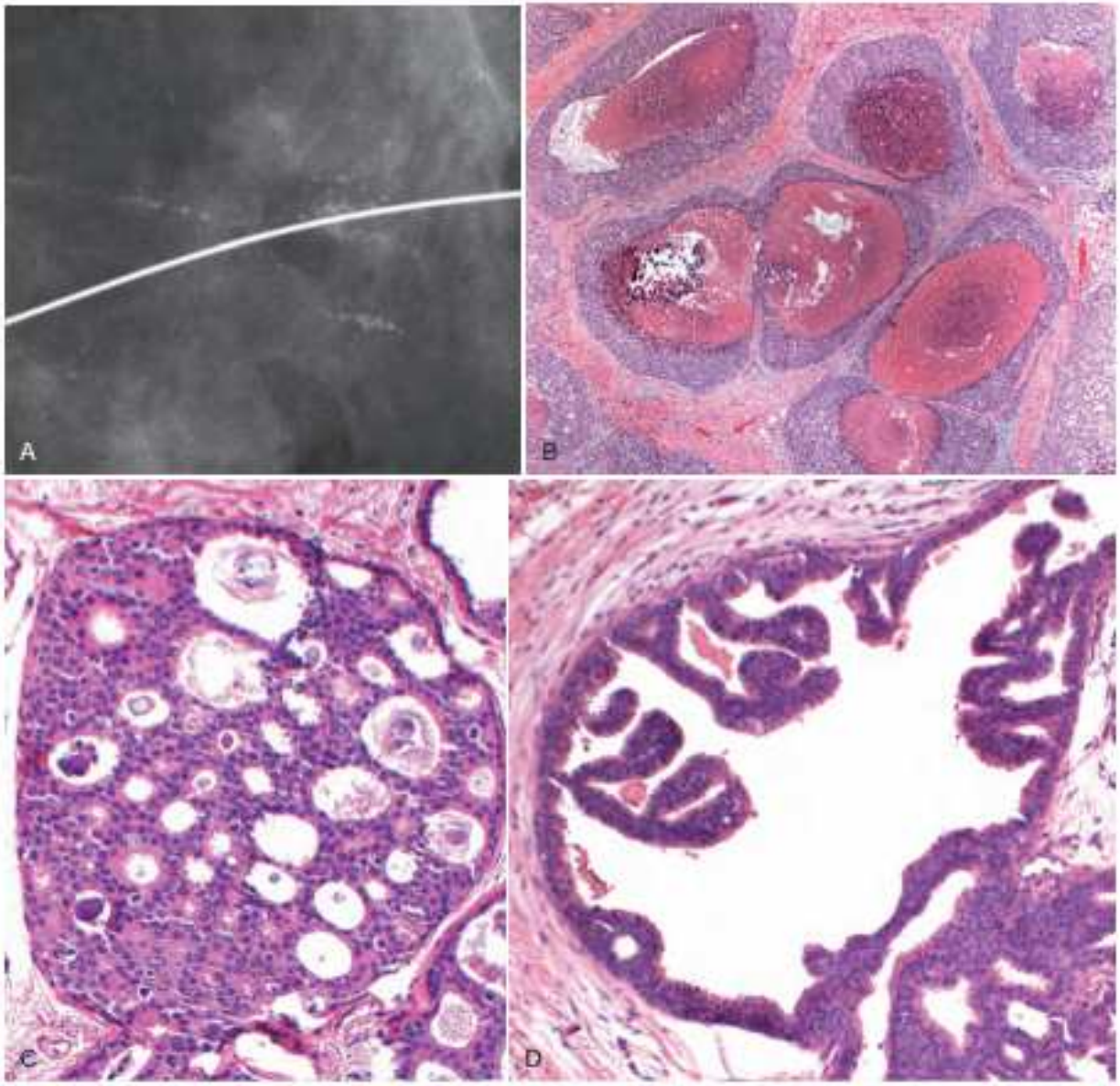


Figure 23-17 Ductal carcinoma in situ (DCIS). A and B, Comedo type. A, The specimen radiogram reveals linear and branching calcifications within the ductal system. B, A high-grade proliferation associated with large central zones of necrosis and calcifications fills several ducts. C and D, Noncomedo types. C, Cribriform DCIS. Note the round, regular ("cookie cutter") spaces containing calcifying secretory material. D, Micropapillary DCIS. The papillary projections lack fibrovascular cores.

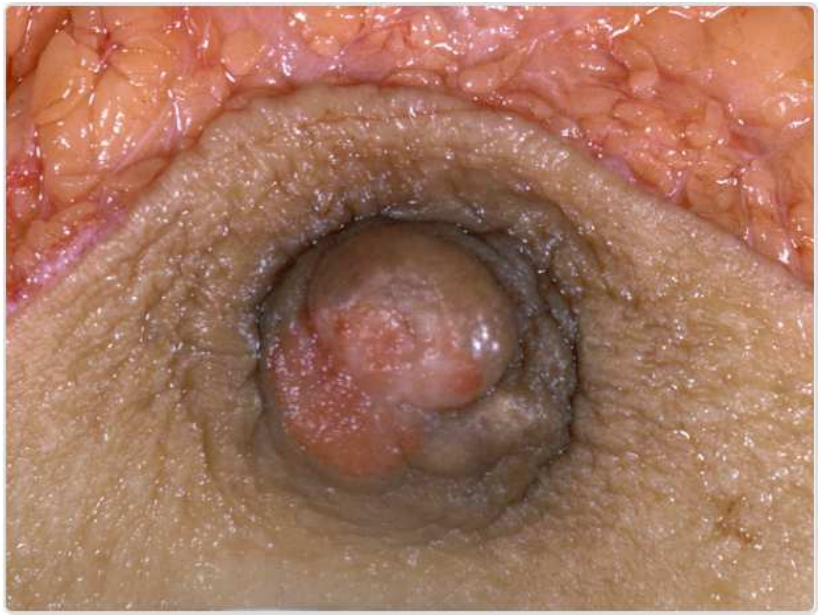
Paget disease of the nipple

- 1% to 4% of cases
- Presents as a pruritic, unilateral erythematous eruption with a scale crust.
- Malignant cells (Paget cells) extend from DCIS within the ductal system via the lactiferous sinuses into nipple skin without crossing the basement membrane.
- The tumor cells disrupt the normal epithelial barrier, allowing extracellular fluid to seep out onto the nipple surface.

Paget disease of the nipple

- A palpable mass is present in 50% to 60% of women with Paget disease, and almost all of these women have an underlying invasive carcinoma that is usually ER-negative and HER2-positive.
- Melanocytic markers positive in 25% of cases
- In the majority of women without a palpable mass only DCIS is present.
- Pagetoid spread is uncommon in lobular carcinoma in situ as the disease process does not involve nipple skin.
- Prognosis of Paget disease depends on the features of the underlying carcinoma

Paget's disease of the breast



The involved skin shows acanthosis and hyperkeratosis. There may be erosion or ulceration as well. Infiltrating the entire thickness of epidermis are large pleomorphic, malignant Paget cells that are scattered singly in a buckshot pattern, arranged in clusters and nests, or as solid sheets. The tumor cells may extend into the adnexal structures.

http://webpathology.com/image.asp?case=303&n=1 and n=8
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Lobular carcinoma in situ

- LCIS is a clonal proliferation of cells within ducts and lobules that grow in a discohesive fashion
- Loss of the tumor suppressive adhesion protein E-cadherin.
- “Lobular” because the cells expand but do not distort involved space. The underlying lobular architecture is preserved.
- Not generally associated with calcifications nor alterations in stromal density.
- Rare to discover by mammography.
- Up to 25% involve both breasts.

Lobular carcinoma in situ

- LCIS consists of a uniform population of cells with oval or round nuclei and small nucleoli involving ducts and lobules.
- Mucin-positive signet-ring cells are commonly present.
- The lack of E-cadherin results in a rounded shape without attachment to adjacent cells. The cells cannot form cribriform spaces or papillae, such as are seen in DCIS.
- Necrosis and secretory activity are not seen.
- LCIS almost always expresses ER and PR. Overexpression of HER2 is not observed.

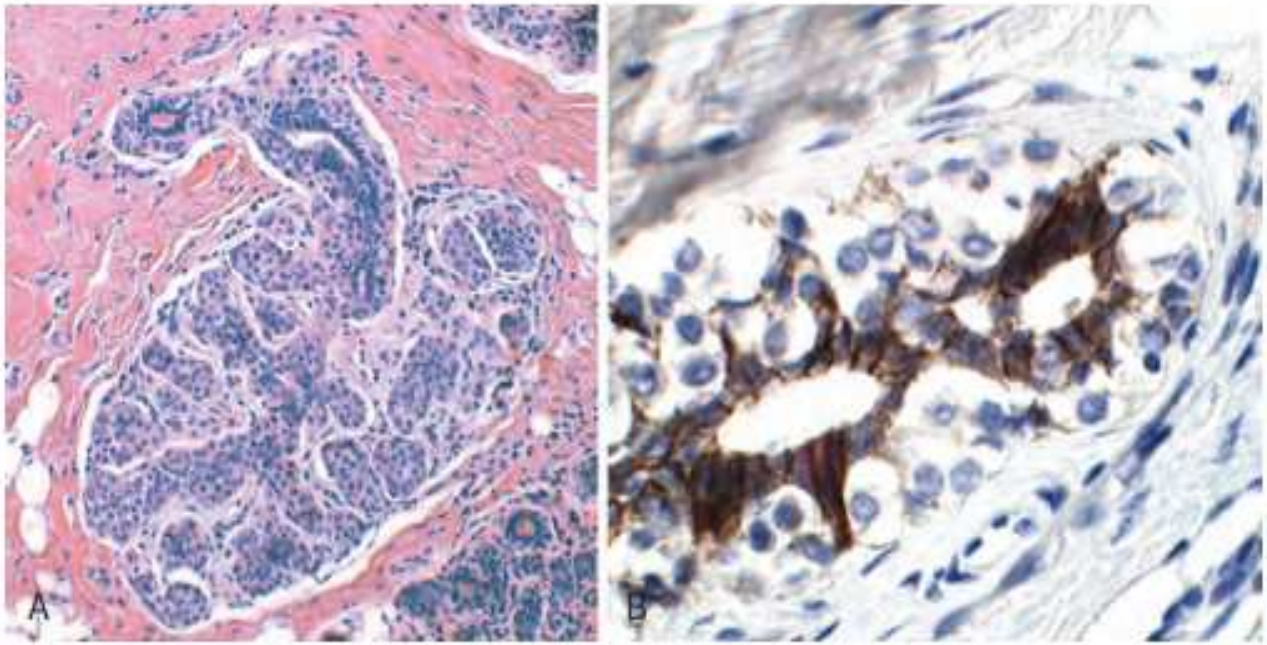


Figure 23-19 Lobular carcinoma in situ. **A,** A monomorphic population of small, rounded, loosely cohesive cells fills and expands the acini of a lobule. The underlying lobular architecture can still be recognized. The cells extend into the adjacent lobule by pagetoid spread. **B,** An immunoperoxidase study shows E-cadherin–positive normal luminal cells that have been undermined by E-cadherin-negative LCIS cells spreading along the basement membrane.

WHO 2019 carcinoma classification

- Ductal carcinoma and variants:
- 80% Ductal carcinoma
- 6% Tubular carcinoma
- Cribiform variant
- 2% Mucinous carcinoma
- <1% Medullary carcinoma
- Lobular carcinoma and variants
- 10% Lobular carcinoma

WHO 2019 carcinoma classification

- Metaplastic carcinoma and subtypes
- Neuroendocrine carcinoma and variants
- Other special subtypes
- Adenoid cystic and solid variants
- Rare subtypes:
- Acinic cell
- Mucoepidermoid
- Oncocytic

Age at presentation

- Caucasian women have an average age on onset of breast cancer in their 50's
- Those of Korean origin, in their early 40's
- Those of Sub-Saharan origin, in their late 40's;
- The frequency of deleterious BRCA1 mutations is highest in those of Ashkenazi ancestry (24%) while those in all other groups is only 14%.

Invasive carcinoma

- Prognosis is dependent upon the molecular characters of the neoplasm, not its pattern.
- Molecular patterns:
- (1) ER-positive, PR-positive, HER2-negative, low proliferation index (Ki67)
- 40% to 55% of cancers
- This group of breast cancers makes up the majority of cancers in older women and in men.
- Luminal A

Molecular subtypes

- (2) “Normal like”
- ER+,PR-,HER2/neu- or ER-/PR+/HER2/neu-
- Ki67 low
- More aggressive than Luminal A, but less than Luminal B cancers

Invasive carcinoma

- (3) ER-positive, HER2-negative, high proliferation index (Ki67)
- 10% of cancers
- Although these tumors are ER-positive, ER levels may be low and progesterone receptor expression may be low or absent.
- Luminal B
- (4) HER2-positive
- 20% of cancers
- 50% of those with Li-Fraumeni syndrome
- ER expression is usually low; progesterone receptor expression is often absent

Table 23-3 Molecular Subtypes of Invasive Breast Cancer

Defining Features	ER-positive, HER2-negative		HER2-Positive (ER-Positive or Negative*)	ER-Negative† HER2-Negative
Frequency	~40-55% (Low proliferation)	~10% (High proliferation)	~20%	~15%
Included special histologic types	Well or moderately differentiated lobular, tubular, mucinous	Poorly differentiated lobular	Some apocrine	Medullary,‡ adenoid cystic,‡ secretory,‡ metaplastic
Typical patient groups	Older women, men, cancers detected by mammographic screening	*BRCA2* mutation carriers	Young women, non-white women, *TP53* mutation carriers (ER positive)	Young women, *BRCA1* mutation carriers, African American and Hispanic women
Metastatic pattern	Bone (70%), more common than visceral (25%) or brain (<10%)	Bone (80%) more common than visceral (30%) or brain (10%)	Bone (70%), visceral (45%),and brain (30%) are all common	Bone (40%), visceral (35%), brain (25%) are all common
Relapse pattern	Late, >10 years, long survival possible with metastases	Intermediate	Usually short, <10 years, survival with metastases rare	Usually short, <5 years, survival with metastases rare
Complete response to chemotherapy	<10%	~10%	ER positive—15% ER negative—>30%	~30%

*About half of HER2-positive cancers are ER positive and half ER negative. ER and PR levels tend to be low in this group.
†This group is also referred to as "triple negative" carcinoma.
‡Some special histologic types have a more favorable prognosis than this group as a whole.

Invasive carcinoma

- (5) ER-negative, HER2-negative tumors ("basal-like") triple negative carcinoma
- 15% of cancers
- 70% of BRCA1 mutated cancers
- The strong expression of basal keratin distinguishes basal like carcinomas from other ER-, PR-, HER2/neu- ("triple negative") tumors.
- More common in those of African ancestry

Molecular subtypes

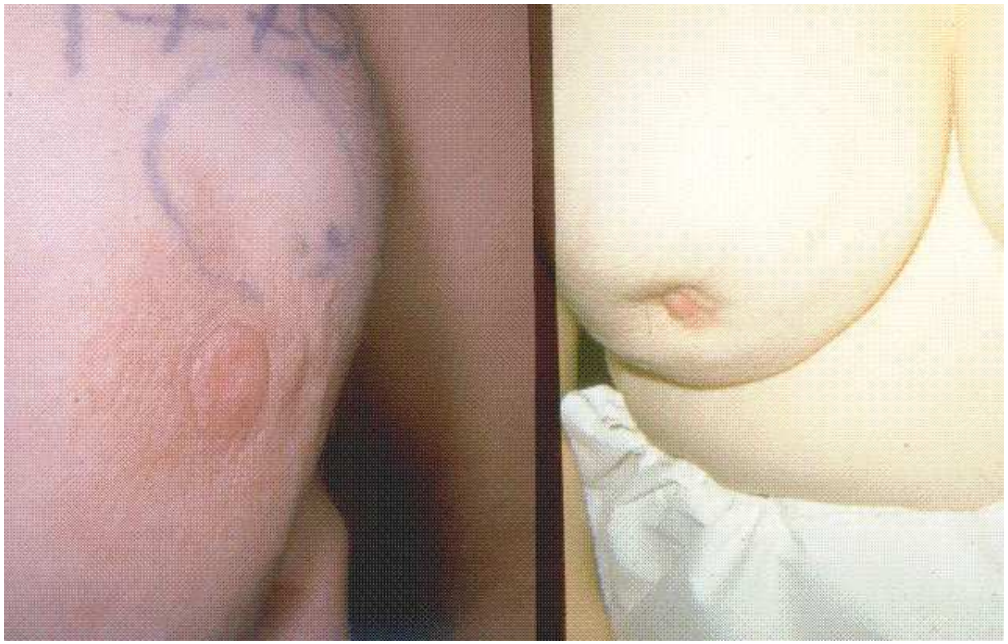
- (6) "Triple negative" carcinomas are heterogeneous.
- More common in women <50 years of age
- Subtypes include:
- Basal-like 1
- Basal-like 2
- Immunomodulatory
- Mesenchymal (myoepithelial cell origin);
- Amesenchymal;
- Luminal androgen receptor

Invasive ductal carcinoma

- Invasive carcinomas presenting on mammography as calcifications without an associated density are generally less than 1 cm in size.
- The mammographic and gross appearance of invasive carcinoma varies widely depending on the stromal reaction to the tumor
- They most commonly present as a hard, irregular radiodense mass associated with a desmoplastic stromal reaction
- Grating sound when cut or scraped

Invasive ductal carcinoma

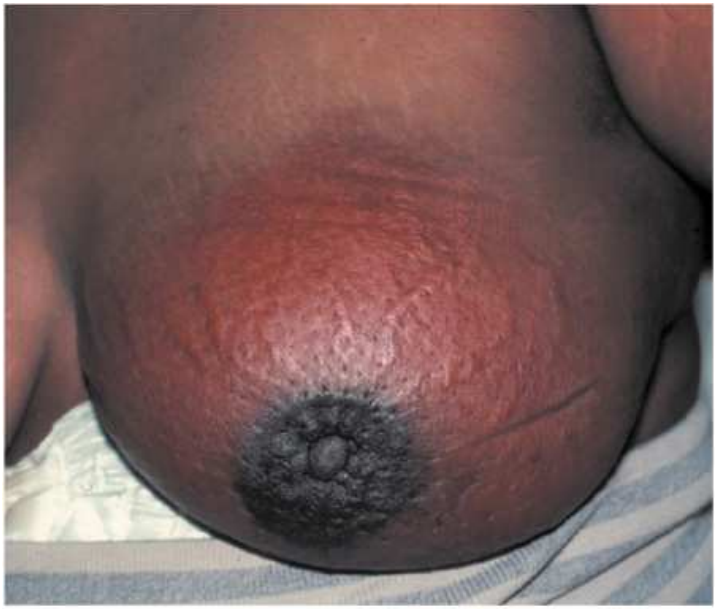
- Contain small, central pinpoint foci or streaks of chalky-white desmoplastic stroma and occasional foci of calcification.
- Less commonly, tumors may be well-circumscribed masses composed of sheets of tumor cells with scant stromal reaction
- May be comprised of scattered neoplastic glands or single tumor cells infiltrating otherwise unremarkable fibrofatty tissue.
- Tubular carcinoma is a subset of invasive ductal carcinoma.



Nipple retraction

Fig. 12-16 Accessed 08/01/2010

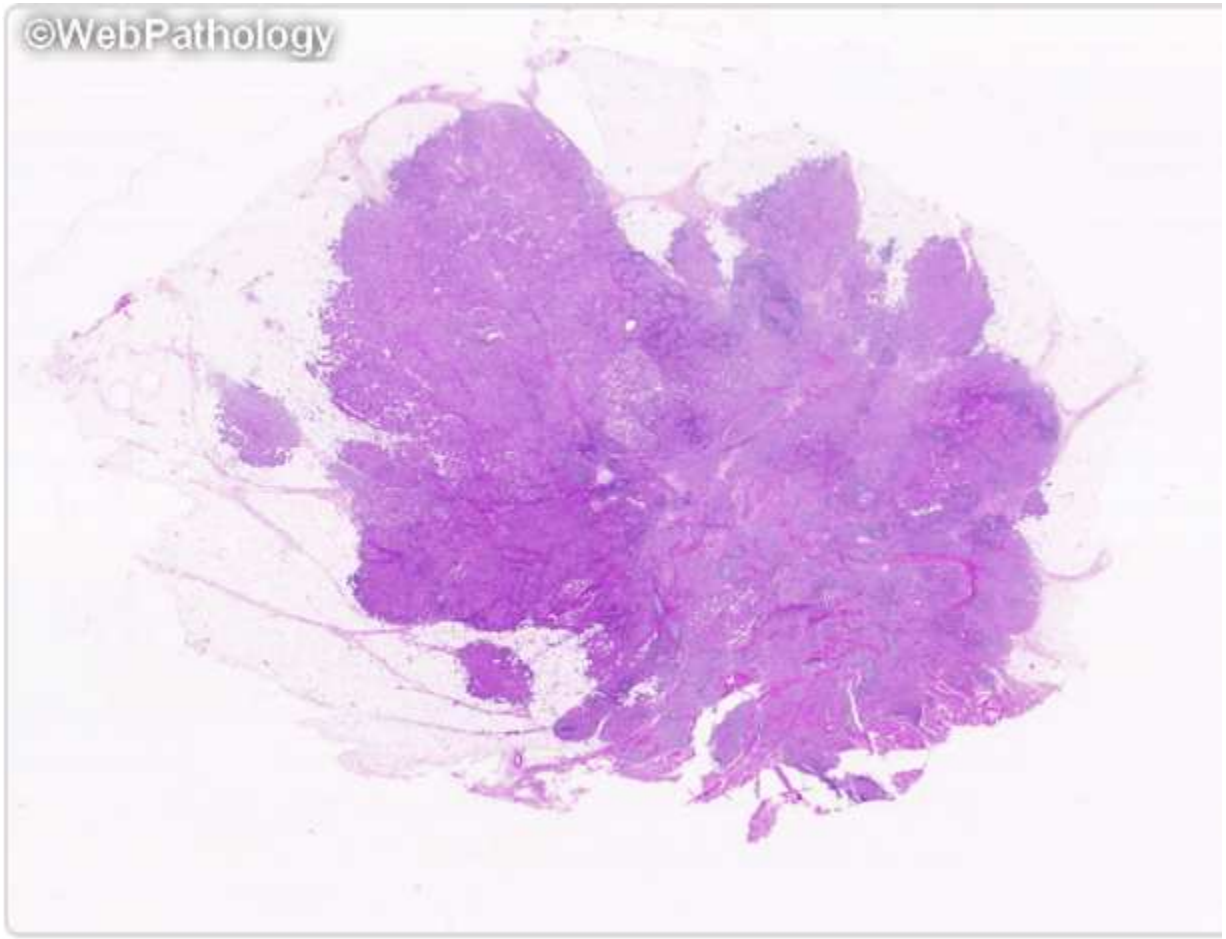
Inflammatory breast cancer



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Invasive ductal carcinoma



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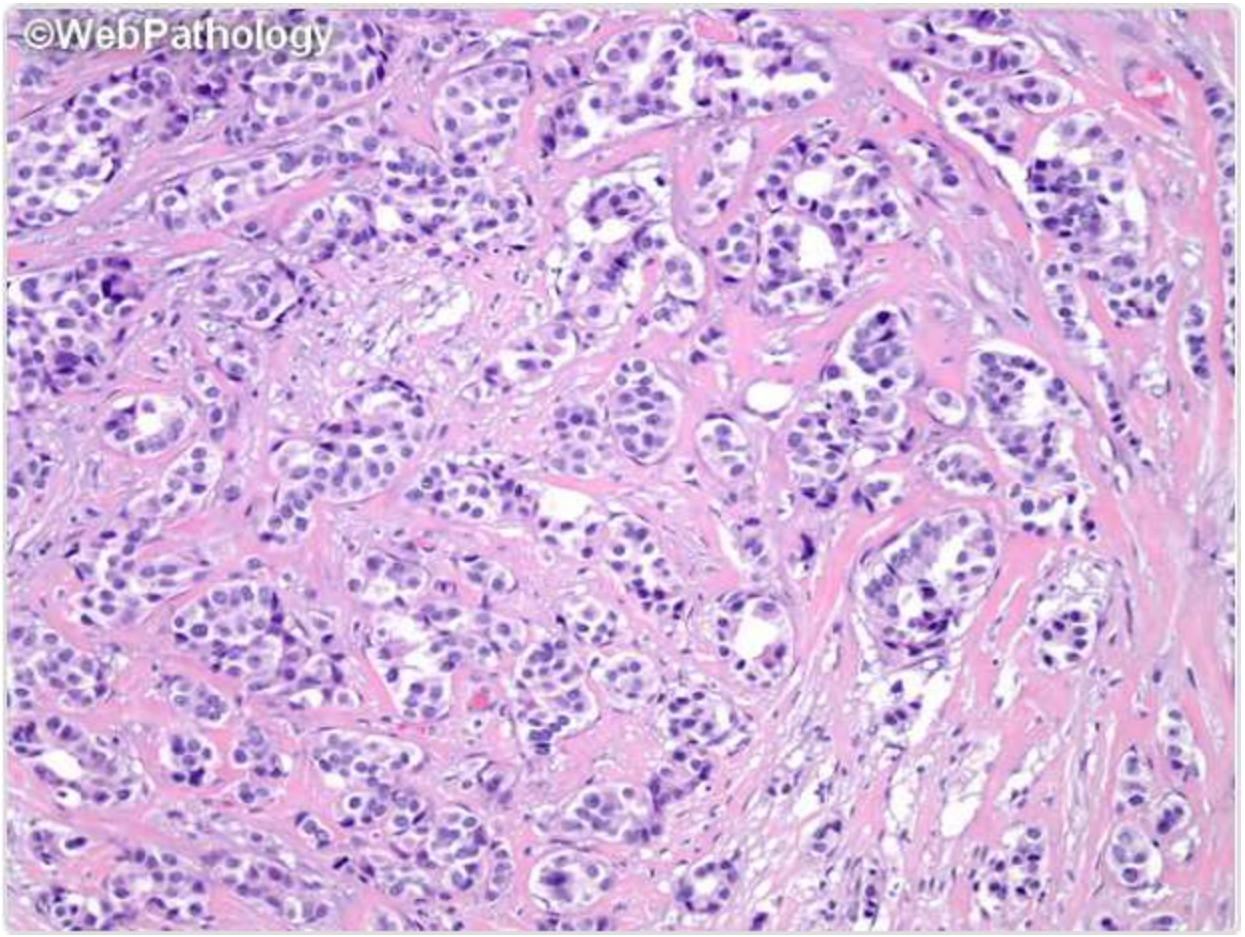
Invasive ductal carcinoma



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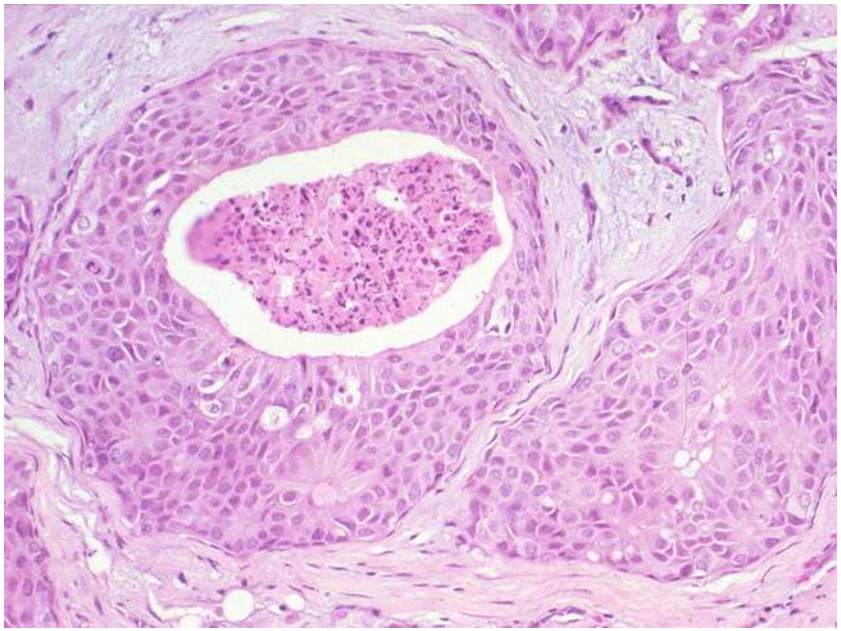
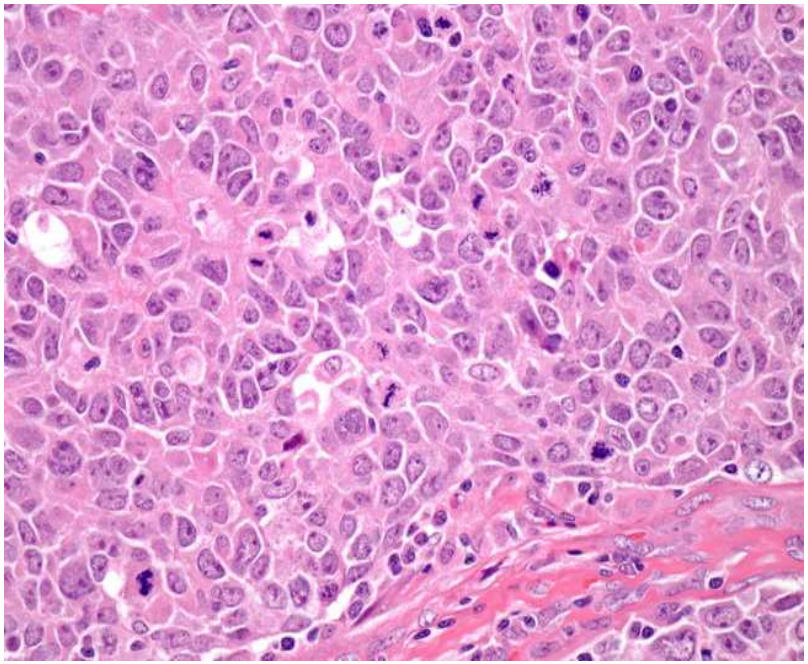
Ductal (comedo) carcinoma





Left: Carcinoma of the duct with tumor cells in the duct. Marked desmoplastic reaction around duct. Right: Uniform infiltrate of neoplastic cells with stromal invasion.

http://webpathology.com/image.asp?case=289&n=10 and http://webpathology.com/image.asp?n=48&Case=290
Accessed 02/20/2020

Tubular carcinoma

- 6% of cases
- Small, non-palpable in 85% of cases
- There is a high incidence of multicentricity (56%), bilaterality (38%) and family history (40%)
- 10% may have axillary metastases
- Diploid and express hormone receptors.
- Her2/neu negative
- Well-differentiated tumors consist of tubules lined by minimally atypical cells but without myoepithelial cells.

Tubular carcinoma

- Stellate or irregular lesions with infiltrating borders.
- Microscopic:
- There is an irregular proliferation of small glands and tubules lined by a single layer of cuboidal or columnar epithelium. Significant atypia is unusual.
- At least 90% or more of the lesion should have this architecture to be classified as tubular carcinoma.
- The glands and tubules have angulated contours and widely open lumens. The tubules are separated by abundant stroma.

Modified Scarff-Bloom-Richardson Histologic Grading

Tubule Formation:

Score 1:	>75% of tumor shows tubules
Score 2:	10-75% of tumor has tubules
Score 3:	<10% of tumor has tubules

Nuclear Size:

Score 1:	small regular nuclei; similar to normal ductal nuclei
Score 2:	intermediate size; 1.5-2 times the size of normal ductal nuclei
Score 3:	high-grade nuclei; > twice the size of normal ductal nuclei

Mitotic Count:

Score 1:	0-7 mitoses/10HPF
Score 2:	8-14 mitoses/10HPF
Score 3:	>15 mitoses/10HPF

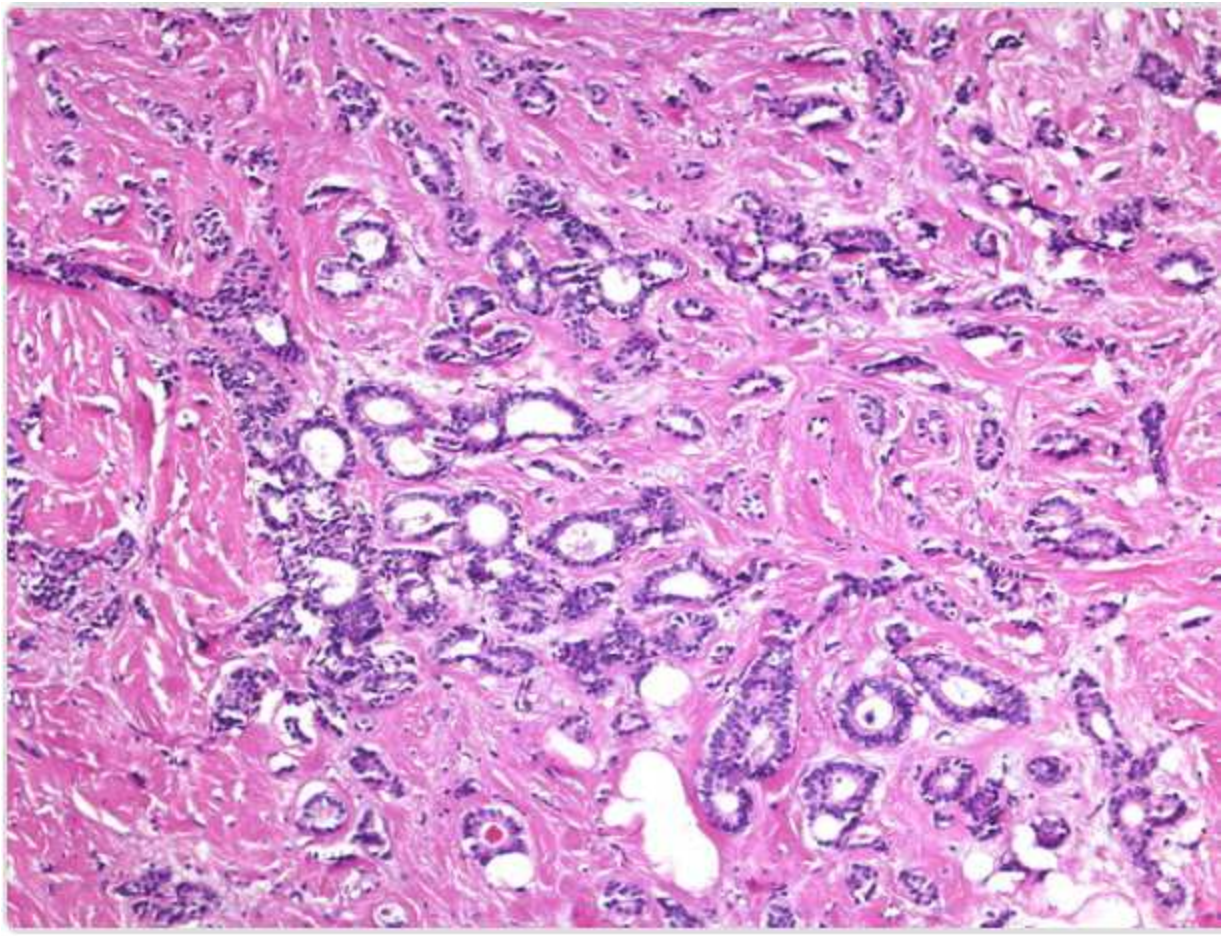
Nottingham Combined Histologic Grade:

Scores 3 to 5:	Well-differentiated (Grade I)
Score 6 to 7:	Moderately-differentiated (Grade II)
Score 8 to 9:	Poorly-differentiated (Grade III)

Tubular carcinoma

- Microcalcifications are present in about 50% of cases.
- Low-grade DCIS (micropapillary and cribriform type) as well as columnar cell hyperplasia with atypia (flat epithelial atypia) are considered to be the precursor lesions and are found in two-thirds of cases.

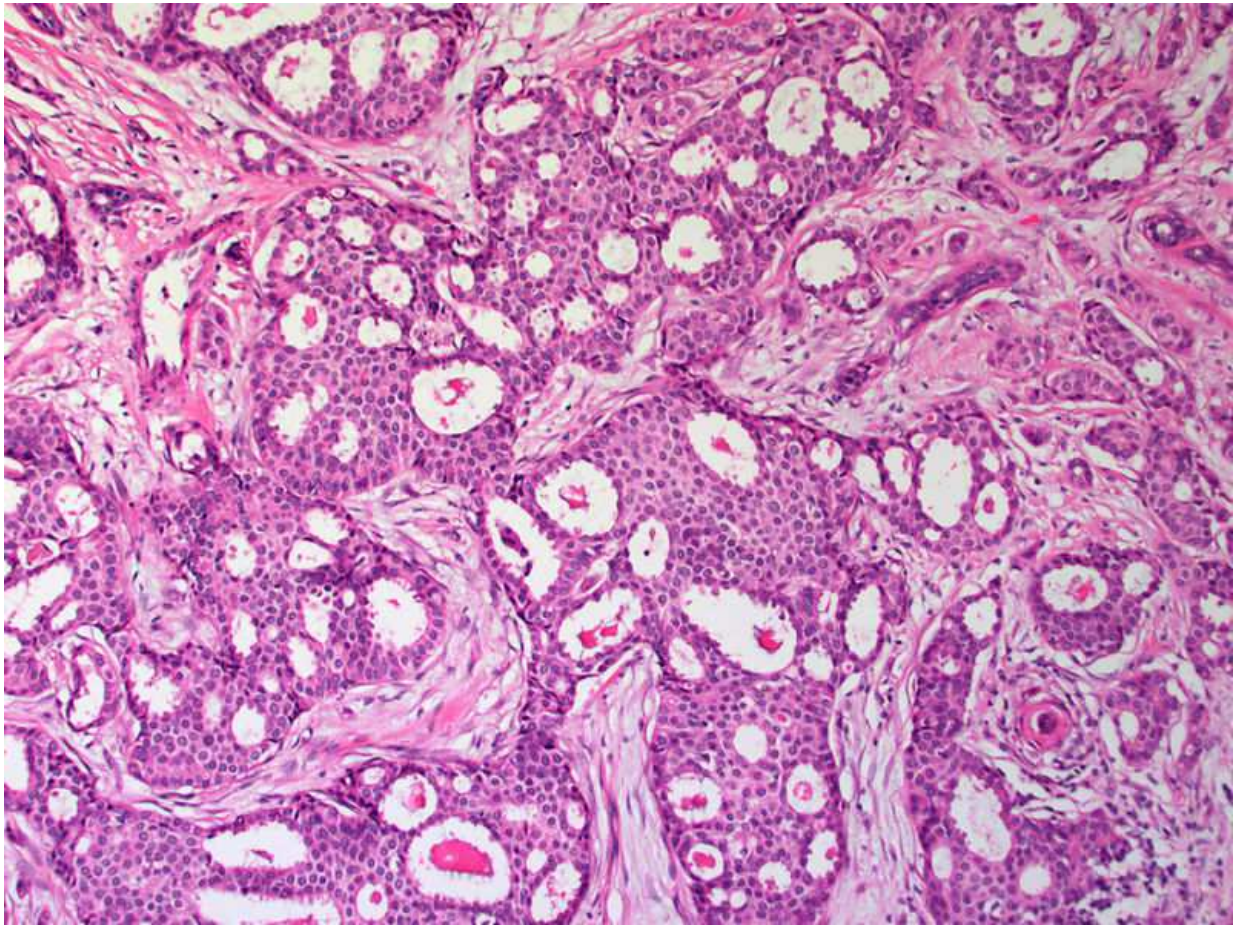
Tubular carcinoma



Well-differentiated invasive carcinoma of the breast. It is composed of well-defined glands with round, oval or angulated contours, open lumina, absence of myoepithelial cell layer, and absence of necrosis or mitoses.

http://webpathology.com/image.asp?case=296&n=1
Accessed 02/20/2020

Cribiform carcinoma



Roman arch pattern. Related to tubular carcinoma.

https://librepathology.org/wiki/File:Breast_CribriformCarcinoma_MP_SNP.jpg Accessed 02/20/2020

Other invasive cancer types

- Micropapillary carcinoma shows a characteristic pattern of anchorage-independent growth.
- Although the cells are adherent to each other and express E-cadherin, they lack adhesion to the stroma.
- Overexpress HER2

Invasive breast cancer

- Inflammatory carcinoma.
- Present with breast erythema and skin thickening
- The edematous skin is tethered to the breast by Cooper ligaments and mimics the surface of an orange peel, an appearance referred to as peau d'orange.
- These clinical signs are caused by dermal lymphatics filled with tumor cells that block lymphatic drainage.
- It is now Stage IIIA. Prior to the new staging criteria, it was T4d.

Nottingham Histologic Score.

- Carcinomas are scored for tubule formation, nuclear pleomorphism, and mitotic rate.
- Grade I carcinomas grow in a tubular pattern with small round nuclei and have a low proliferative rate.
- Grade II carcinomas may also show some tubule formation, but solid clusters or single infiltrating cells are also present. There is a greater degree of nuclearpleomorphism and mitotic figures are present.
- Grade III carcinomas invade as ragged nests or solid sheets of cells with enlarged irregular nuclei. A high proliferative rate and areas of tumor necrosis are common

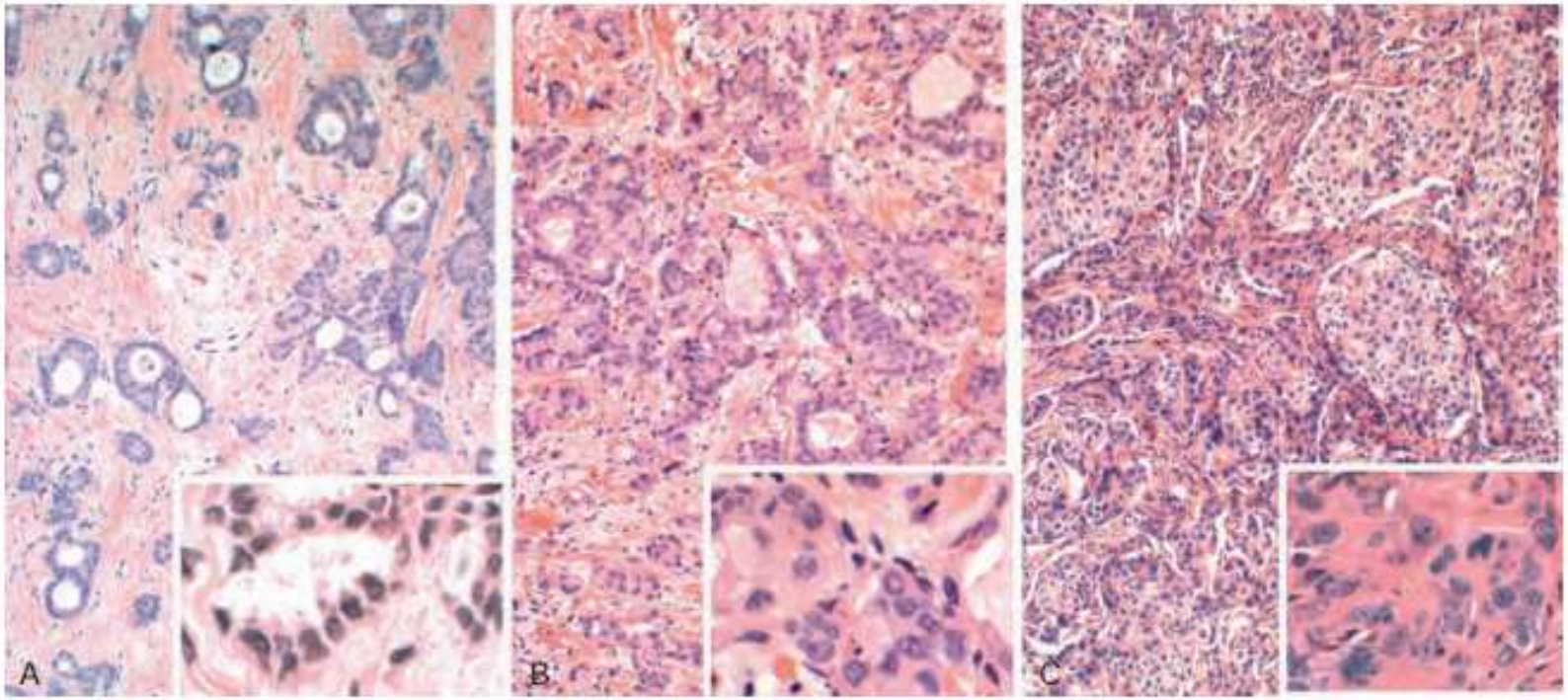


Figure 23-23 Grading of invasive carcinoma. **A,** A well-differentiated carcinoma of no special type consists of tubules or a cribriform pattern of cells with small monomorphic nuclei. **B,** A moderately differentiated carcinoma of no special type shows less tubule formation and more solid nests of cells and pleomorphic nuclei. **C,** A poorly differentiated carcinoma of no special type infiltrates as ragged sheets of pleomorphic cells and contains numerous mitotic figures and central areas of tumor necrosis.

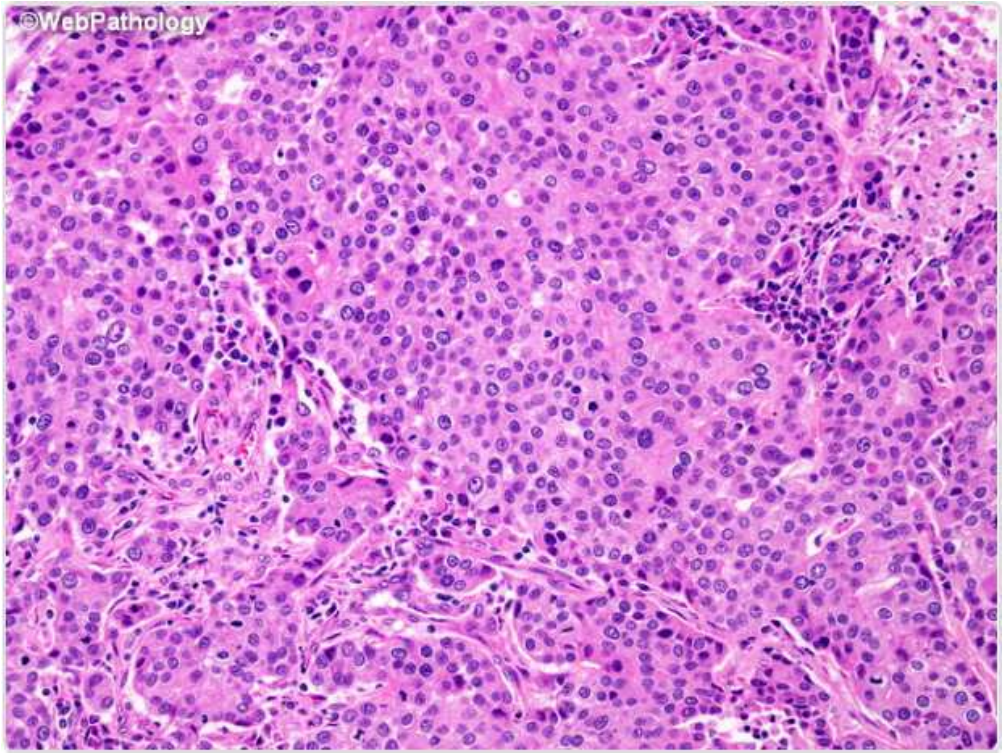
Medullary carcinoma

- Characterized by:
- (1) solid, syncytium-like sheets of largecells with pleomorphic nuclei, and prominent nucleoli, which compose more than 75% of the tumor mass;
- (2) frequent mitotic figures;
- (3) a moderate to marked lymphoplasmacytic infiltrate surrounding and within the tumor;
- (4) a pushing(non-infiltrative) border.
- DCIS is minimal or absent.

Medullary carcinoma

- ER-negative, PR-negative, HER2-negative
- Of those cancers that arise in BRCA 1 carriers, 13% are medullary and up to 60% have medullary components.
- 67% of these are due to hypermethylation of the BRCA 1 promoter.
- TP53 mutation as well
- Usually aneuploid

Medullary carcinoma



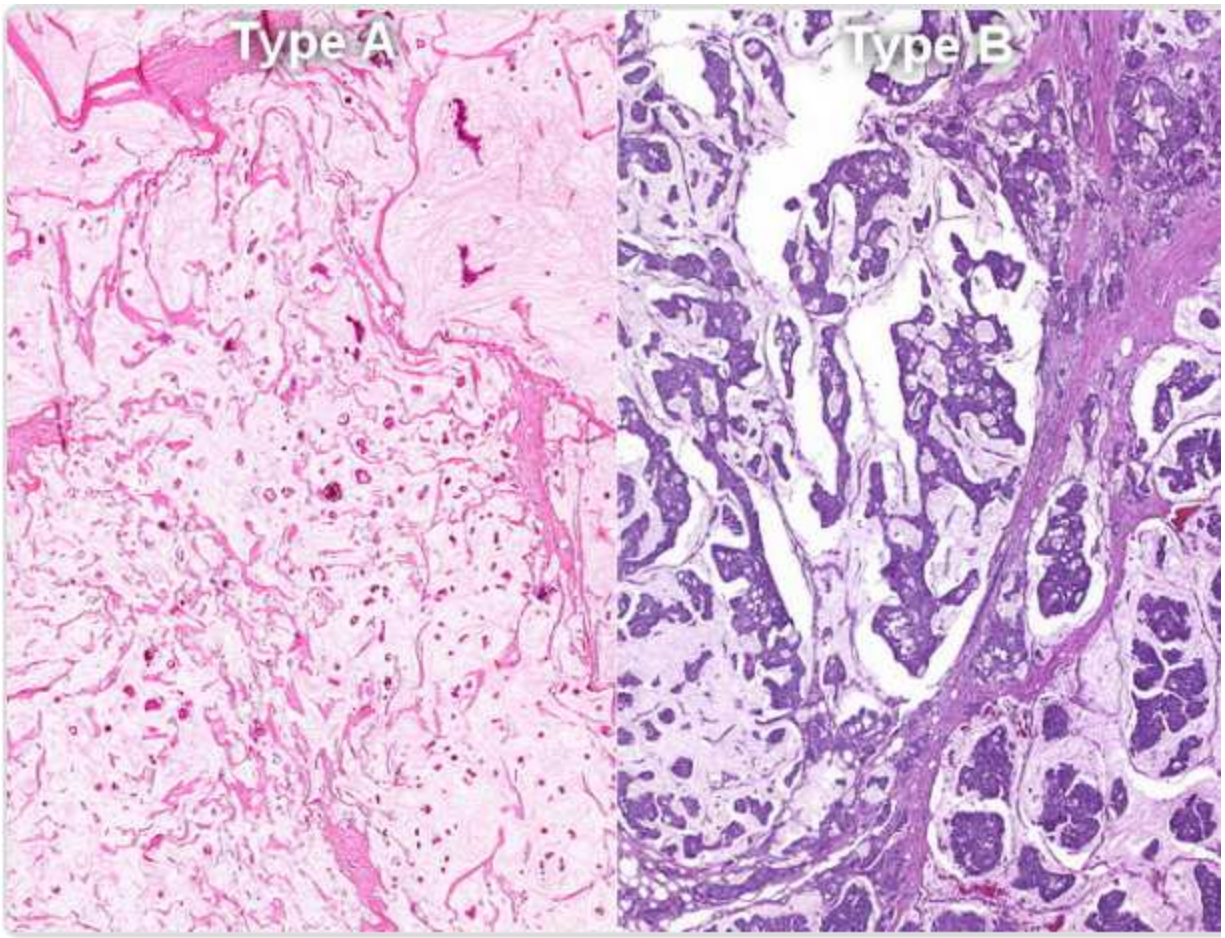
Medullary carcinoma shows a diffuse growth pattern with no glandular differentiation or intraductal component. The cells are arranged in broad sheets, nests, or anastomosing trabeculae. The cytoplasmic borders are indistinct creating a syncytial appearance. There is a prominent lympho-plasmacytic infiltrate within and around the tumor.

http://webpathology.com/image.asp?case=298&n=6
Accessed 02/20/2020

Mucinous (colloid) carcinoma

- Rubbery with the consistency and appearance of pale gray-blue gelatin.
- The borders are pushing or circumscribed.
- The tumor cells are arranged in clusters and small islands of cells within large lakes of mucin.
- MUC2 positive
- BRCA1 promoter is hypermethylated.
- Many cases express WT1.
- 25%-50% of cases show neuroendocrine differentiation

Mucinous (colloid) carcinoma



http://webpathology.com/image.asp?case=297&n=18
Accessed 02/20/2020

Type A mucinous carcinomas have more abundant extracellular mucin and are seen in younger patients.

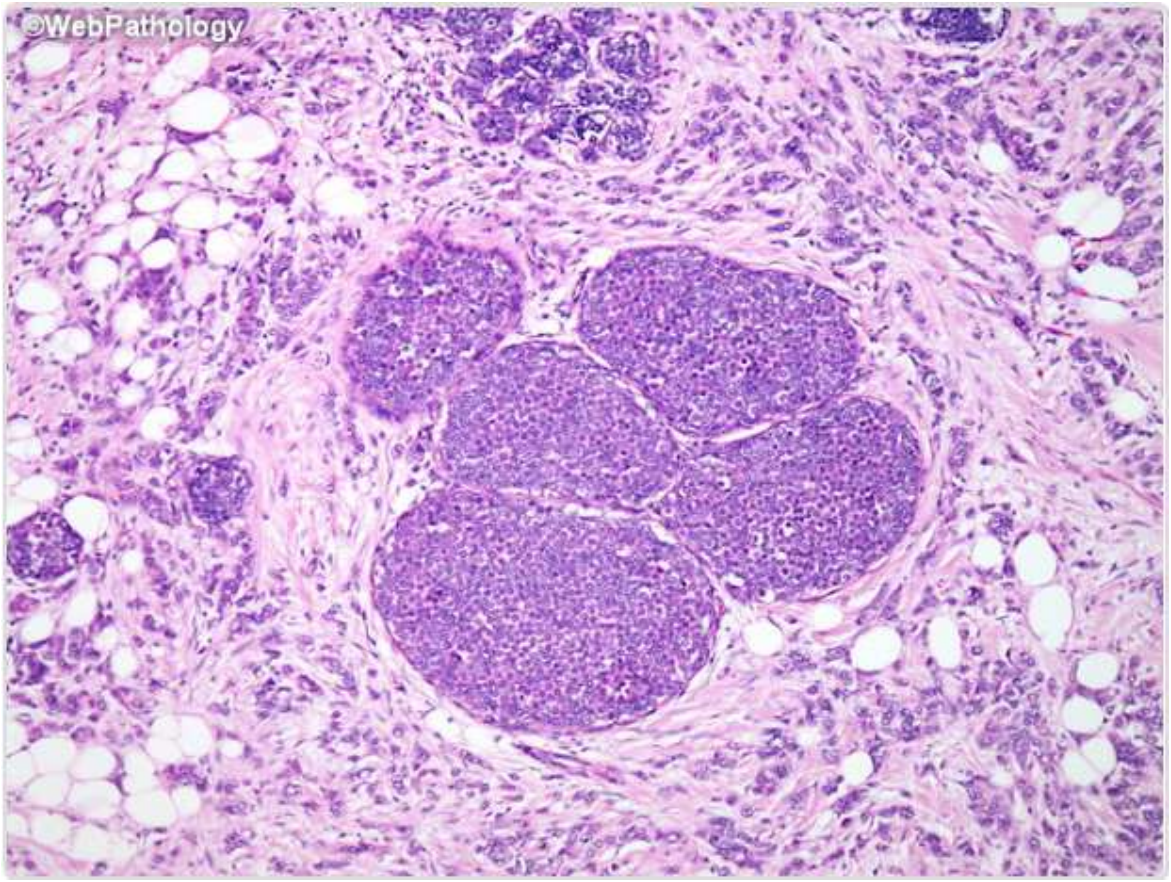
Type B tumors show neuroendocrine differentiation and have less abundant extracellular mucin than type A tumors.

Similar prognosis.

Invasive lobular carcinoma

- Biallelic loss of CDH1 (E-cadherin) gene
- Metastases involving the peritoneum and retroperitoneum, the leptomeninges ("carcinomatous meningitis"), the gastrointestinal tract, the ovaries and uterus as preferred sites.
- Men and women with a single germline mutation have increased risk of gastric signet ring adenocarinoma.

Invasive lobular carcinoma



Low power view of invasive lobular carcinoma. Slender strands and cords, no more than one to two cells across, are seen diffusely infiltrating breast tissue and fat. A few expanded lobules with lobular carcinoma-in-situ are also present. The top of the image shows a few uninvolved lobular units.

http://webpathology.com/image.asp?case=292&n=3
Accessed 02/20/2020

Metastasis

- Transport through lymphatics is the most common pathway for the initial dissemination of carcinomas.
- Tumors do not contain functional lymphatics, but lymphatic vessels located at the tumor margins are apparently sufficient for the lymphatic spread of tumor cells.
- The pattern of lymphatic spread follows the normal lymphatic drainage of the organ.

Metastasis

- To avoid the considerable surgical morbidity associated with dissection of a regional lymph node basin, biopsy of a sentinel node is often used to assess the presence or absence of metastatic lesions in the lymph nodes.
- A sentinel lymph node is defined as “the first node in a regional lymphatic basin that receives lymph flow from the primary tumor.”
- This is usually employed for staging in breast and colon cancers as well as melanoma.
- Dye or radioisotope is injected and the involved node is identified at surgery.

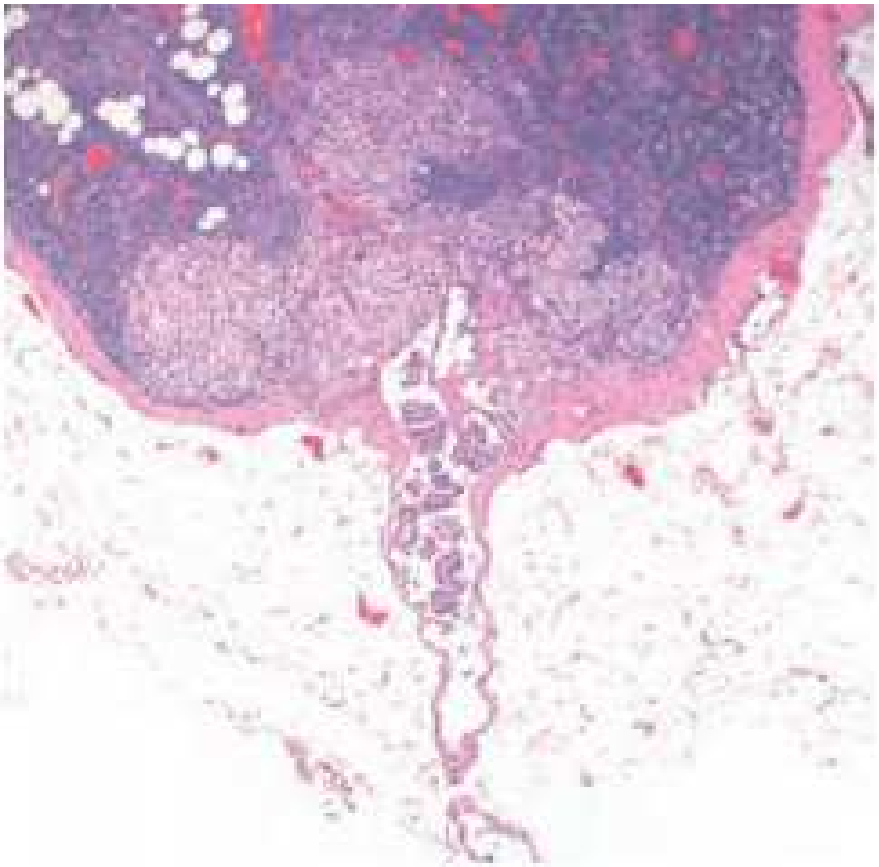
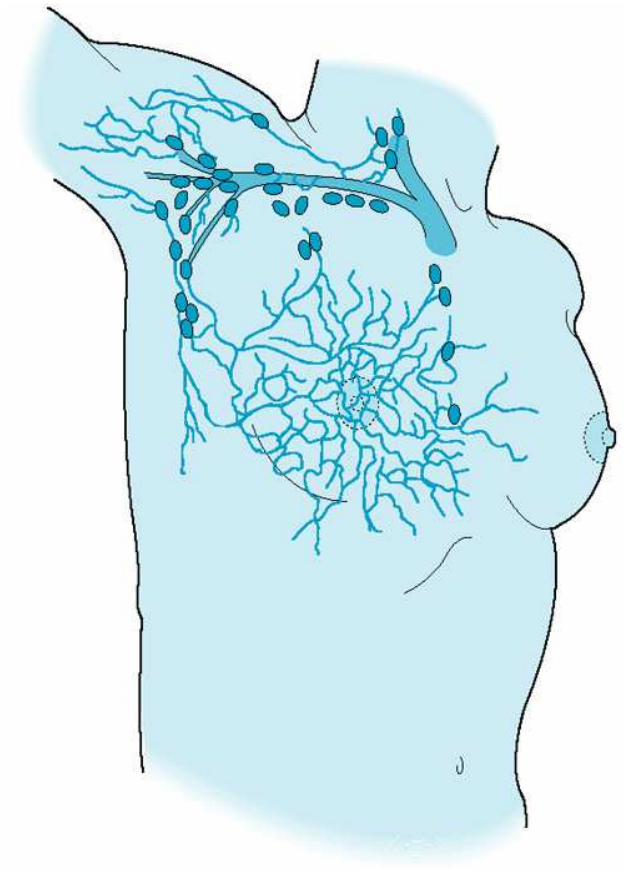


Figure 7-16 Axillary lymph node with metastatic breast carcinoma. Note the aggregates of tumor cells within the substance of the node and the dilated lymphatic channel. (Courtesy Dr. Susan Lester, Brigham and Women's Hospital, Boston, Mass.)

Metastasis

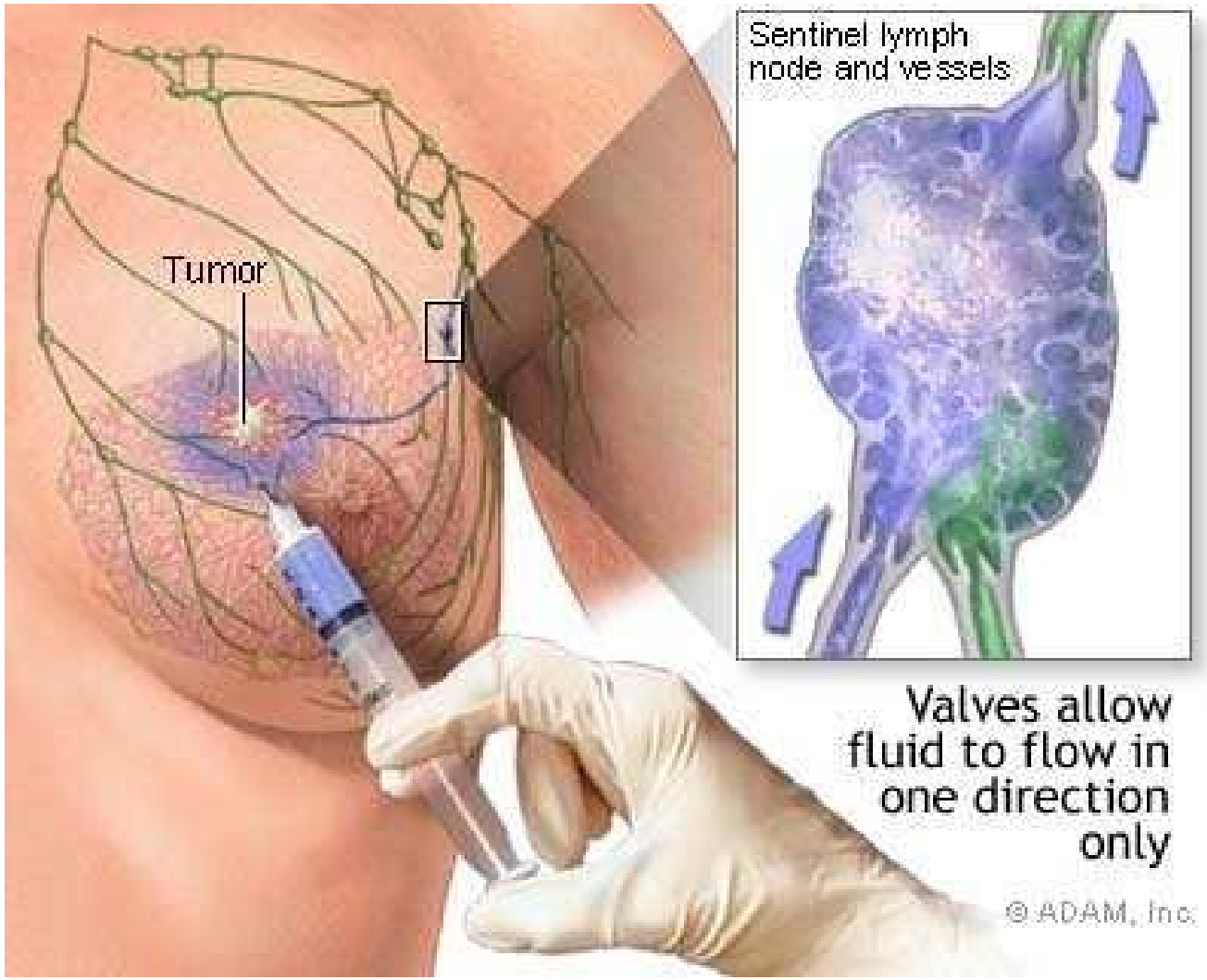
- Because carcinomas of the breast usually arise in the upper outer quadrants, they generally disseminate first to the axillary lymph nodes.
- Cancers of the inner quadrants drain to the nodes along the internal mammary arteries.
- Thereafter, the infraclavicular and supraclavicular nodes may become involved.
- SRC activation associated with bone metastases.

Lymphatic drainage of the breast



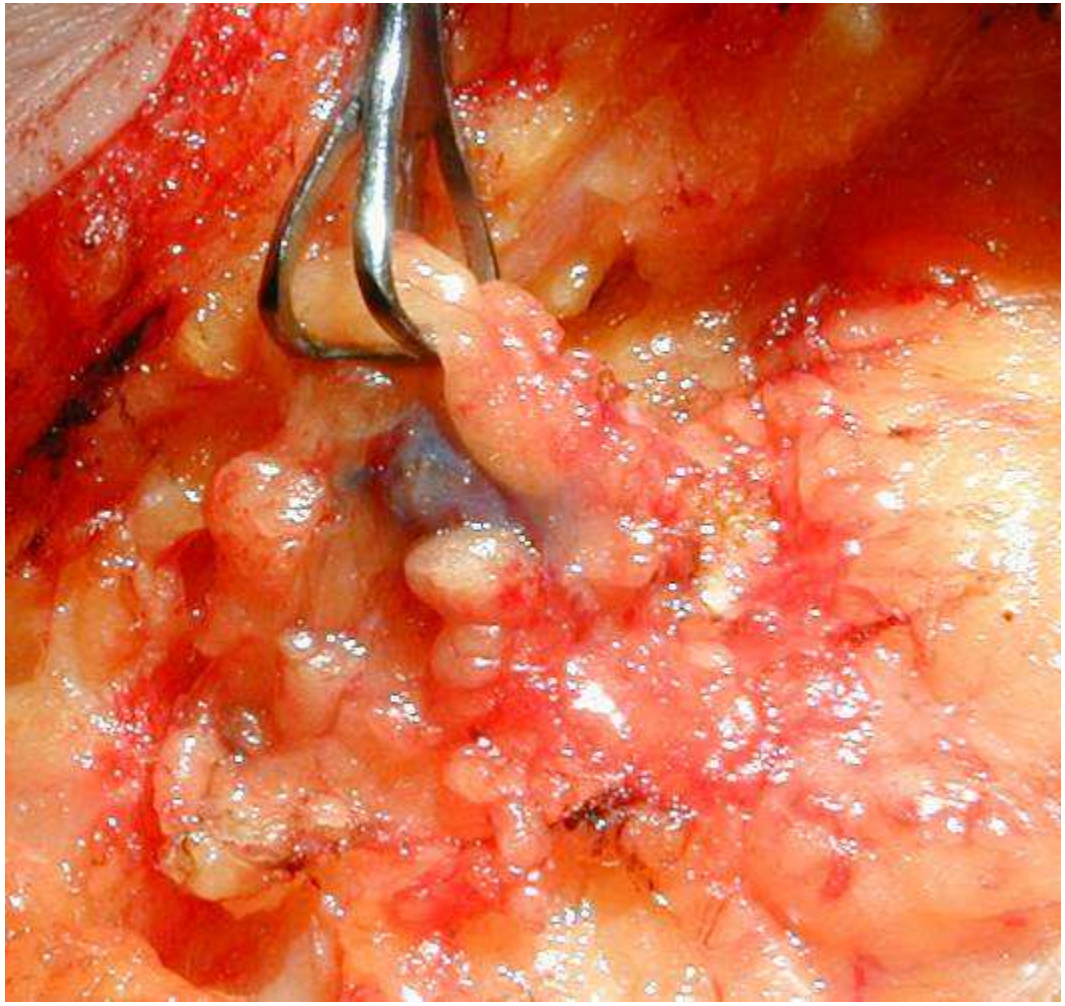
Principal drainage is to anterior axillary nodes. Some, to parasternal nodes; small amount, to abdominal nodes

Fig. 63-3 Accessed 08/01/2010



99m-Technetium is injected in the tumor and allowed to spread. Prior to surgery a blue dye is also injected. The sentinel node(s) are identified by radioactivity and blue color.

Sentinel node



Prognostic factors

- Axillary node status is the most important prognostic factor for invasive breast carcinoma in the absence of metastases. (0,1-3, >3)
- The size of the tumor is the second most important prognostic factor and is independent of node status. (<2,2-5,>5cm)
- Estrogen receptor status is a third important prognostic factor as is HER/2neu over-expression and tumor cell differentiation.
- Only high grade lesions have prognostic value.
- Locally advanced disease is associated with elevated rates of local recurrence after therapy.

Supraclavicular lymph node metastasis

- Isolated supraclavicular lymph node metastasis should not be treated as distant metastasis.
- Neck dissection to remove nodes and soft tissue in levels III-V may be undertaken.
- 5, 10 year survivals for local relapse: 39%, 26%
- 5, 10 year survivals for supraclavicular lymph node metastasis post neck dissection: 31%, 16%
- If no neck dissection: 15%, 5%
- 5, 10 year survivals following distant metastasis: 14%, 7%

2018 AJCC Staging

Stage (Seventh Edition)	Risk Profile	No. of Patients	5-Year DSS (%)	95% CI (%)	5-Year OS (%)	95% CI (%)
I (IA and IB)	0	36	100		97.0	80.4–99.6
	1	1,173	99.4	98.7–99.7	96.7	95.4–97.0
	2	274	98.8	96.4–99.6	94.6	91.0–96.8
	3	119	96.6	91.1–98.7	93.8	87.5–97.0
IIA	0	31	100		96.8	79.2–99.5
	1	634	99.4	97.5–99.8	97.1	94.7–98.4
	2	236	97.5	93.2–99.1	94.1	88.7–97.0
	3	98	91.0	81.8–95.7	88.2	78.5–93.8
IIB	0	11	100		100	
	1	309	96.9	92.6–98.8	94.6	89.6–97.2
	2	107	92.9	83.6–97.1	89.3	80.1–94.4
	3	40	91.5	75.6–97.2	91.5	75.6–97.2
IIIA	0	3	100		100	
	1	134	98.3	88.2–99.8	91.5	82.6–96.0
	2	50	92.2	77.2–97.5	90.3	75.7–96.3
	3	7	68.6	21.3–91.2	68.6	21.3–91.2
IIIC	0	0				
	1	39	92.2	72.1–98.0	84.4	63.7–93.9
	2	16	80.8	51.4–93.4	80.8	51.4–93.4
	3	10	33.3	6.3–64.6	33.3	6.3–64.6

Abbreviations: DSS, disease-specific survival; OS, overall survival.

Stromal tumors

- Fibroadenomas are well-circumscribed, rubbery, grayish white nodules that bulge above the surrounding tissue and often contain slitlike spaces.
- The delicate and often myxoid stroma resembles normal intralobular stroma. The epithelium may be surrounded by stroma (pericanicular pattern) or compressed and distorted by it (intracanicular pattern)
- In older women, the stroma typically becomes densely hyalinized and the epithelium atrophic.

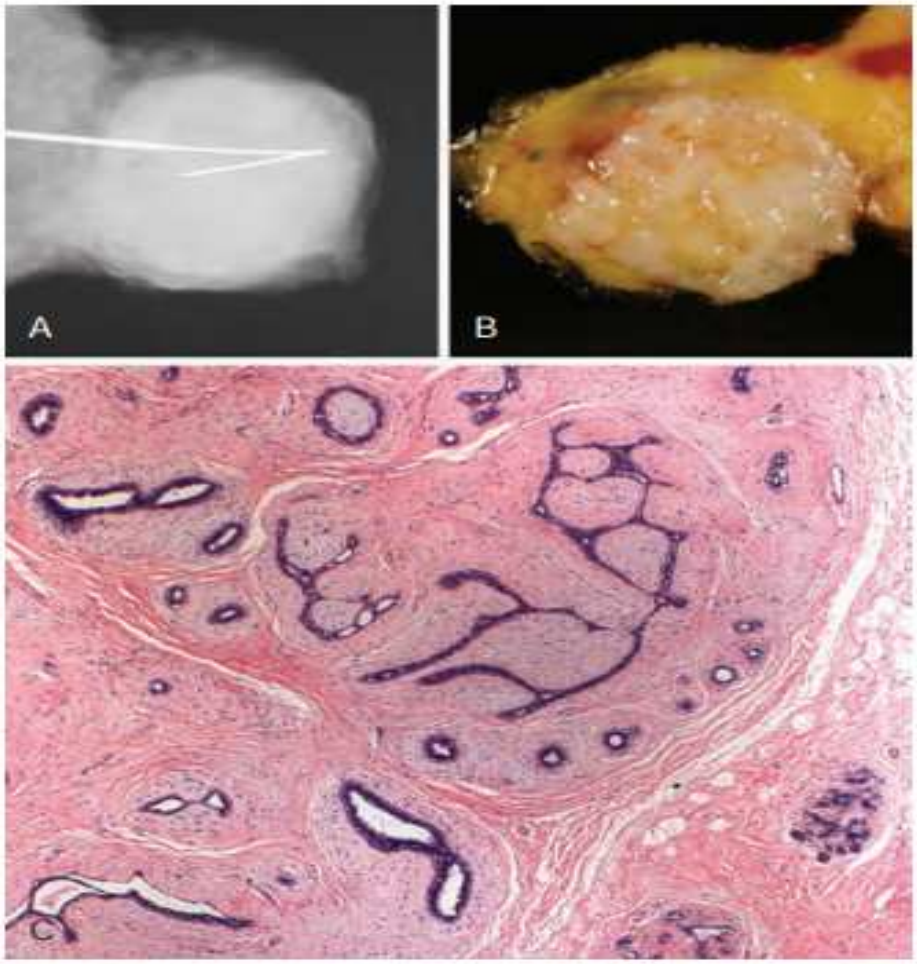
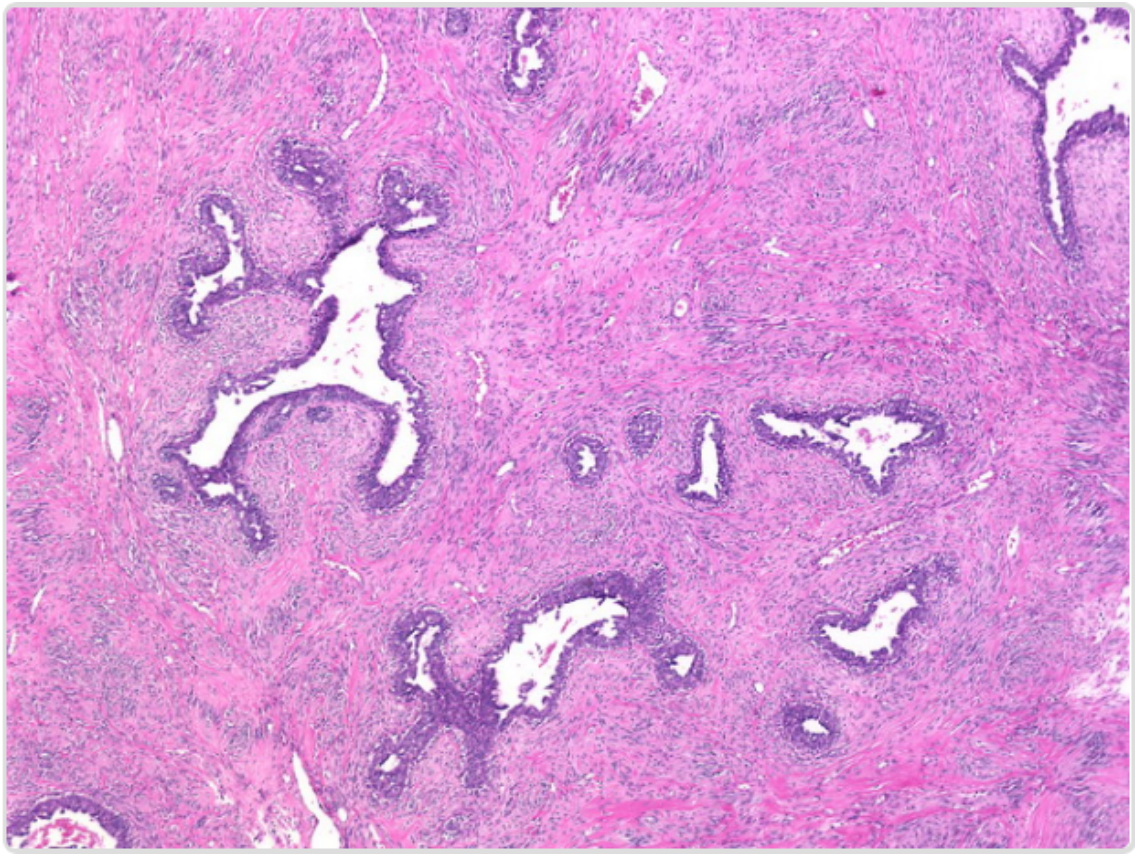


Figure 23-27 Fibroadenoma. **A,** The radiograph shows a characteristically well-circumscribed mass. **B,** Grossly, a rubbery, white, well-circumscribed mass is clearly demarcated from the surrounding yellow adipose tissue. The absence of adipose tissue accounts for the radiodensity of the lesion. **C,** The proliferation of intralobular stroma surrounds, pushes, and distorts the associated epithelium. The border is sharply delimited from the surrounding tissue.

Juvenile fibroadenoma



Large, Hypercellular mass that generally occurs in young adolescents.
The lesion occurs more often in those of sub-Saharan origin and may be bilateral.

http://webpathology.com/image.asp?n=10&Case=276
Accessed 02/20/2020

Phylloides tumor

- Arise from intralobular stroma
- Average age 45 years
- 20-30 years in Asians
- The majority are detected as palpable masses.
- Stromal neoplasm that induces gland formation.
- Underlying cause is unknown.
- Separated into low grade or high grade neoplasms.
- 10% are malignant.

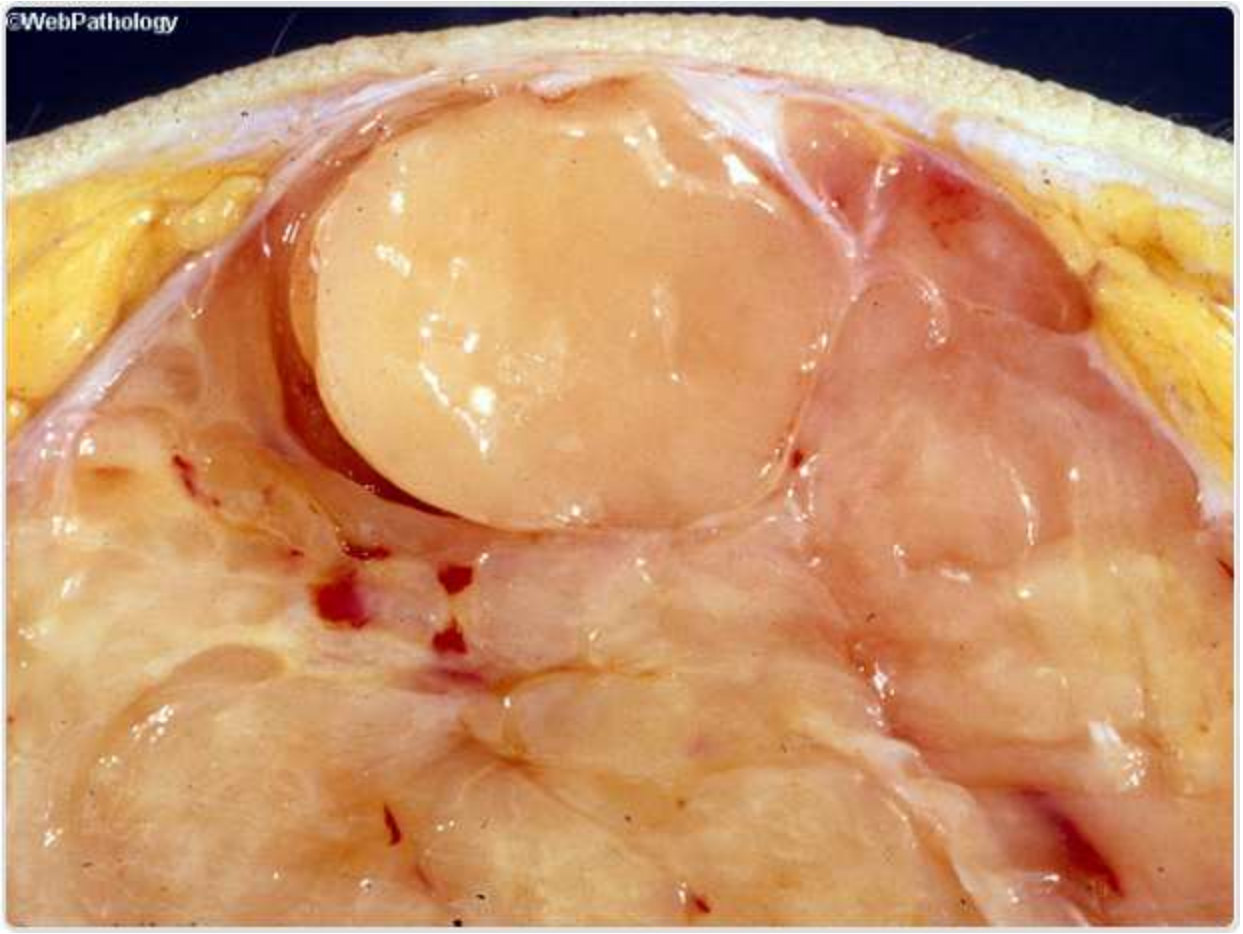
Phylloides tumor

- The tumors vary in size from a few centimeters to massive lesions involving the entire breast.
- The larger lesions often have bulbous leaf-like protrusions due to the presence of nodules of proliferating stroma covered by epithelium.
- In some tumors these protrusions extend into a cystic space.
- Cellular, with nuclear pleomorphism, mitotic activitym, stromal overgrowth, and infiltrative borders characterize the tumor.

Phylloides tumor

- Cellular stroma distinguishes phylloides tumor from fibroadenoma.
- May see sarcomatous development in high-grade lesions.
- MED12 mutation at Xq13.1 as in fibroadenoma
- CDK8 in preinitiation complex that functions in protein assembly
- TERT mutations at 5p13.3
- Rate limiting step in production of active telomerase
- Resection with 1cm margins adequate therapy

Phylloides tumor



The cut surface is pink-tan and shows several cleft-like spaces. Foci of necrosis, hemorrhage, or cystic degeneration may also be seen.

http://webpathology.com/image.asp?case=311&n=2
Accessed 02/20/2020

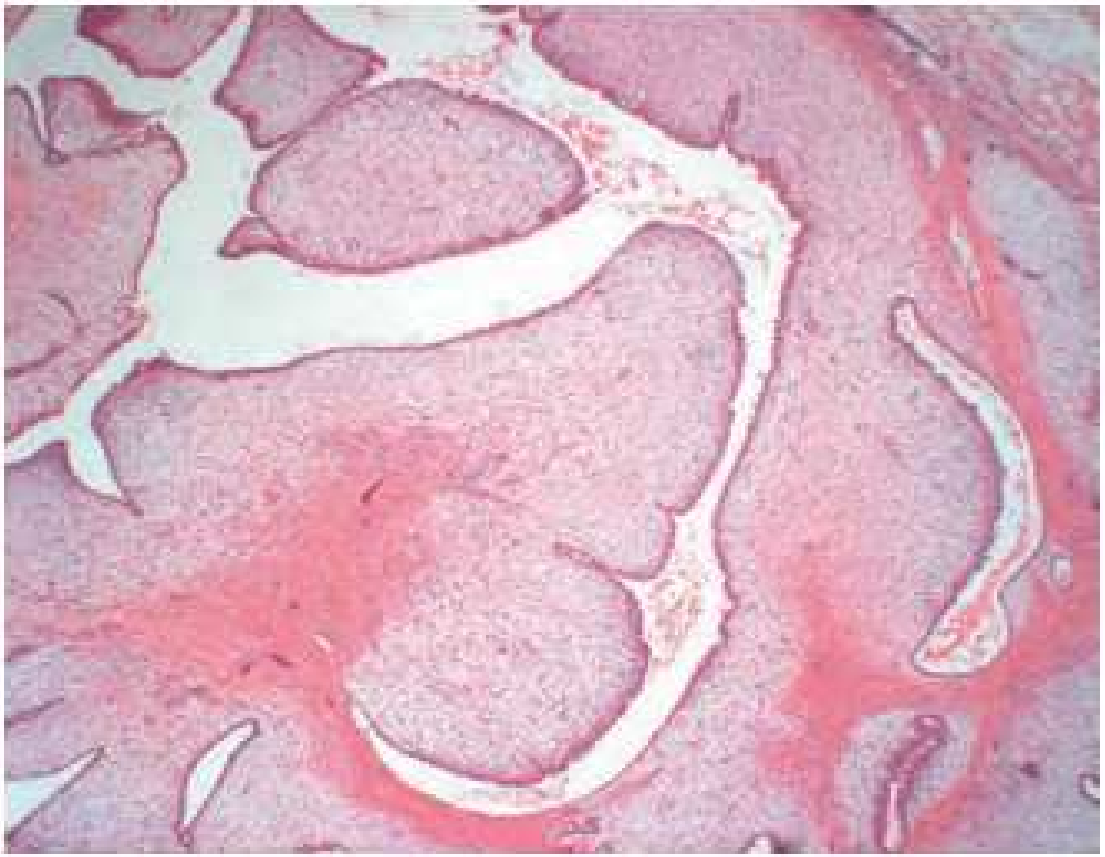


Figure 23-28 Phyllodes tumor. Compared to a fibroadenoma, there is increased stromal cellularity and overgrowth, giving rise to the typical leaflike architecture.

Malignant stromal tumors

- Desmoid (Fibromatosis)
- Microscopic:
- Long intersecting fascicles composed of bland spindle cells with indistinct borders
- Hyperchromatic nuclei with occasional nucleoli and eosinophilic cytoplasm
- Cells infiltrate normal ducts and lobules, adipose tissue and skeletal muscle
- 61% CTTNB1 mutation at 3p22.1
- β-catenin/WNT signaling

Malignant stromal tumors

- Associated with familial adenomatous polyposis
- Resection with excision to negative margins
- Sorafenib if CTTNB1 mutation
- Radiation therapy not useful if resected

Malignant stromal tumors

- Angiosarcoma
- Median age <40 years of age if primary
- >64 years of age if secondary
- 9-16 years post radiotherapy
- May follow lymphedema
- PI3KCA mutations
- Treat with mastectomy (and all irradiated skin, if secondary)
- High grade lesions, remove underlying wall as well
- Short responses to use of paclitaxel
- Median survival <6 years

Malignant stromal tumors

- Microscopic:
- Anastomosing, branching, often dilated vascular channels lined by atypical endothelial cells with plump, hyperchromatic nuclei
- Mitoses and tufting of endothelial cells reflects extent of dedifferentiation
- Key distinguishing feature from benign vascular lesions is an infiltrative growth pattern

Male breast cancer

- Uncommon
- Carcinomas usually present as a palpable subareolar mass, 2-3 cm in size or with a nipple discharge.
- 60-70 years of age
- 3-8% of cases are associated with Klinefelter syndrome and decreased testicular function. .
- 81% ER-positive
- 4-14% of cases are attributed to germline BRCA2 mutations.
- There is a 60% to 76% chance of a BRCA2 mutation in families with at least one affected male.

Therapeutic considerations

- Inflammatory carcinoma is by definition Stage IIIB when first diagnosed.
- Inflammatory carcinoma is treated with chemotherapy before mastectomy.
- The skin is not conserved at mastectomy as it often harbors residual disease.
- Sentinel node examination in the axilla offers little prognostic information.
- 30% present with de novo Stage IV disease.

Therapeutic considerations

- Mastectomy involves the removal of breast tissue (into the tail of the axilla).
- The pectoralis major muscle is removed frequently in the presence of tumors that extend deep to the fascia.
- Nipple preserving surgery is possible with small tumors. An inframammary incision is preferred for cosmesis.
- Post-operative radiation reduces local recurrence rates from 4% to 1% following mastectomy.

Arteries and veins of the breast

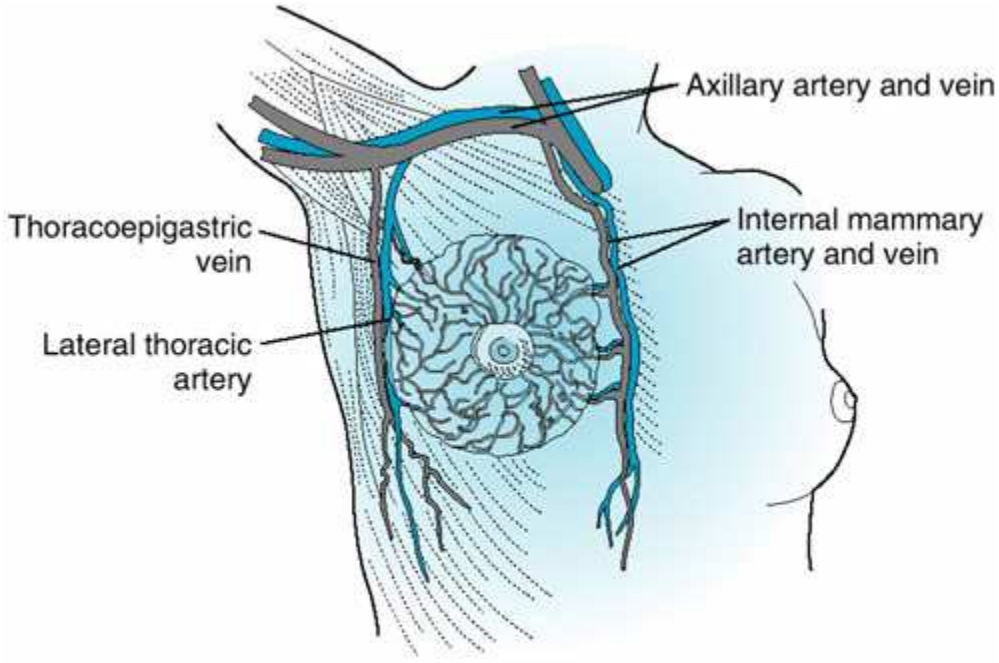


Fig. 63-2 Accessed 08/01/2010

Therapeutic considerations

- Tumors <1.0cm may be treated by quadrant excision alone. Larger tumors will benefit from post-operative radiotherapy. Both approaches will leave cosmetic defects.
- Mastectomy and sentinel node biopsy (to guide axillary exploration for prognostic reasons) remains the mainstay of all treatment approaches.
- Ultrasound detection of supraclavicular, infraclavicular, or intermammary nodes may change staging and influence later radiation therapy fields.

Therapeutic considerations

- There is a 6% to 8% increased risk of mortality for each 4-week delay in time to surgery
- Surgical management within 21 days of completion of neoadjuvant therapy had better overall survival and relapse-free survival.
- A surgery date within 6 weeks of chemotherapy completion may improve recurrence-free survival and disease-specific survival

Therapeutic considerations

- There is a consensus that 26 Gy in five fractions over 1 week is the standard of care in whole-breast irradiation, chest wall irradiation, and partial breast irradiation.
- Prophylactic mastectomy of the “uninvolved” breast is a viable treatment option particularly if lobular carcinoma (25% risk of developing a second cancer over the succeeding 10 years) or the breast is difficult to follow closely with imaging studies.

Therapeutic considerations

- Differentially expressed genes as drivers are noted depending upon European or African ancestry
- Genomic sequencing determines chemotherapy.
- Genomic changes associated with low probability of tumor progression are more important than clinical determination of high risk.
- Such subset of patients will not require chemotherapy
- Estrogen suppression is important in the pre-menopausal patient

Therapeutic considerations

- Patients with low-risk biologic features (e.g., favorable pathology, low score on genomic profile, strong hormone receptor expression, low grade, lobular disease, and luminal A subtype [HER2 negative, low Ki-67]) are considered likely to experience limited benefit from neoadjuvant chemotherapy.
- Neoadjuvant chemotherapy likely to benefit those with high-risk features (e.g., unfavorable pathology, high score on genomic profile, weak HR expression [estrogen receptor < 20%], high grade, and premenopausal)

Therapeutic considerations

- Patients with Ki67>105 benefit by chemotherapy
- Inflammatory carcinoma is by definition Stage IIIA.
- Inflammatory carcinoma is treated with chemotherapy before mastectomy.
- The skin is not conserved at mastectomy as it often harbors residual disease.
- Sentinel node examination in the axilla offers little prognostic information.
- 30% present with de novo Stage IV disease.
- They do not benefit from surgery or radiation

Early Breast Cancer Trialists Collaborative Group:

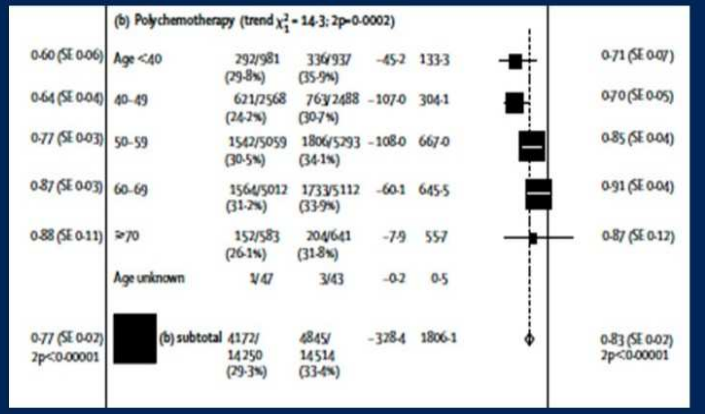
Greater treatment effect of adjuvant chemotherapy with younger age

"…polychemotherapy (eg, with FAC or FEC) reduces the annual breast cancer death rate ….

… by about 38% (SE 5) for women younger than 50 years of age and …

… by about 20% (SE 4) for those of age 50–69 years …

…largely irrespective of the use of tamoxifen and of … (ER) status, nodal status, or other tumour characteristics."



Breast cancer mortality at 15 years

EBCTCG. Lancet. 2005 May 14-20;365(9472):1687-717

Table 1

Summary of the breast tumor molecular subtypes

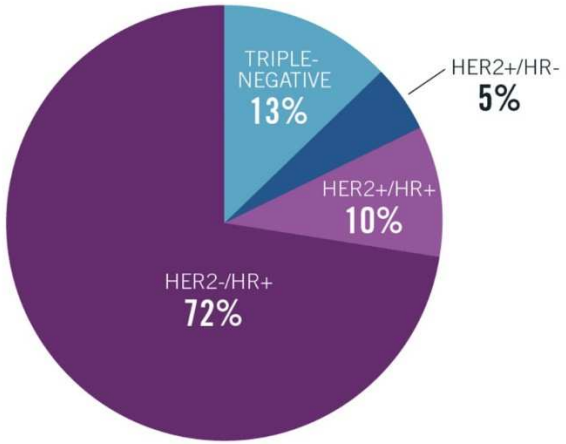
Intrinsic subtype	IHC status	Grade	Outcome	Prevalence[Δ]
Luminal A[*]	[ER+|PR+] HER2-KI67-	1|2	Good	23.7% [p1] [10]
Luminal B[*]	[ER+|PR+] HER2-KI67+	2|3	Intermediate	38.8% [p1] [10]
	[ER+|PR+] HER2+KI67+		|Poor	14% [p1] [10]
HER2 over-expression[*]	[ER-PR-] HER2+	2|3	Poor	11.2% [p1] [10]
Basal[*]	[ER-PR-] HER2-, basal marker+	3	Poor	12.3% [p1] [10]
Normal-like	[ER+|PR+] HER2-KI67-	1|2|3	Intermediate	7.8% [p2] [15]

[*]Subtypes with detailed expression patterns and clinical implications discussed in the text, which take the majority of the breast tumor cases and are most commonly referred to.

[Δ]The prevalence of each subtype is taken from the publication indicated in the square bracket.

Dai, X, Bai, Z, Yang, Y, Liu, X, Zhan, J, Shi, B, “Breast cancer intrinsic subtype classification, clinical use and future trends.” Am J Cancer Res 2015; 5(10): 2929-2943.
Accessed 02/20/2020

Distribution of Breast Cancer Subtypes in the US



[3]

American Cancer Society 2020

Therapeutic considerations

- HER2/neu-, ER+, high PR, low Ki67 tumors respond best to hormone therapy (luminal type A tumors) and may not require chemotherapy.
- Low risk tumors do not benefit from radiotherapy.
- Taxanes of use in HER2/neu-, ER+, high Ki67 expressing tumors (luminal type B tumors, usually with PI3KCA mutation).
- However, low or negative PR luminal B type tumors do not respond well to taxanes regardless of high or low Ki67.
- Ribociclib plus anti-estrogens as effective as chemotherapy in HER2/neu-, ER+ cancers

Therapeutic considerations

- HER2/neu+ tumors do not respond well to anthracyclines.
- ER-, HER2/neu+ tumors are the group most responsive to anti-EGFR antibodies.
- HER2/neu+ tumors respond best to docetaxel (taxane) plus a combination of anti-EFGR antibodies (trastuzumab and pertuzumab).
- For patients with unresectable disease or metastatic disease, the combination of tucatinib (HER2-TKI) with transtuzumab and capcetabine

Therapeutic considerations

- Trastuzumab enamestine successful for lapatinib-capcetabine failures in HER2/neu+ cancers.
- PI3KCA mutations associated with poor response to trastuzumab.
- ER- tumors likely sensitive to cisplatin.
- Drugs that inhibit CYP2D6 are associated with increased cancer recurrence risk.
- The addition of anti-EGFR drugs is beneficial only if EFGR over-expression is noted.

Therapeutic considerations

- Paclitaxel with gemcitabine maintenance chemotherapy for high risk premenopausal women with visceral metastases.
- Continue if respond;
- Else the regimen is not as effective as weekly paclitaxel in patients with visceral metastases.
- Anti-angiogenic drugs in combination with chemotherapy do not appear to confer survival benefit.
- Bleeding and hypertension are the major complications.

Therapeutic considerations

- Valaparib is the only poly(ADP-ribose) polymerase (PARP) inhibitor that has demonstrated efficacy in basal-like cancer.
- What is not yet clear is if it is effective only if a BRCA mutation is present.

Therapeutic considerations

- Chemotherapy is the only option for ER/PR-, HER/2neu- tumors (triple negative or basal-like tumors)
- MAPK activated.
- Anthracycline and taxane based therapy
- Substitution of anthracycline with platinum (effective in BRCA1 mutation) associated with excessive toxicity
- Capecitabine preferred if no previous adjuvant regime
- 78% of tumors that persist post-chemotherapy show epithelial to mesenchymal transition

Therapeutic considerations

- Sacituzumab govitecan if failed previous regimens
- Antibody drug combination attaches to TROP2 protein and releases topoisomerase inhibitor

Therapeutic considerations

- If KRAS mutation, irinotecan may be effective;
- mTOR inhibitors are not
- But effect may be reversed with zoledronic acid
- If BRAF mutation, MEK and AKT inhibitors may be effective.
- If NFI, PTEN mutations, a PI3K inhibitor may be effective.
- No benefit of PD-1 check point inhibitor in triple negative breast cancer

Therapeutic considerations

- CHEK 4/6 inhibition clears ESR1 (ERα) mutation within first month of treatment; restores sensitivity to anti-estrogen therapy.
- Employed in HR+, HER2- tumors with fulvestrant
- Tuatinib, trastuzumab, and capcetbine effective treatment for brain metastases
- HR+, 14% will have brain metastases
- TNBC, 40%
- HER2+, 50% will have brain metastases
- Breast is second to lung for metastasizing to brain
- The presence of p16 is associated with senescence; these patients age faster

Hormone modulation

- Tamoxifen is an anti-estrogen.
- Selective estrogen receptor modulators as well as tamoxifen compete for uptake with estrogen.
- Bind to both ERα and ERβ receptors.
- Conformation of ligand binding determines which co-repressors and co-activators are recruited.
- ERα is degraded; TGF-β is upregulated.
- Resistance develops through cross-talk with epithelial growth factor pathways.
- ESRα (ESR1) expressed in rapidly growing tumors

Hormone modulation

- Selective estrogen receptor modulators (SERM) also promote T_{H2}, inhibit dendritic cell activation and maturation, block B cell maturation.
- Tamoxifen as drug of choice in pre-menopausal patients as aromatase inhibitors may lead to increased ovarian production of estrogen.
- Raloxifene is a selective estrogen modulator.
- Toremifine is a nonsteroidal anti-estrogen
- Anastrazole more effective than SERMs in limiting cancer development in high risk post-menopausal patients.

Hormone modulation

- Anastrazole and letrozle are non-steroidal estrogen antagonists that bind to the heme groups of CYP19, blocking aromatase activity.
- Both diminish CD24+CD25+ T_{reg} cells, and sensitize cells to ADCC.
- Neither affects plasma lipid levels.
- Arthralgias a common complaint.
- Managed with exercise.
- Minimal increase in the probability of developing osteoporosis.

Hormone modulation

- Exemestane is a steroidal estrogen antagonist that irreversibly inactivates aromatase, blocking estrogen peripheral action.
- No effect on cognition.
- Reduces risk of invasive breast cancer in high-risk postmenopausal women.
- No cross-talk.
- Greater risk of osteoporosis than with tamoxifen.
- Better clinical outcomes, however.

Hormone modulation

- Fulvestrant antagonizes estrogen receptor.
- Fulvestrant binding configuration prevents ER dimer formation.
- ESR1 (Erα) is not degraded.
- Cross-talk is not a problem.
- Useful in tamoxifen and aromatase inhibitor failures as well as first-line therapy.

- Tamoxifen preferred in low risk patients
- Goserlin (gonadotropin inhibitor) preferred in high risk patients

Hormone use

- In postmenopausal patients, if de novo use or if there has been more than one year free of disease post tamoxifen therapy,
- Employ (in order of preference) anastrazole, letrozole, fulvestrant (500mg, and in high-risk patients), or exemestane.
- If recurrence on tamoxifen,
- Employ (in order of preference) anastrazole, letrozole, or fulvestrant.

Hormone use

- If there has been more than one year free of disease post aromatase inhibitor therapy,
- Employ (in order of preference) fulvestrant (500mg), exemestane, or tamoxifen.
- If recurrence or progression on aromatase inhibitor, fulvestrant is hormone of choice.
- If premenopausal, LHRH agonist and fulvestrant is preferred combination.

Other agents

- Responsiveness to hormones restored with eninostat (an HDAC inhibitor) or everolimus (mTOR inhibitor) plus exmestane.
- Proton pump inhibitors modulate PgP, leading to higher intracellular concentrations of doxorubicin, for example; also prevent breakdown of 5FU
- Cabozantinib (tyrosine kinase inhibitor) inhibits MET, VEGFR2, RET, and KIT.
- Slows tumor growth and is associated with elimination of bone metastases.

Biphosphonates

- The principal molecular target for biphosphonates is farnesyl pyrophosphate synthetase and geranugeranyl pyrophosphate synthetase downstream in the mevalonate pathway
- Important in the synthesis of cholesterol as well as the proteins needed for protein prenylation (G proteins such as RAS).
- Compete with RBMS, a protein binding protein that upregulates Type I collagen as well as COLIA, both important in bone metastases.

Biphosphonates

- Biphosphonates inhibit osteoclast mediated bone resorption (independently of estrogen status) and reduce risk of bone metastases.
- Those with bone metastases are 5.8 times more likely to have osteonecrosis of the jaw while receiving monthly zoledronic acid (presenting with mouth ulcer, bleeding, tooth mobility).

Anticoagulation

- Elevated risk of venous thromboembolism in patients with metastatic cancer or while undergoing therapy
- 4% will have recurrent venous thromboembolism
- LMWH anticoagulation while undergoing therapy
- Risk of venous thromboembolism diminishes as cancer treated

Pregnancy

- Mammography is not a good screening tool as the increased density of breast may lower the sensitivity of mammography.
- Fetal radiation exposure is 0.4mrad.
- Ultrasonography poses no radiation risk to the fetus as well as differentiates cystic and solid breast lesions and their vascular patterns.
- Fetal malformations associated with 5 rad cumulative exposure.
- Gadolinium contrast (MRI) associated with fetal abnormalities.

Pregnancy

- Chemotherapy is avoided in the first 12 weeks of gestation.
- Fetal malformation rate with anthracycline chemotherapy in 2nd or 3rd trimester is not higher than that reported in the general population.
- Chemotherapy withheld two weeks before planned delivery to avoid hematologic nadir.
- Taxanes are employed if tumor progression is noted with anthracycline therapy.
- Drug metabolism may be a problem as the P450 system is highly upregulated in pregnancy.

Pregnancy

- Trastuzumab and the anti-estrogens are contraindicated in pregnancy because of the high rate of fetal malformations associated with their use.
- The fetal kidney expresses HER2/neu. Oligohydramnios results.
- Methotrexate is contraindicated in pregnancy as it is a known abortifacient.

Pregnancy

- Chemotherapy radically diminishes milk production.
- Further, chemotherapy agents have been shown to be excreted into breast milk.
- Formula feeding is recommended in women concomitantly receiving chemotherapy.