

The Pathology of the BREAST

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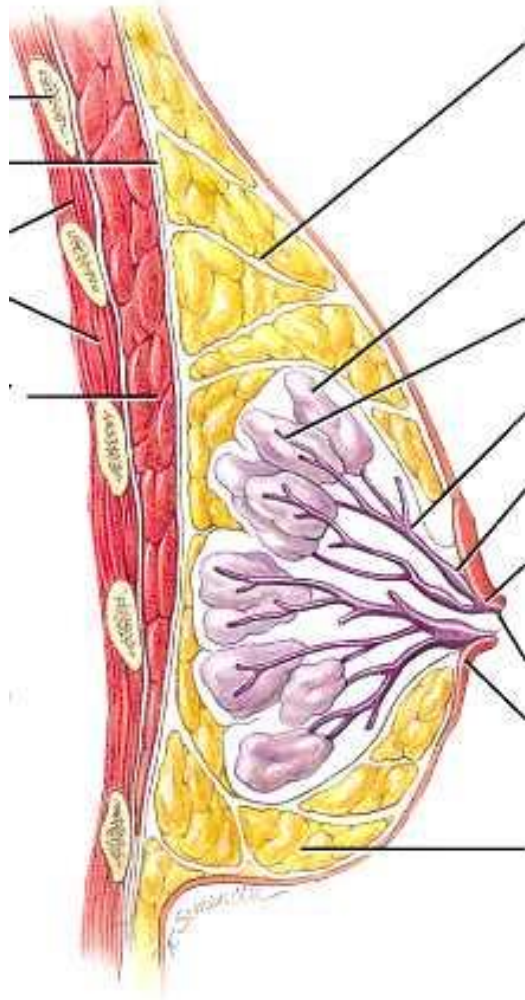
M.B.,B.CH.,

Egyptian board of pathology (Cairo university)

Palestinian board of pathology

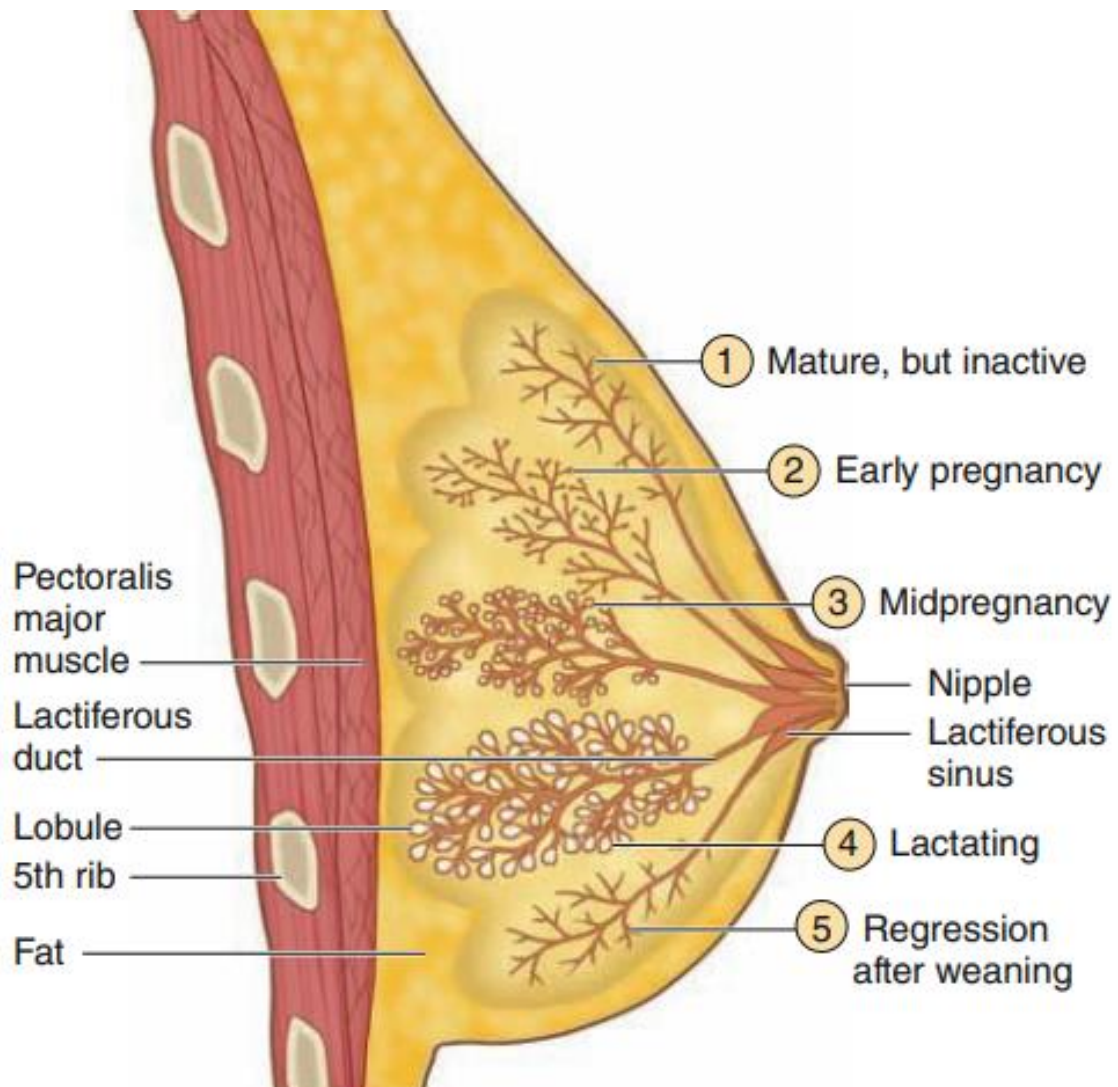
Anatomy & Physiology

- The areolar tissue: melanin, smooth muscle, elastic fibers.
- Montgomery's areolar sebaceous glands (prevent chapping) undergo hyperplasia during pregnancy; they are the little bumps.
- The breast contains about 20 lobes.
- Each lobe is drained by a lactiferous duct.
- Elastic fibers surround the lactiferous ducts and their branches.
- The lactiferous duct widens to become the lactiferous sinus underneath the nipple.

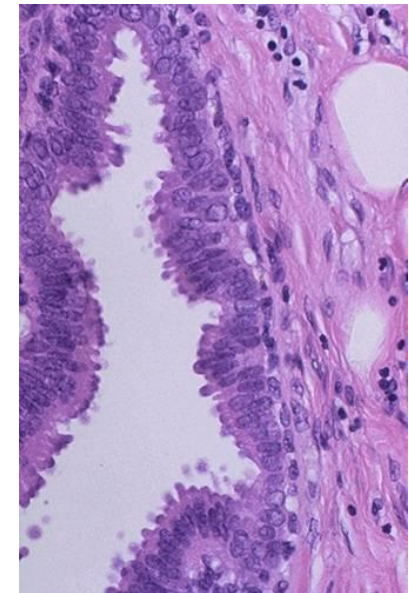
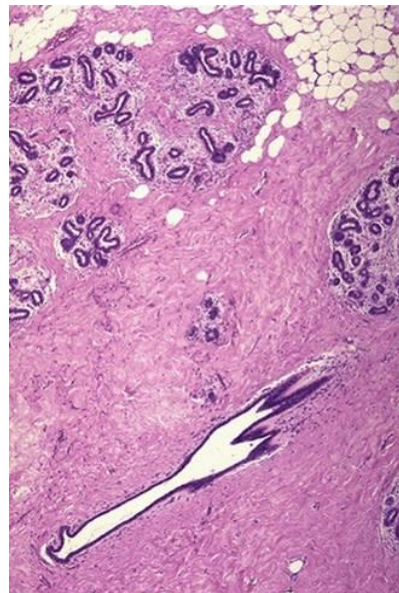
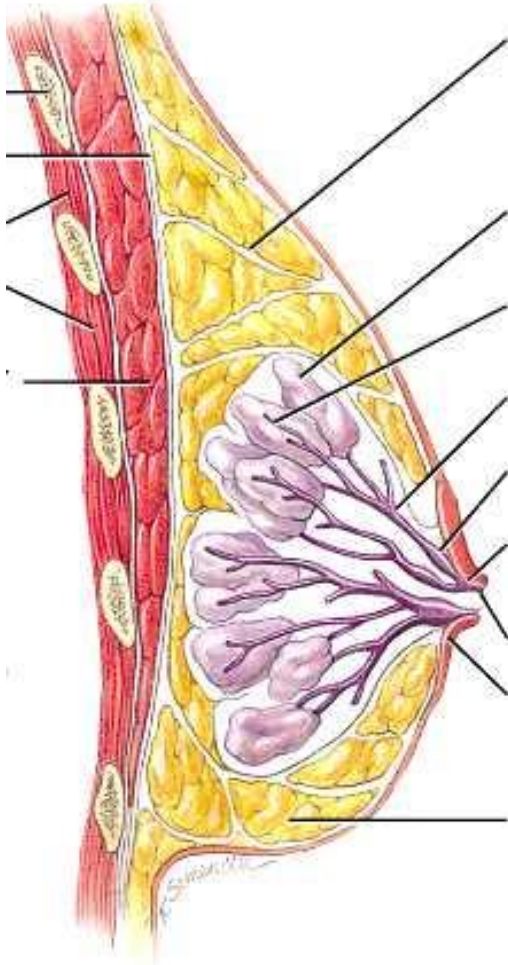


One collecting duct and its terminal ductules, plus the accompanying acinus and stroma, is called a "lobule".
Lobules → lobes.

The breast contains about 20 lobes arranged like the sections of a half-orange cut along its equator.

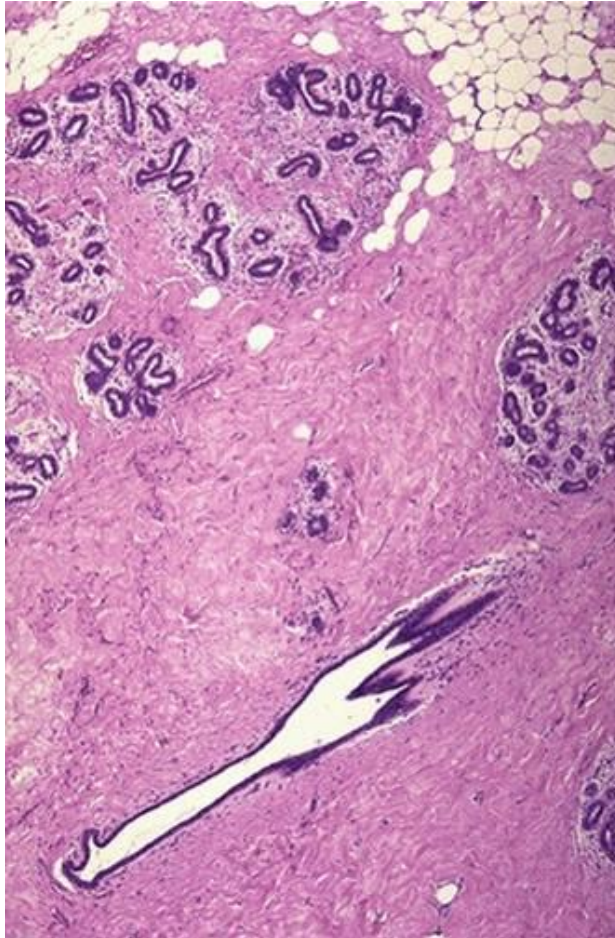


Normal Breast tissue

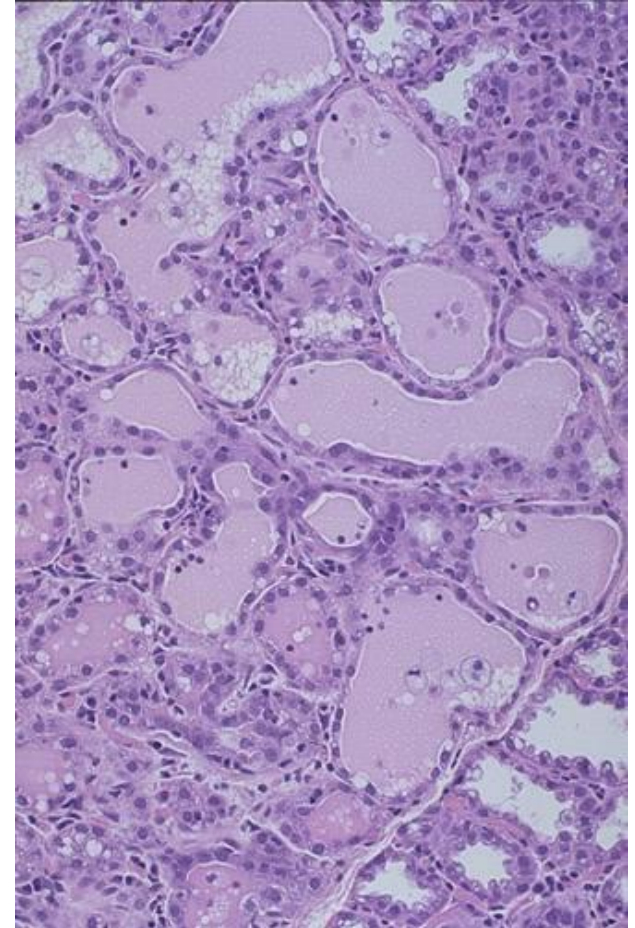


- The stroma between the lobes is fibrofatty.
- As a woman gets older, there is usually more fat relative to stroma in the breast.
- During pregnancy, true secretory units sprout from each terminal duct, coming to dominate the breast histology.
- After delivery, milk production (lactation) begins.

Lactation



Before lactation



During lactation

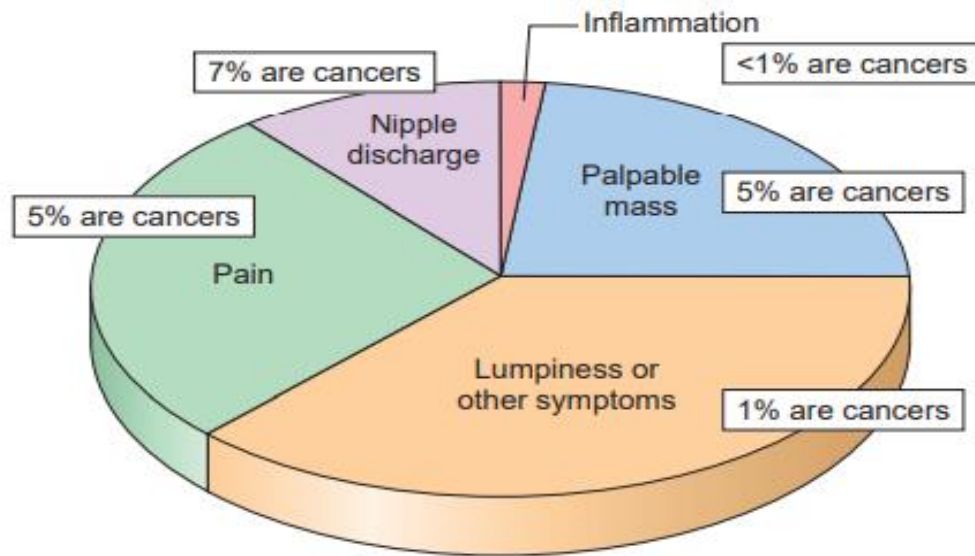
Hormones to remember...

- **Estrogen:** Develops the large ducts
- **Progesterone:** Develops the lobules and ductules ("acini")
- Stimulation of the nipple causes production of both:
 - **Prolactin** (which develops the secretory units and causes milk production)
 - **Oxytocin** (which causes the contraction of myoepithelial cells → the milk go through the ducts and come down).

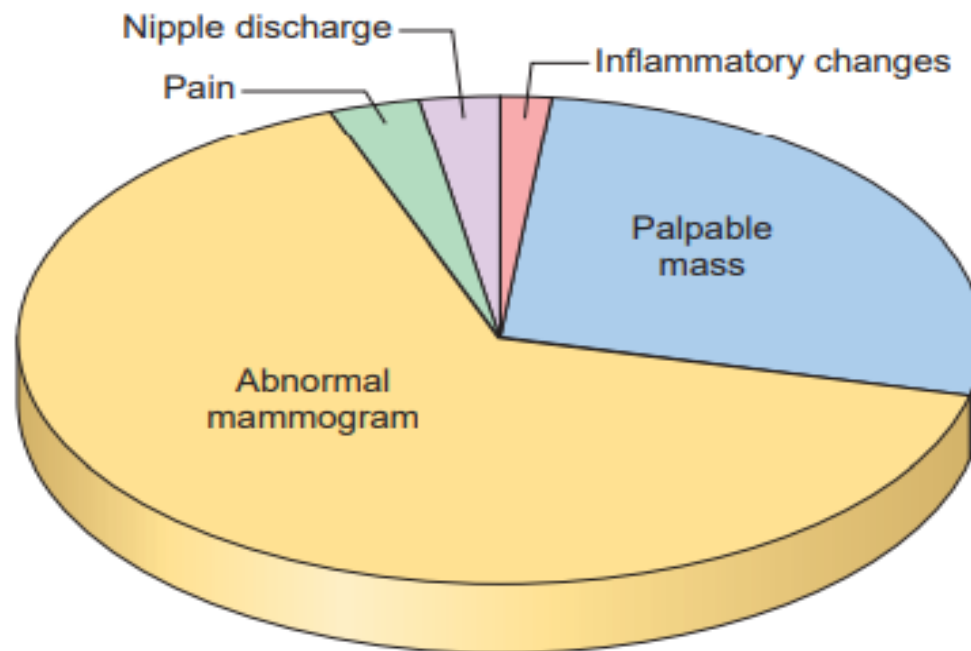
- During the second half of the monthly cycle, progesterone causes some proliferation of ducts and stroma in the lobules.
- When the cycle ends, these changes regress.
- After menopause, the lobules may vanish, leaving only the larger ducts.

DEVELOPMENTAL PROBLEMS

- **Inverted nipples**: common, especially in larger breasts, and may make nursing more difficult.
 - If a previously-normal nipple inverts, there is a problem, i.e., something has retracted underneath, and it's the stroma of a cancer until proven otherwise.
- **Accessory axillary breast**: The extension of normal breast tissue over the entire anterolateral chest wall into the axillary fossa.
- **Virginal hypertrophy (macromastia)**: very large breast(s) developing around puberty.
- **Hypomastia**: almost complete failure of breast development.
 - Around half of these women have mitral-valve prolapse.



A SYMPTOMS OF PATIENTS



B PRESENTATIONS OF BREAST CANCERS

INFLAMMATIONS

- Acute mastitis and breast abscess

- Usually occurs during early lactation,
- Usually *Staph. aureus* (abscess), less often streptococcus (spreading cellulitis).

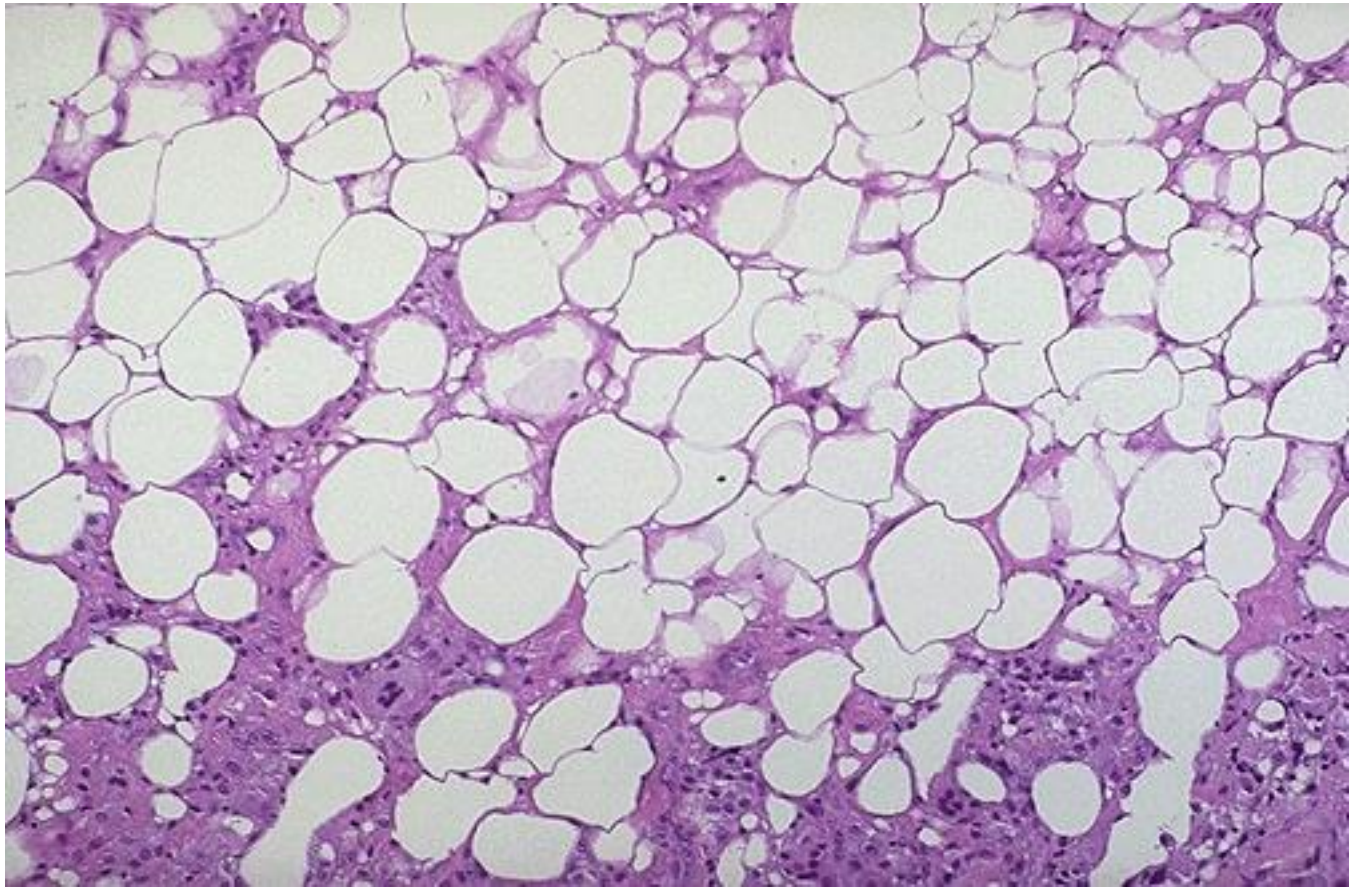
- Traumatic Fat necrosis

- A solid mass, often in a fatty breast tissue, caused by an injury.
- Necrotic fat cells surrounded by mixed inflammatory infiltrate, later with calcification, foreign body reaction, scarring.

- Periductal mastitis (recurrent subareolar abscess)

- A hyperkeratinizing squamous metaplasia with inflammation
- Almost all these women are smokers.

Fat necrosis



▶ Duct ectasia

- ▶ An uncommon cause of a breast mass, usually in older women, usually tender and with nipple retraction.
- ▶ Chronic inflammation and fibrosis around ducts are typical.
- ▶ The ducts are loaded with a lipid-and-macrophage rich material.
- ▶ The underlying cause is unknown; many of these women turn out to have pituitary prolactinomas.

▶ Granulomatous lobular mastitis

- ▶ All these women have been pregnant.
- ▶ There is some autoimmune reaction against the secretory units.
- ▶ Differential diagnosis: Tbc, sarcoidosis, and reaction to a ruptured implant.

▶ Galactocele

- ▶ One or more ducts becomes plugged during lactation.

▶ Mondor's disease

- ▶ Thrombophlebitis of the breast.

FIBROCYSTIC CHANGE OF THE BREAST

- This is the most common “condition” of breast
- Always multifocal
- The cause is obscure;
 - Estrogen is a known factor,
 - Women on the estrogen-progesterone balanced pills get less fibrocystic change.

Three patterns occur separately or together:

- 1. fibrosis
- 2. cyst formation (>3 mm)
- 3. adenosis.

FIBROCYSTIC CHANGE OF THE BREAST

•1. Fibrosis

- Dense collagenization distorting and compressing the epithelial structures.
- This is most common in upper outer quadrants, patients in 30's.

FIBROCYSTIC CHANGE OF THE BREAST

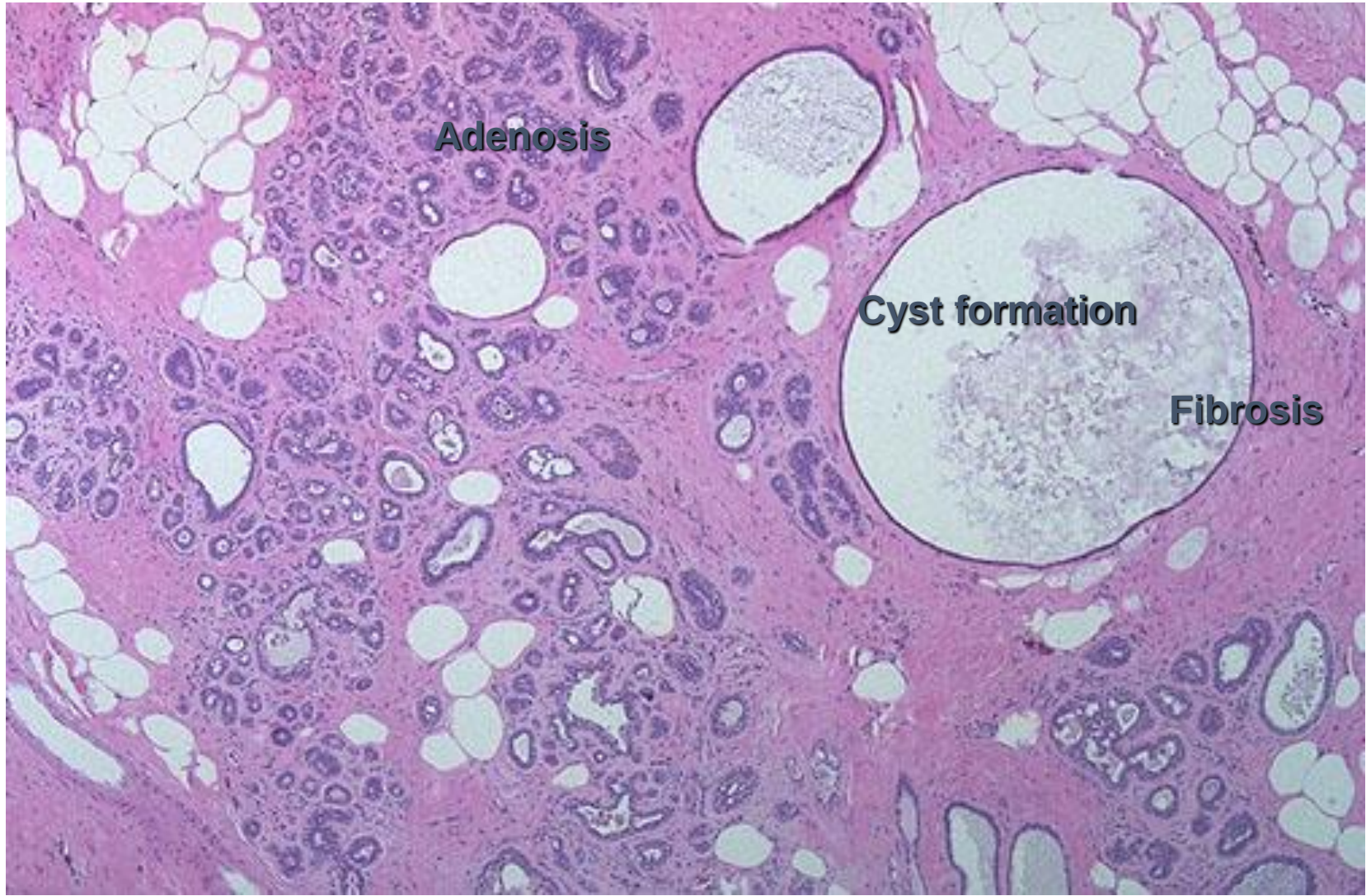
▶ 2. Cyst formation (>3 mm) :

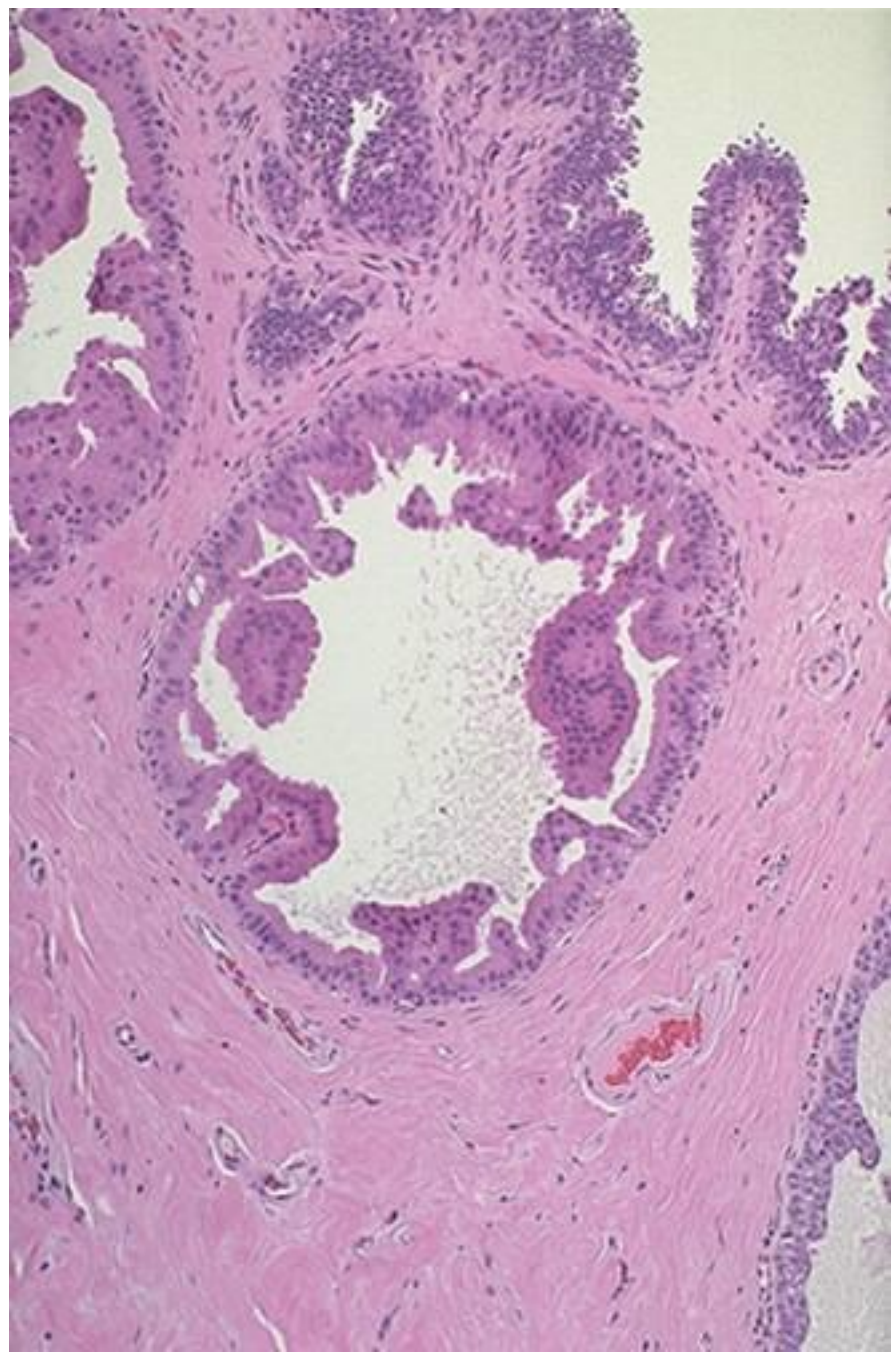
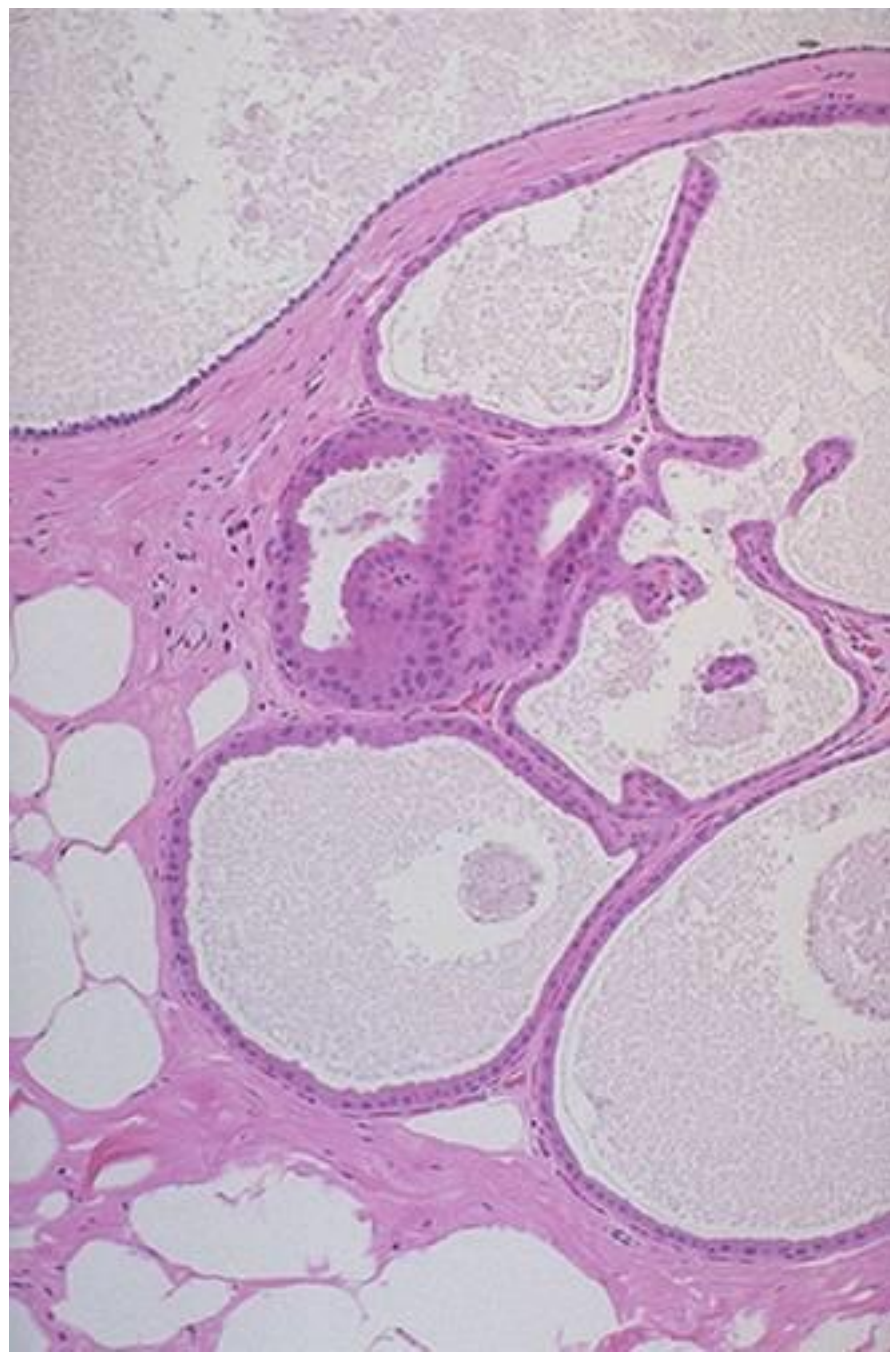
- ▶ Dilated ducts containing cloudy serous fluid (sometimes bloody or infected)
- ▶ All breasts, during childbearing, contain microscopic cysts.
 - ▶ They are abnormal when they got larger than 2 mm or so.
- ▶ Grossly, the blue-dome cyst is very familiar.
- ▶ Epithelium may be flattened, cuboidal, columnar, or even show **apocrine metaplasia**.
- ▶ Surrounding stroma likely to be fibrous.
- ▶ Cysts likely to be tender before menses.

FIBROCYSTIC CHANGE OF THE BREAST

- **3. Adenosis:**

- This extremely common change means extra, crowded ductules in some of the lobules.
- Often the lumens are a bit distended ("blunt duct adenosis"), but they are not deformed, compressed or distorted.





PROLIFERATIVE BREAST DISEASES

- Three entities have been removed from the "fibrocystic change" category because they confer a significant cancer risk:
 - **1. Epithelial hyperplasia**
 - Totally benign-looking hyperplasias
 - Atypical ductal hyperplasias
 - Atypical lobular hyperplasia
 - **2. Sclerosing adenosis**
 - **3. Small duct papillomas**

PROLIFERATIVE BREAST DISEASES

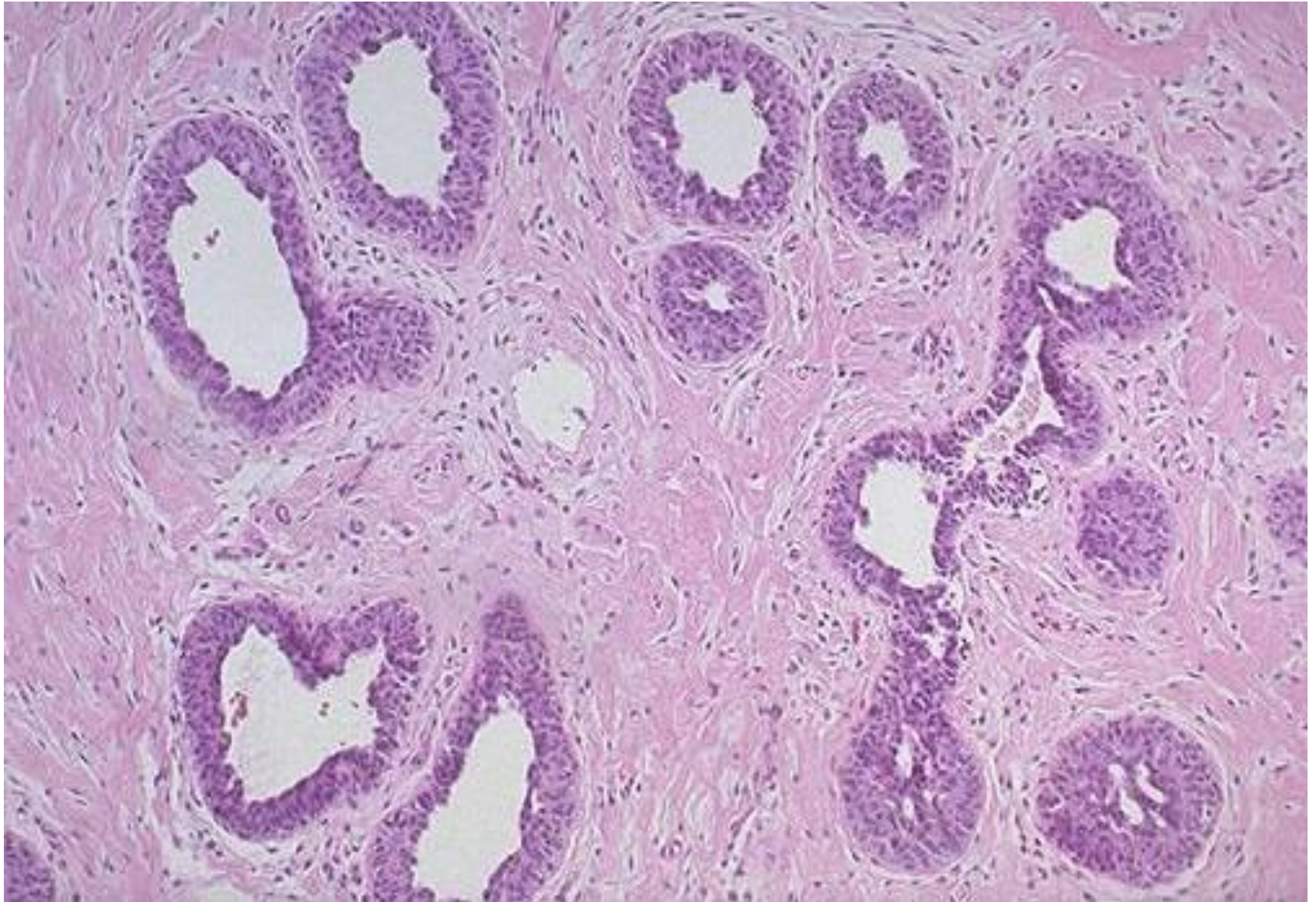
▶ Epithelial hyperplasia

- ▶ More than the usual two layers of cells in ducts and/or lobules.
 - ▶ At least one layer will be myoepithelial cells.
- ▶ Epithelial hyperplasia is usually an incidental finding, and does not produce a mass.
- ▶ Cells are piled up and may even fill ducts and/or ductules.
- ▶ Most often, there is a mixed population of cells.
 - ▶ Epithelial cells,
 - ▶ Myoepithelial cells.

ALERTS

- Atypical hyperplasia:
 - If there is some anaplasia of architecture (swiss cheese) or cells (with ugly nuclei).
 - The cells do not fill the ducts or acini ("in-situ cancer").
- Carcinoma in situ (CIS):
 - CIS is only slightly more likely to progress to invasive cancer than is "atypical hyperplasia."

Epithelial hyperplasia



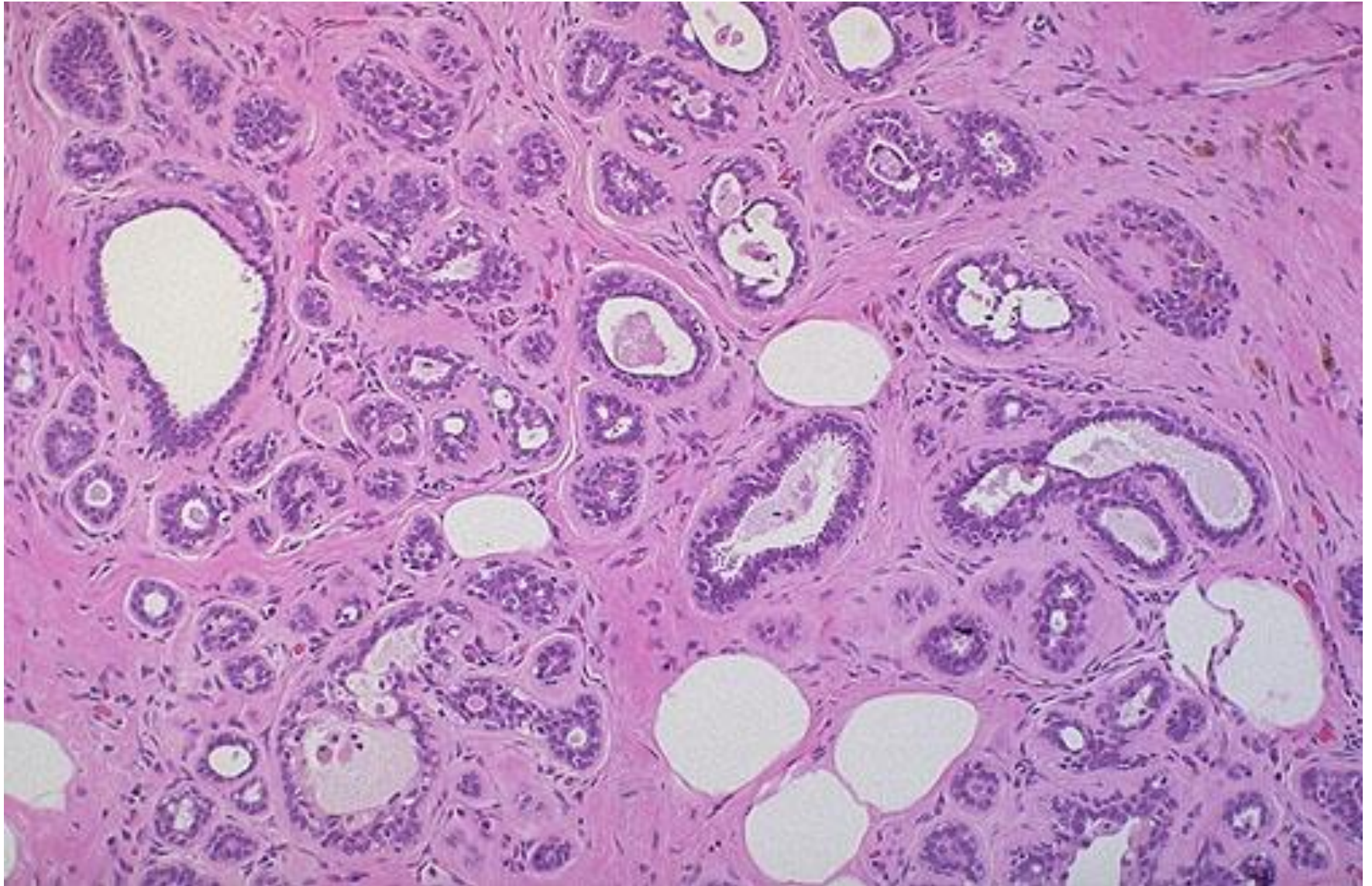


PROLIFERATIVE BREAST DISEASES

▶ Sclerosing adenosis

- ▶ Proliferation of small ductules and sometimes even acini in a fibrous stroma
- ▶ Usually it's a tender lump in the upper outer quadrant.
- ▶ Patients are usually around age 30-40.
- ▶ This mimics cancer both clinically and microscopically:
 - ▶ (1) There'll always be myoepithelium, expressing smooth-muscle actin, S100, high MW keratin and P63 antigens.
 - ▶ (2) The normal lobular architecture is preserved, though lobules may be expanded (under low-magnification).
 - ▶ (3) Sclerosing adenosis can be solitary, but it never cuts "gritty" like many breast cancers.

Sclerosing adenositis



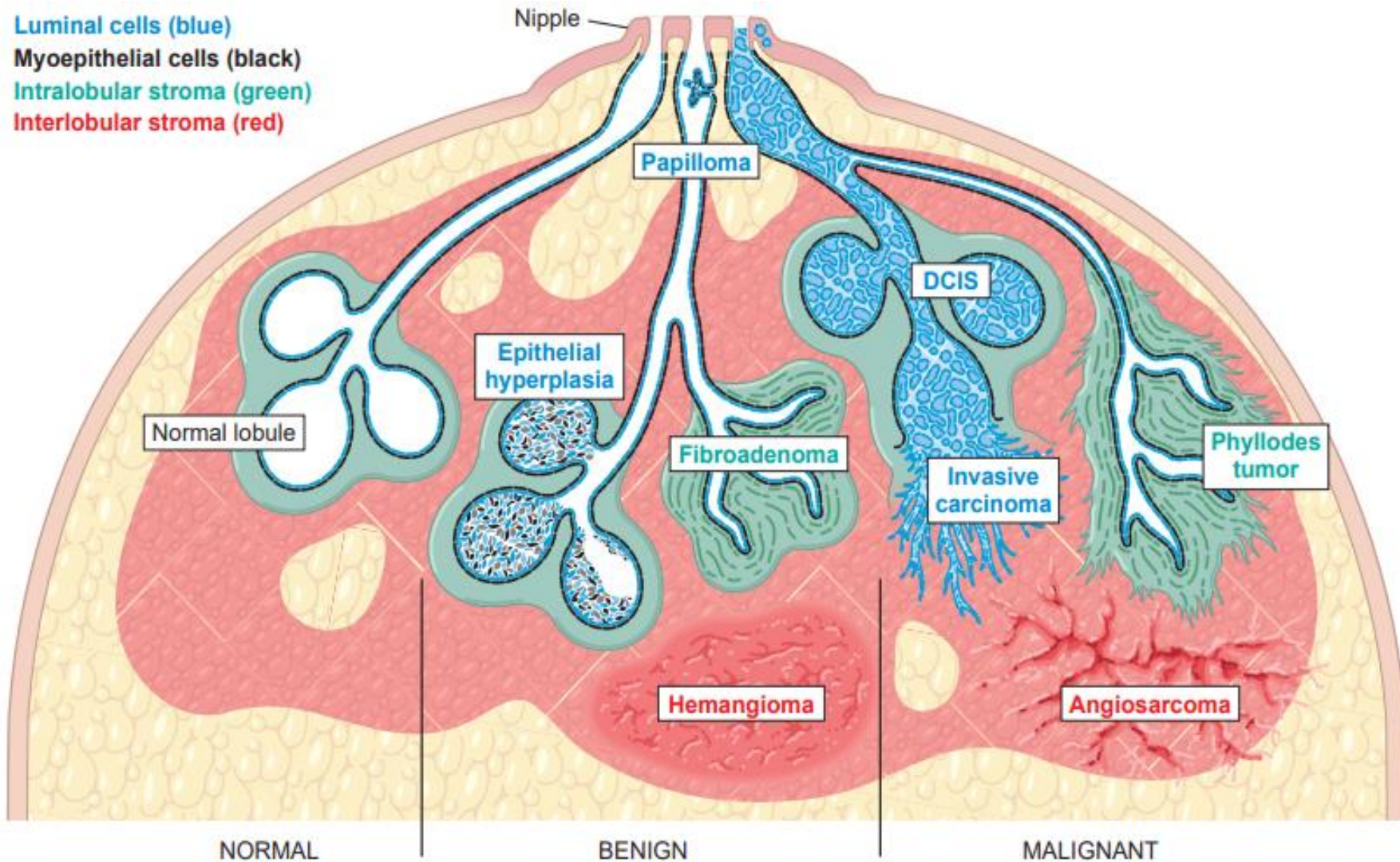
PROLIFERATIVE BREAST DISEASES

Radial scar

- It is a star-shaped fibrosing lesion that looks like a typical crablike cancer on mammography
- Benign on biopsy
- No increased risk for cancer!

Small duct papillomas

- Seldom produce masses.
- These possess fibrovascular cores, with epithelial hyperplasia-type lesions.

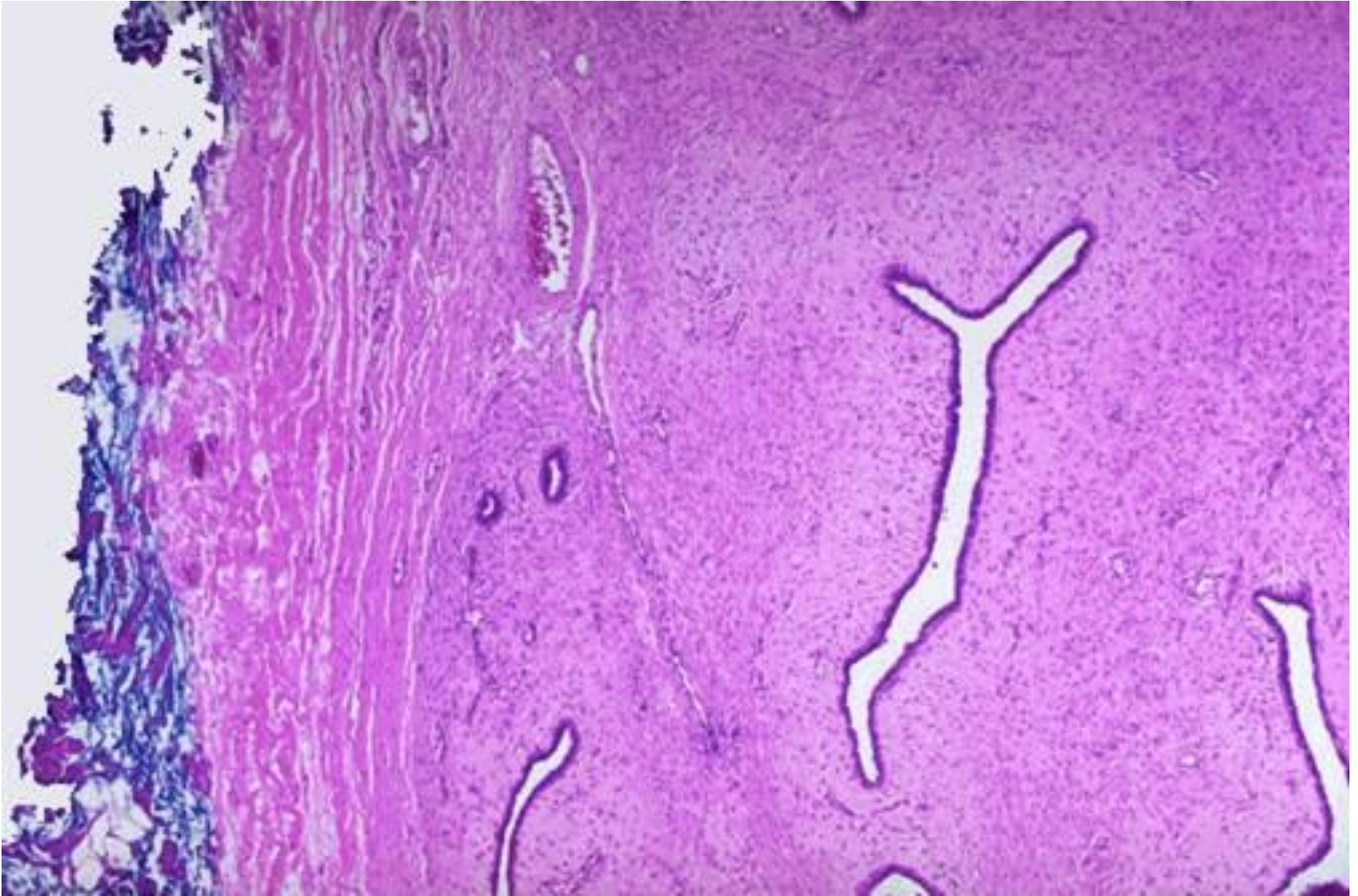


STROMAL TUMORS

FIBROADENOMA

- The most common benign breast tumor,
- Occurs at any time during reproductive life,
 - most often under age 30.
- It presents a small, sharply circumscribed, freely movable nodule within the breast substance.
- A loose stroma surrounds ducts that are often crushed flat.

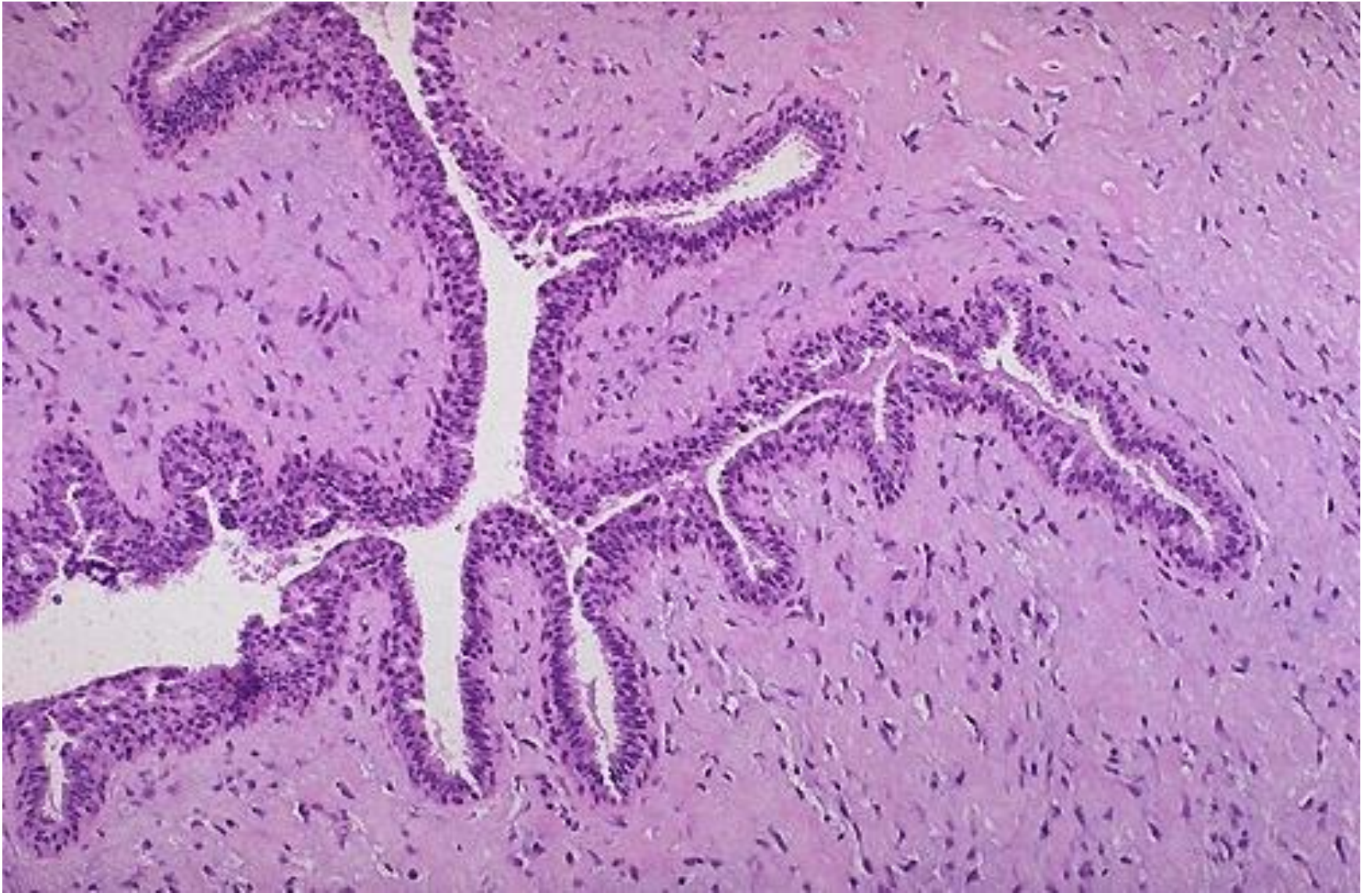
Fibroadenoma



Phylloides tumor

- Cystosarcoma phylloides
- "Phylloides" means "leaves", referring to the artichoke-like appearance of many of these tumors
- Phyllodes tumor, like fibroadenoma, arises from intralobular stroma but is much less common. Cystosarcoma phyllodes is a term sometimes used for these lesions, but phyllodes tumor is preferred, since most behave in a benign fashion and are not cystic. Like fibroadenomas, the majority of phyllodes tumors have MED12 mutations. Benign-appearing phyllodes tumors that have only a slight propensity to recur often have MED12 mutations and few other genetic changes. In contrast, tumors that display malignant behavior are more likely to have mutations in additional genes, such as TERT, the gene that encodes telomerase
- Exhibits metaplastic and/or anaplastic stroma and supposedly rapid growth
- If it metastasizes, it will be as a sarcoma

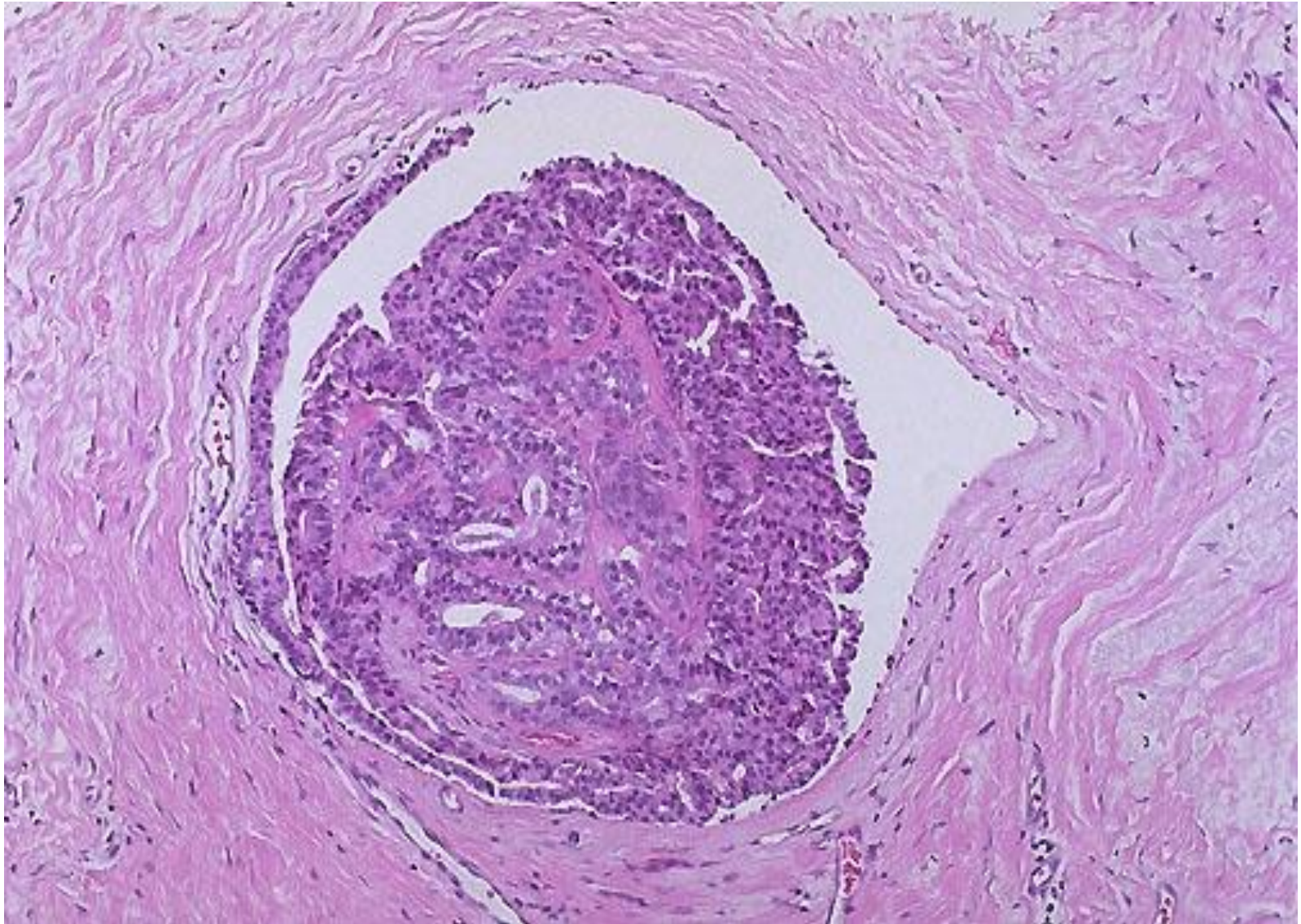
Phylloides tumor

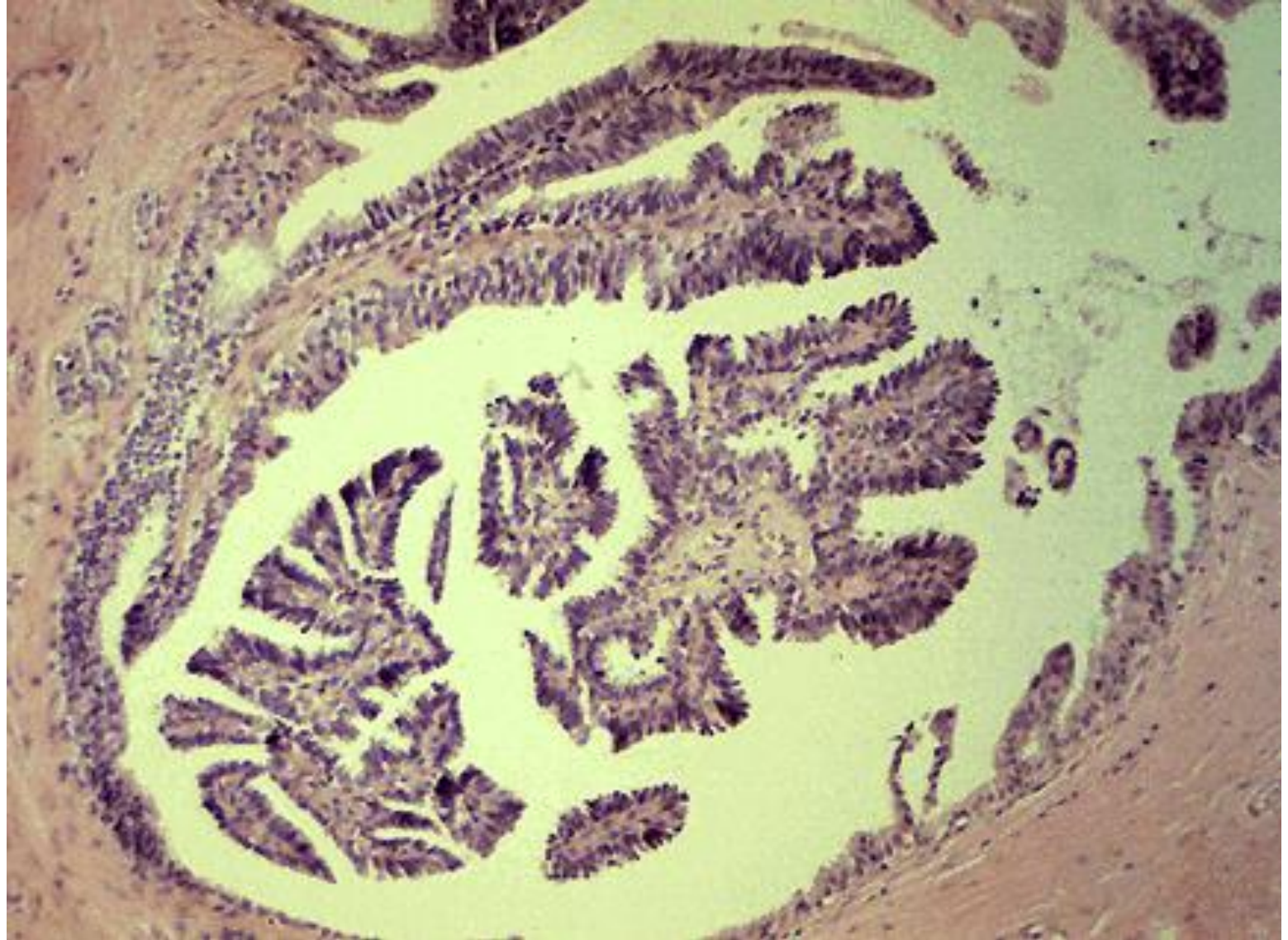


LARGE DUCT PAPILLOMA

- Intraductal papilloma
- This is a small (less than 1 cm) lesion in a major duct just below the nipple.
- It produces bloody nipple discharge.
- Occasionally it causes nipple retraction.
- Radiology (galactogram): injecting dye into each of the lactiferous sinuses.

Intraductal papilloma





CARCINOMA OF THE BREAST

- This is the most common cancer in women
- It is rare before age 25,
 - more common with increasing age.
- Around 1 in 9 women will develop breast cancer during their life.
- Breast cancer usually presents as a dominant, painless mass.
- Nowadays it is often found on mammography long before symptoms appear.

Risk factors

▶ Female gender

- ▶ 100x as common as in men

▶ Ethnic group

- ▶ Ashkenazi (a Jewish ethnic group) ancestry (the effect is explained by the high prevalence of BRCA1 mutations in the Ashkenazi population)
- ▶ Every ethnic group has a high incidence of breast cancer; American Indians have the least.

▶ Geography

- ▶ The US and Northern Europe have the highest rates

▶ Increasing age

- ▶ breast cancer is rare before age 25

▶ Obesity

- ▶ supposedly; "synthesis of estrogens in fat deposits"

▶ Longer reproductive life: Estrogen

- ▶ menarche before age 13 or menopause after 50

- Nulliparous women or those having their first child at a late age (over 30)
- Family history of breast cancer
 - father's side as well as mother's
- History of high-dose radiation
 - atom bomb survivors, women radiated for breast abscesses
 - Hodgkin's disease treatment only in younger women
- History of epithelial hyperplasia (especially Atypical)
- Previous breast cancer
- Previous cancer of the endometrium

- **Alcoholism**
 - because of folic acid deficiency
- **Previous fibroadenoma**
 - triples the risk
- **Genetic Factors:** Germ line mutations in BRCA1 and BRCA2, p53 (Hereditary breast-ovarian cancer syndrome) ATM gene (Ataxia Telangiectasia), 10q locus in Cowden Syndrome.
- **Estrogen replacement**
 - as a risk factor for breast cancer after menopause remains controversial.

NONINVASIVE ("in situ") CARCINOMA

- Non-invasive, but they may form masses by filling ducts and/or lobules.
- **Ductal carcinoma in situ (DCIS)**
- **Comedocarcinoma**
- **Solid DCIS**
- **Cribriform DCIS**
- **Papillary DCIS**
- **Micropapillary DCIS**
- **"Paget's disease of the nipple"**
- **DCIS with microinvasion**
- **Non-infiltrating (in situ) lobular "carcinoma" .**

Ductal carcinoma in situ ("DCIS")

- This is the most commonly-identified lesion on mammography.
- These lesions are usually unilateral, they often present around for decades, and probably only a minority ever invade.

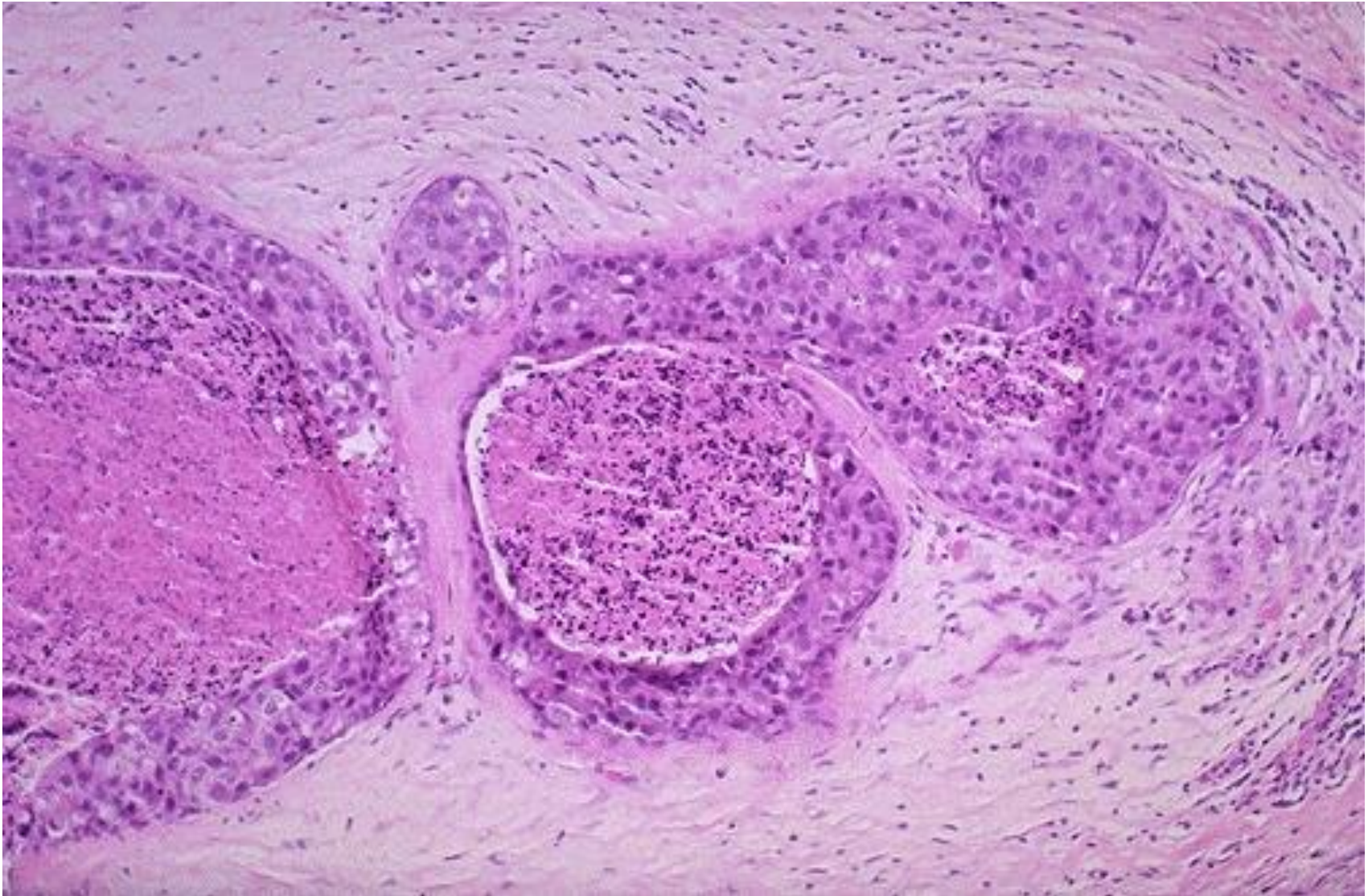
Comedocarcinoma

- ▶ The most common
- ▶ Solid intraductal proliferation, central necrosis
- ▶ Unlike the other "DCIS" lesions, the cells of comedocarcinoma are usually quite anaplastic and vary widely in size.
- ▶ Often the necrotic cores calcify, making them easy to spot on mammography.

Solid DCIS

- ▶ Simply fills ducts.
- ▶ The cells are monomorphic and monotonous.

Comedocarcinoma



Cribriform DCIS

- ▶ Swiss-cheese appearance.

Papillary DCIS

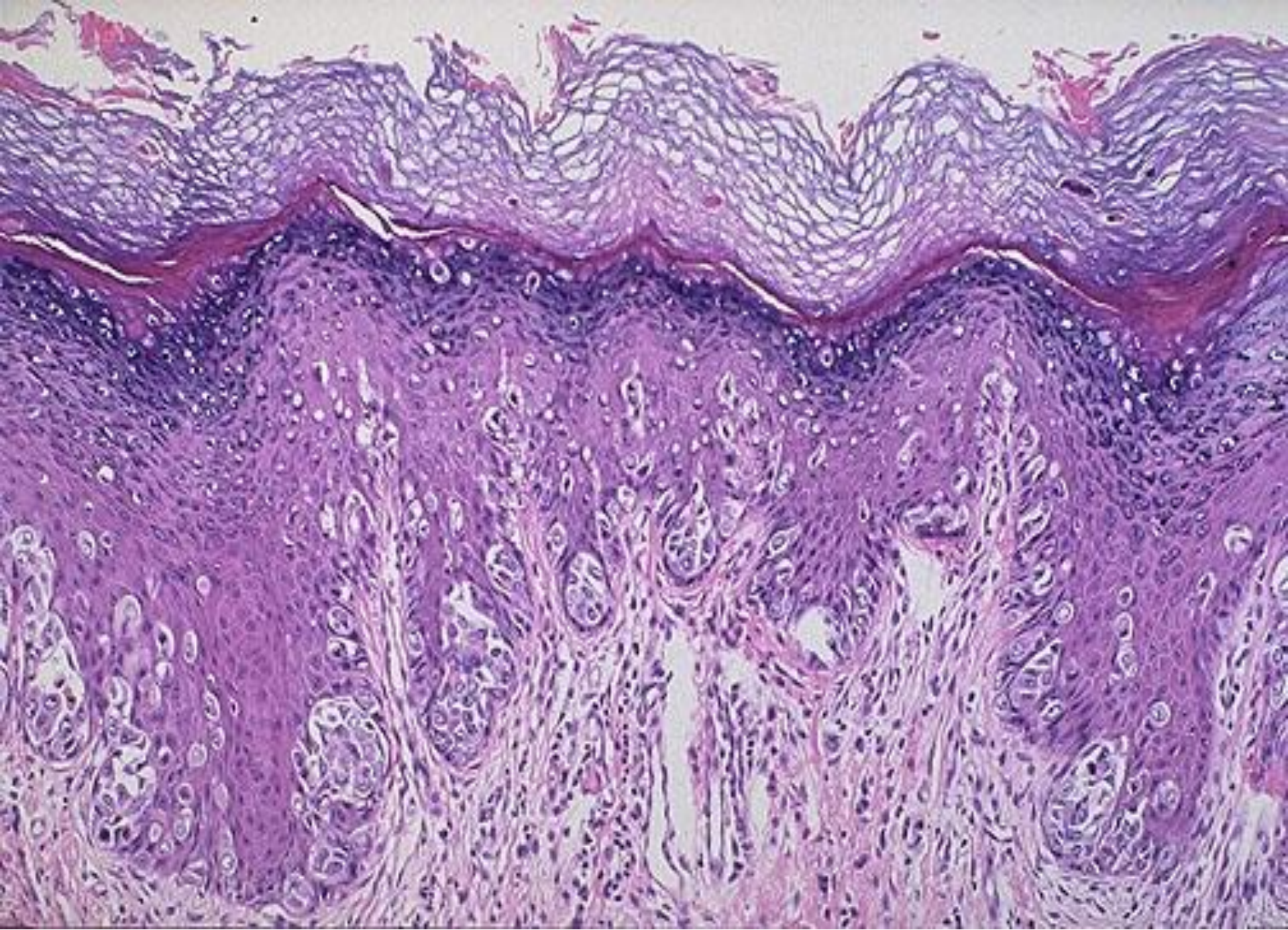
- ▶ Looks like the papillary lesions of proliferative breast disease, with fibrovascular cores, but has a monomorphic cell population.

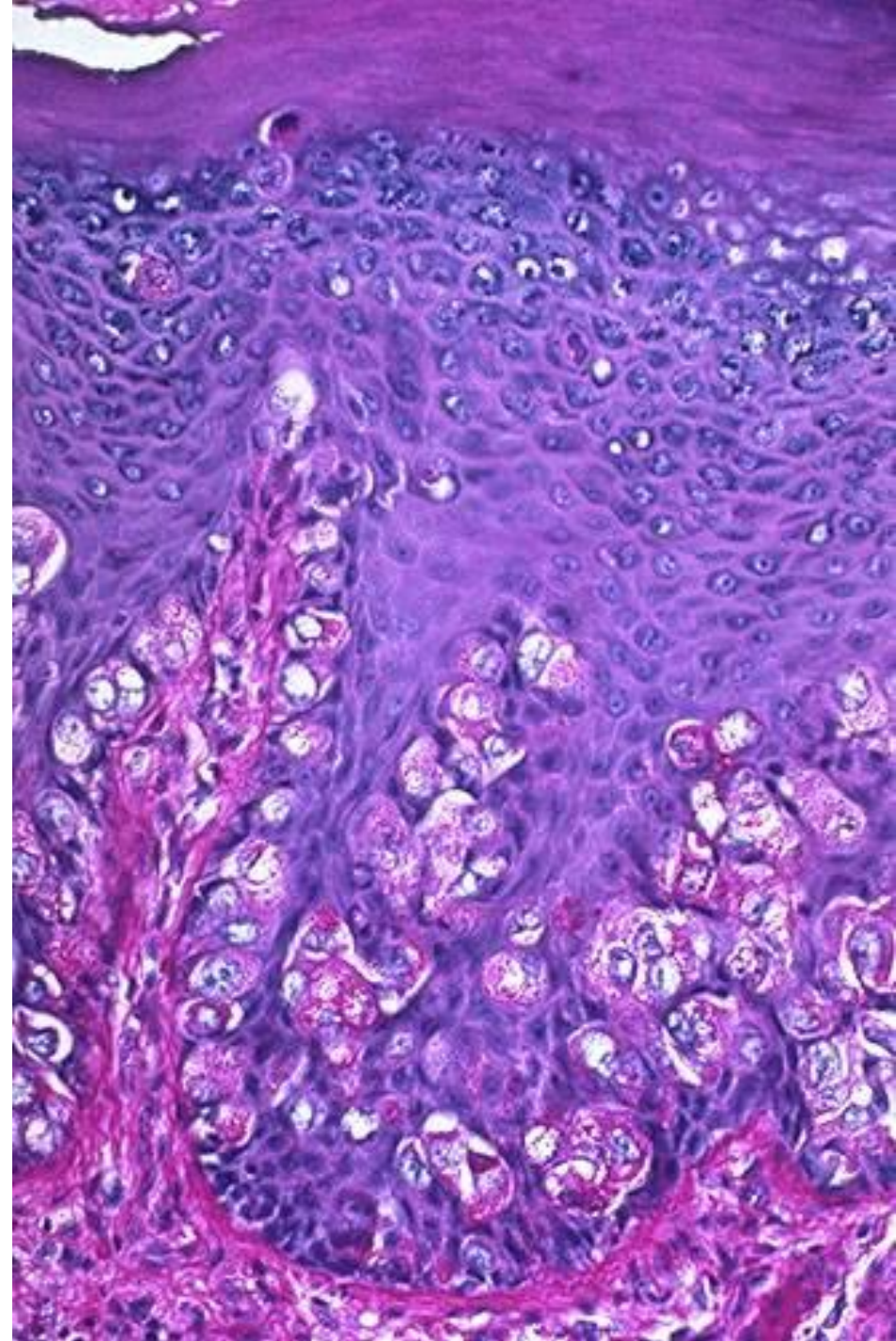
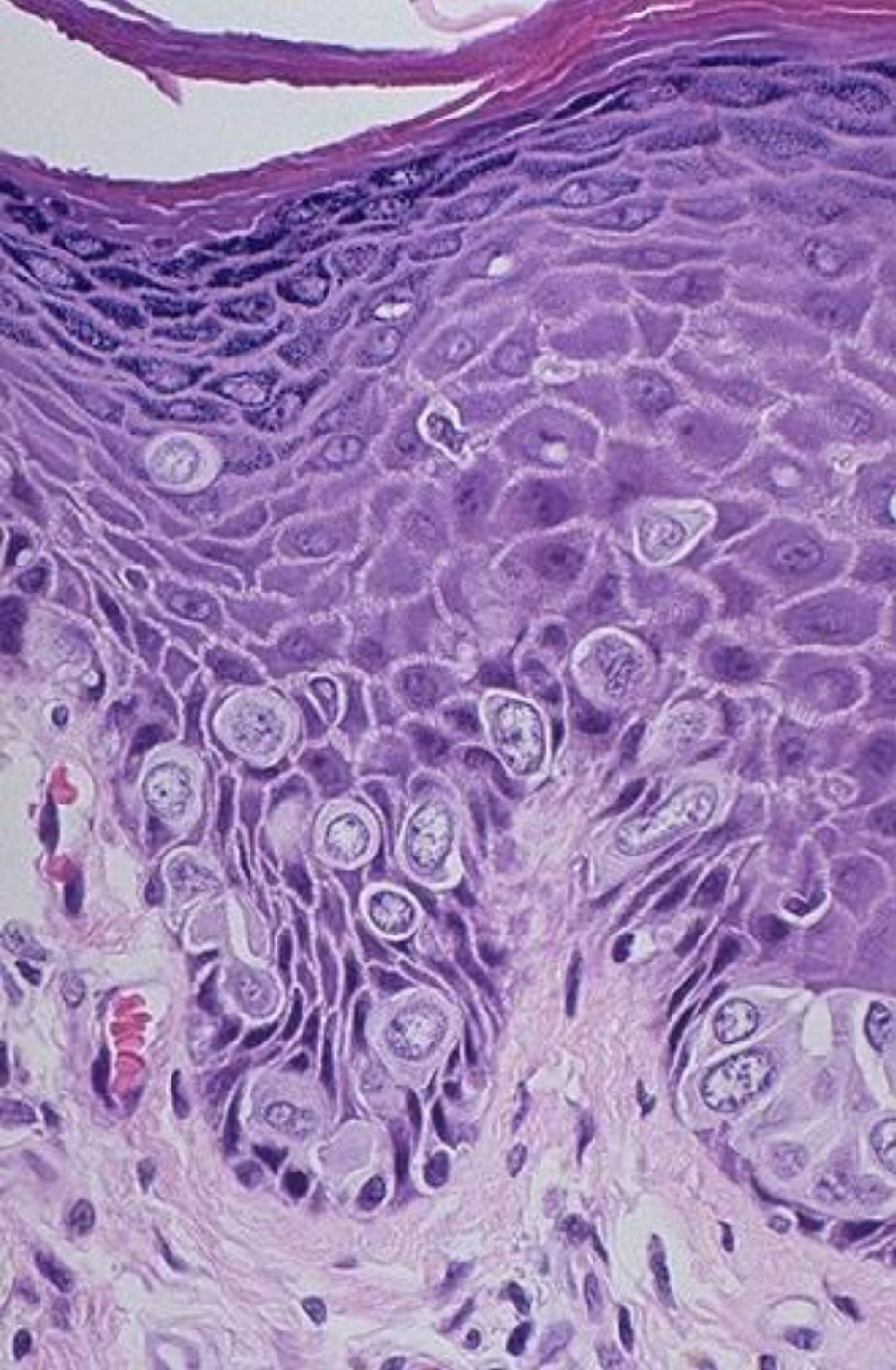
Micropapillary DCIS

- ▶ It is little mounds of cells along the wall without fibrovascular cores.

Paget's disease of the nipple

- ▶ Intraepithelial growth of large, pale, mostly-single cancer cells in the nipple.
- ▶ Breast looks inflamed (misdiagnose: "eczema of the nipple")
- ▶ There is most often an underlying duct carcinoma.





DCIS with microinvasion

- Usually is comedocarcinoma with invasive cancer confined to 1 mm away from the ducts.

Non-infiltrating (in situ) lobular "carcinoma"

- This is a distinctive proliferation of tame-looking cells, slightly larger than normal, filling the ductules of one or more lobules.
- The lobules are expanded but not distorted.
- Often there are signet-ring cells.
- It heralds infiltrating ductal or lobular carcinoma; however, the invasive cancer is just as likely to be in the opposite breast.
- "Lobular CIS" is usually an incidental finding when tissue from the breast is excised and examined for some other reason.
- If you get a chance to examine both breasts, it's usually bilateral.

INFILTRATING (invasive) BREAST CARCINOMA

- Invasive ductal carcinoma

- **No Special Type (NST)**
- **Medullary carcinoma**
- **Mucinous (colloid, gelatinous) carcinoma**
- **Adenoid cystic**
- **Papillary carcinoma**
- **Tubular carcinoma**
- **Metaplastic cancers**

- Infiltrating lobular carcinoma

Table 23.1 Epithelial Breast Lesions and Risk of Developing Invasive Carcinoma

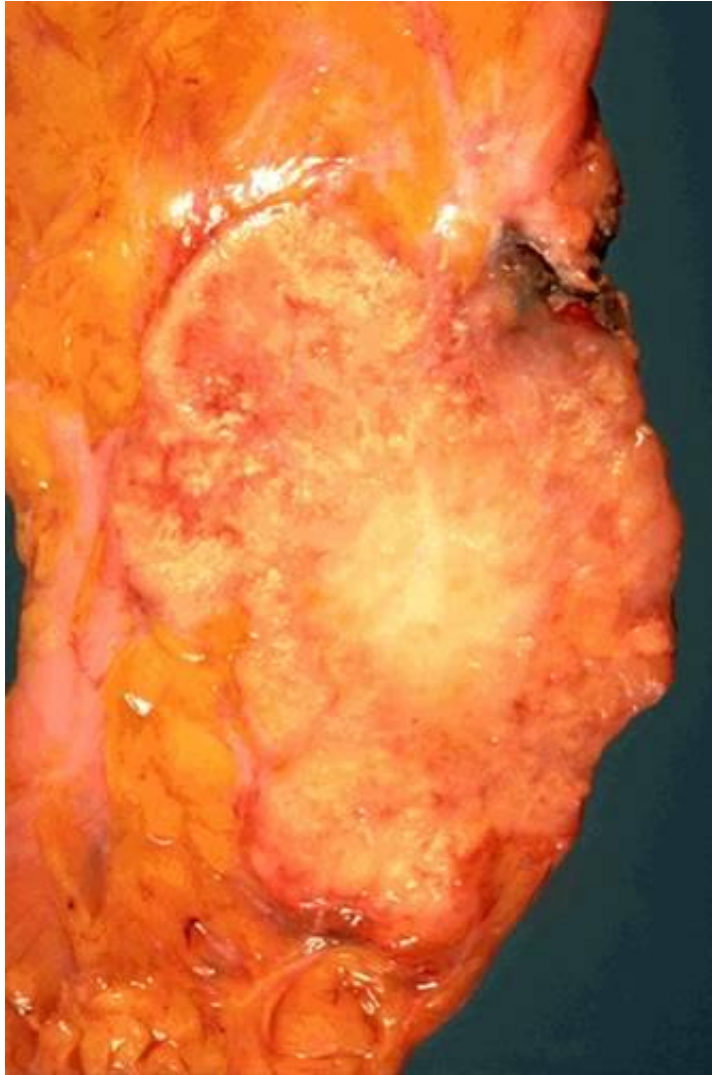
Pathologic Lesions	Relative Risk (Absolute Lifetime Risk)^a
Nonproliferative breast changes (mild hyperplasia, duct ectasia, cysts, apocrine metaplasia, adenosis, fibroadenoma without complex features)	1.0 (~3%)
Proliferative disease without atypia (moderate or florid hyperplasia, sclerosing adenosis, complex sclerosing lesion, fibroadenoma with complex features)	1.5–2 (~5%–7%)
Proliferative disease with atypia (atypical ductal hyperplasia, atypical lobular hyperplasia)	4–5 (~13%–17%)
Carcinoma in situ (lobular carcinoma in situ, ductal carcinoma in situ)	8–10 (~25%–30%)

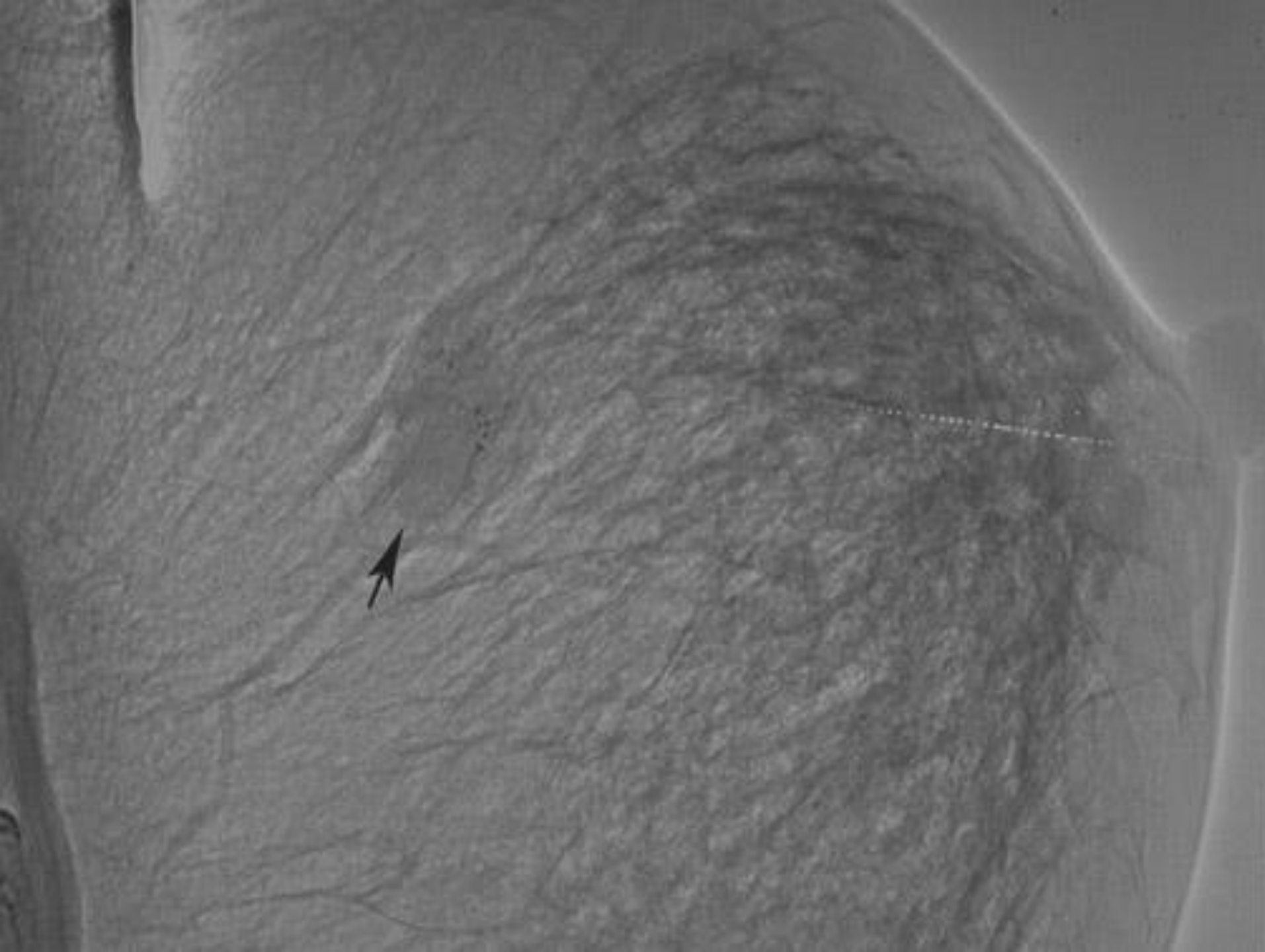
Invasive ductal carcinoma

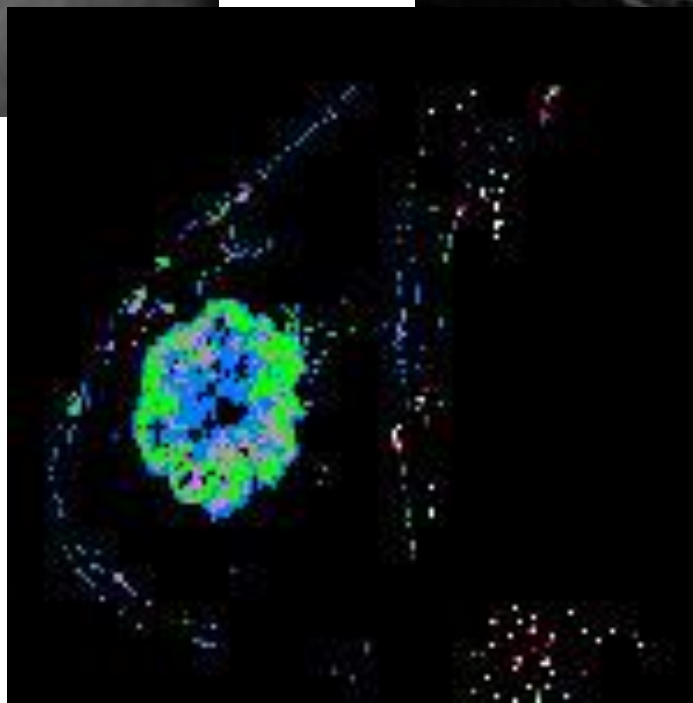
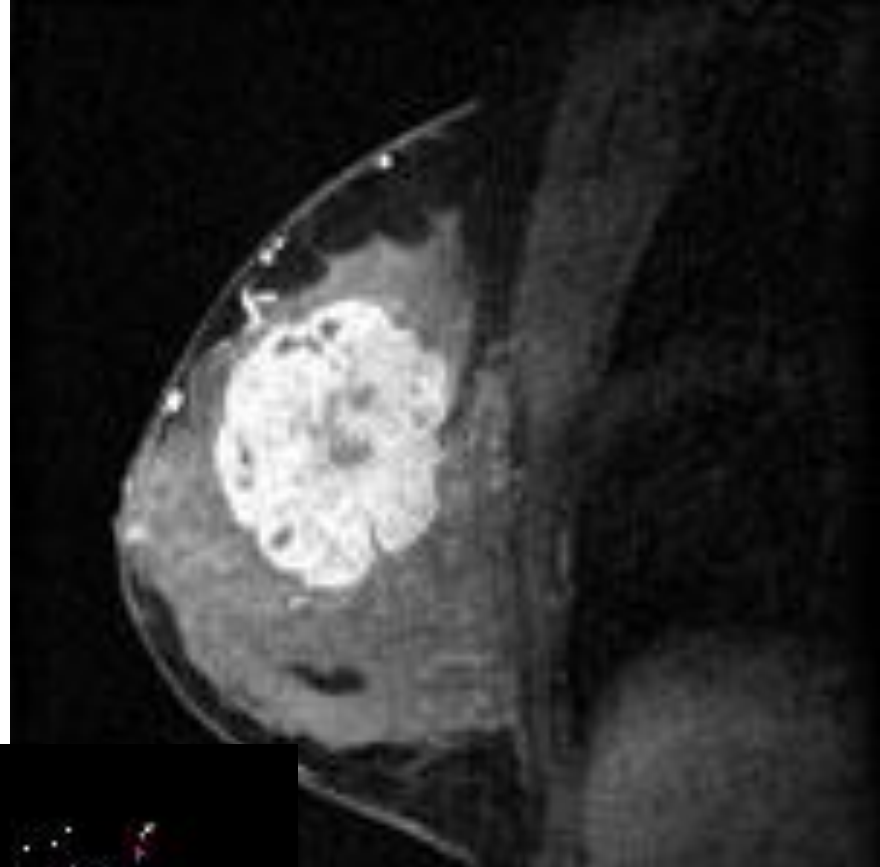
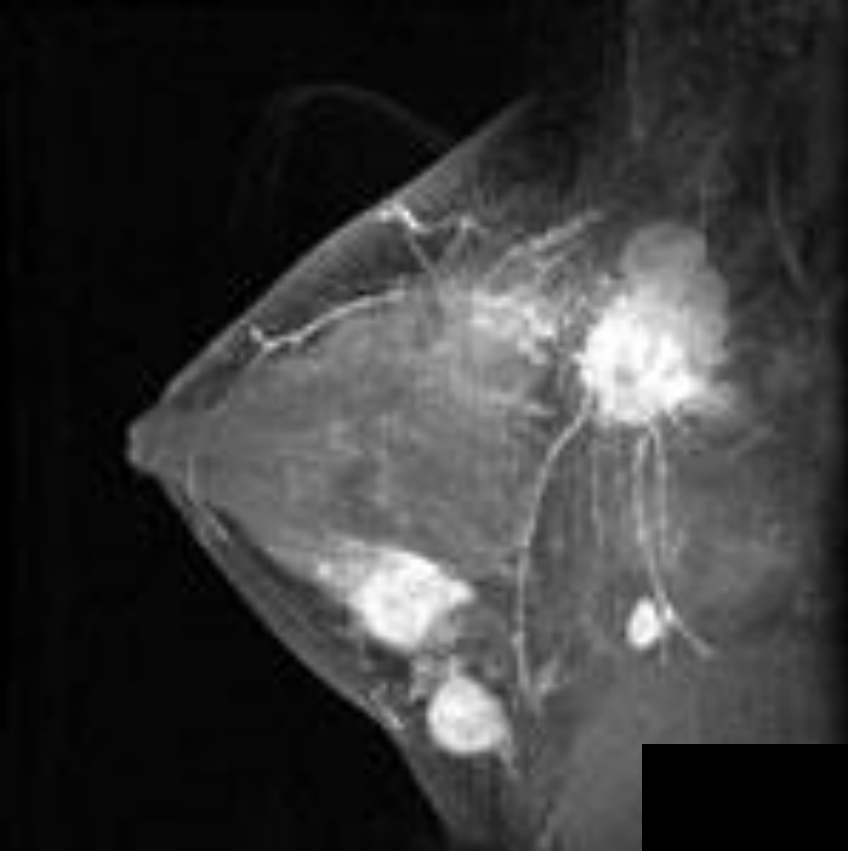
No Special Type (NST)

- Usual type;
- About 75% of infiltrating ductal carcinomas.
- Most of these are
 - stellate or micronodular,
 - quite hard (scirrhous),
 - on cut section:
 - a chalky-white look flecked with yellow (elastin bands),
 - produces the gritty sensation of cutting an unripe pear.
- Microscopy (scirrhous carcinoma):
 - cells often arranged in nests or cords or streams
 - a very desmoplastic stroma.

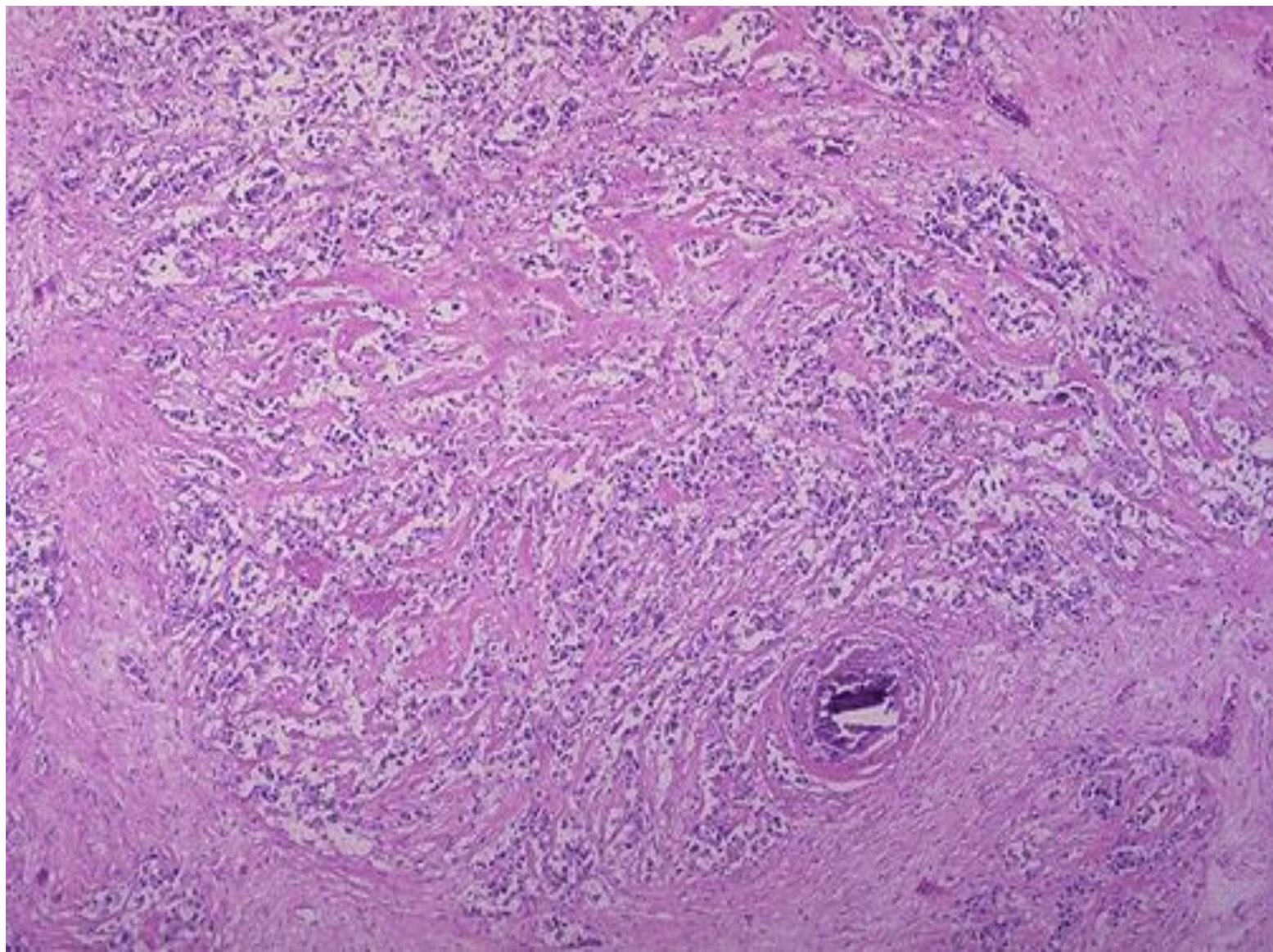
Invasive ductal carcinoma (Scirrhus)



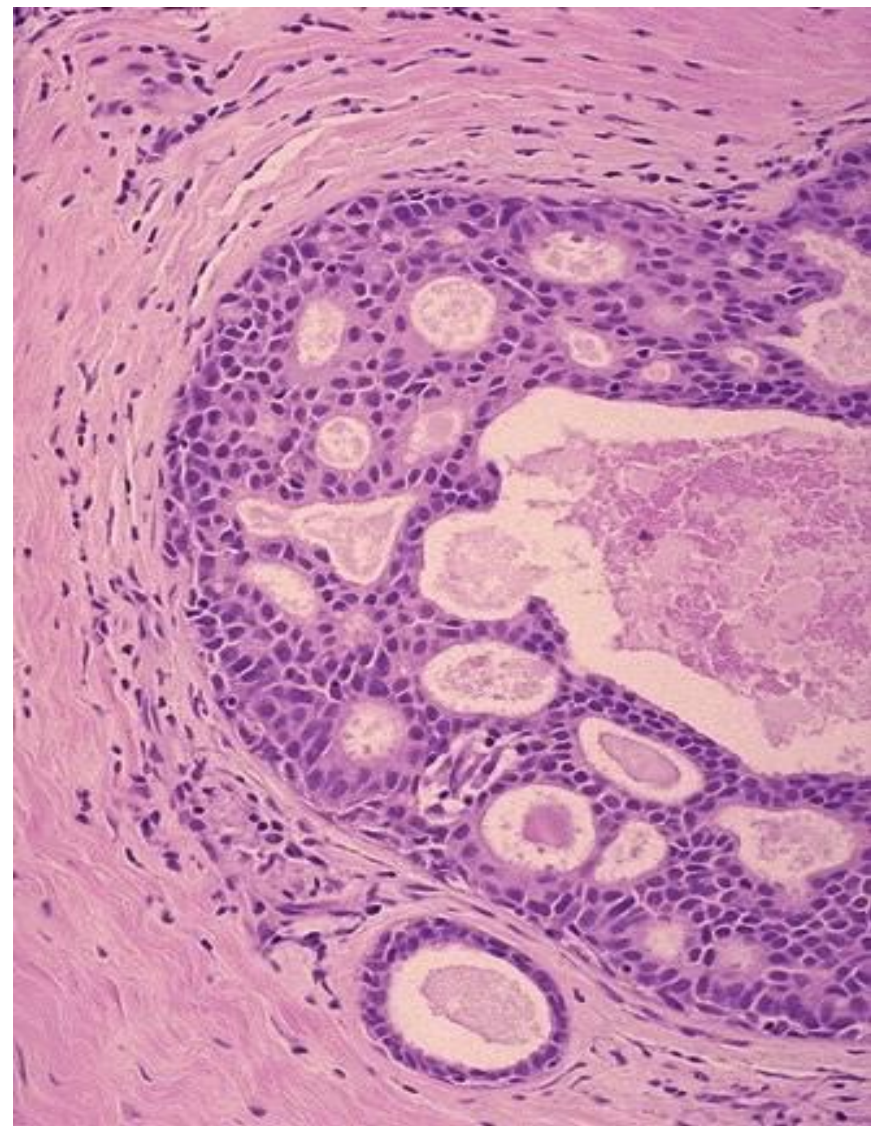
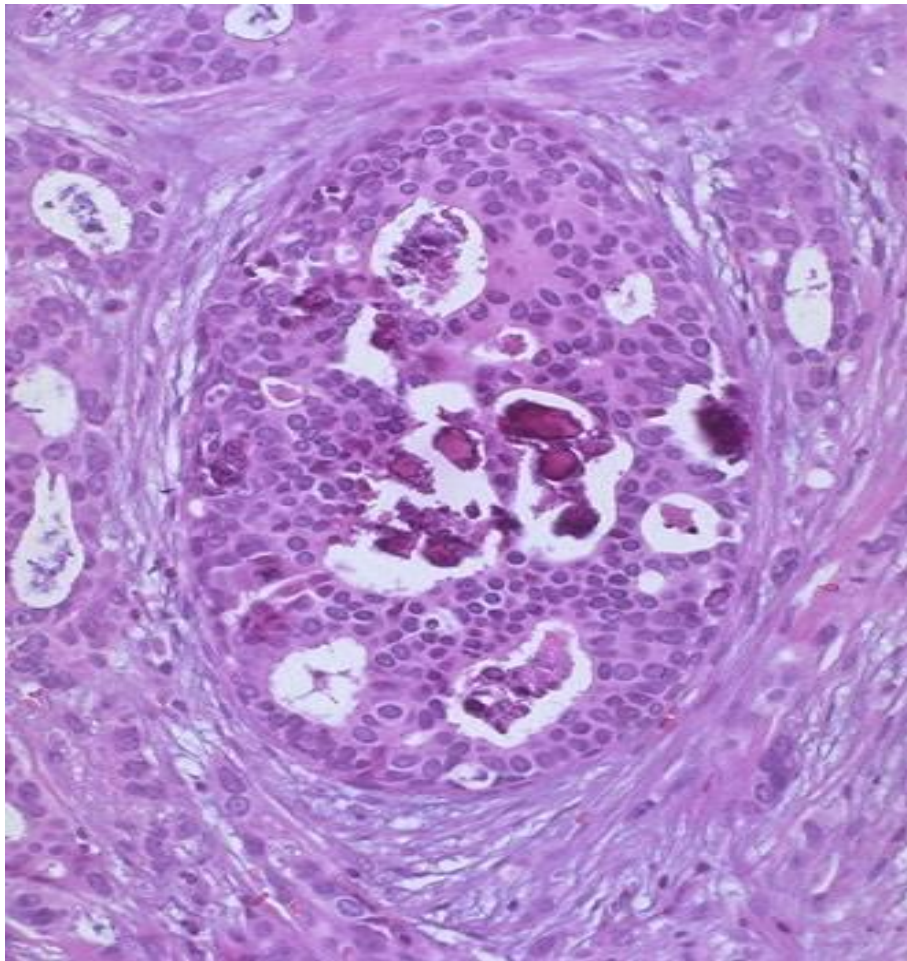




Invasive ductal carcinoma

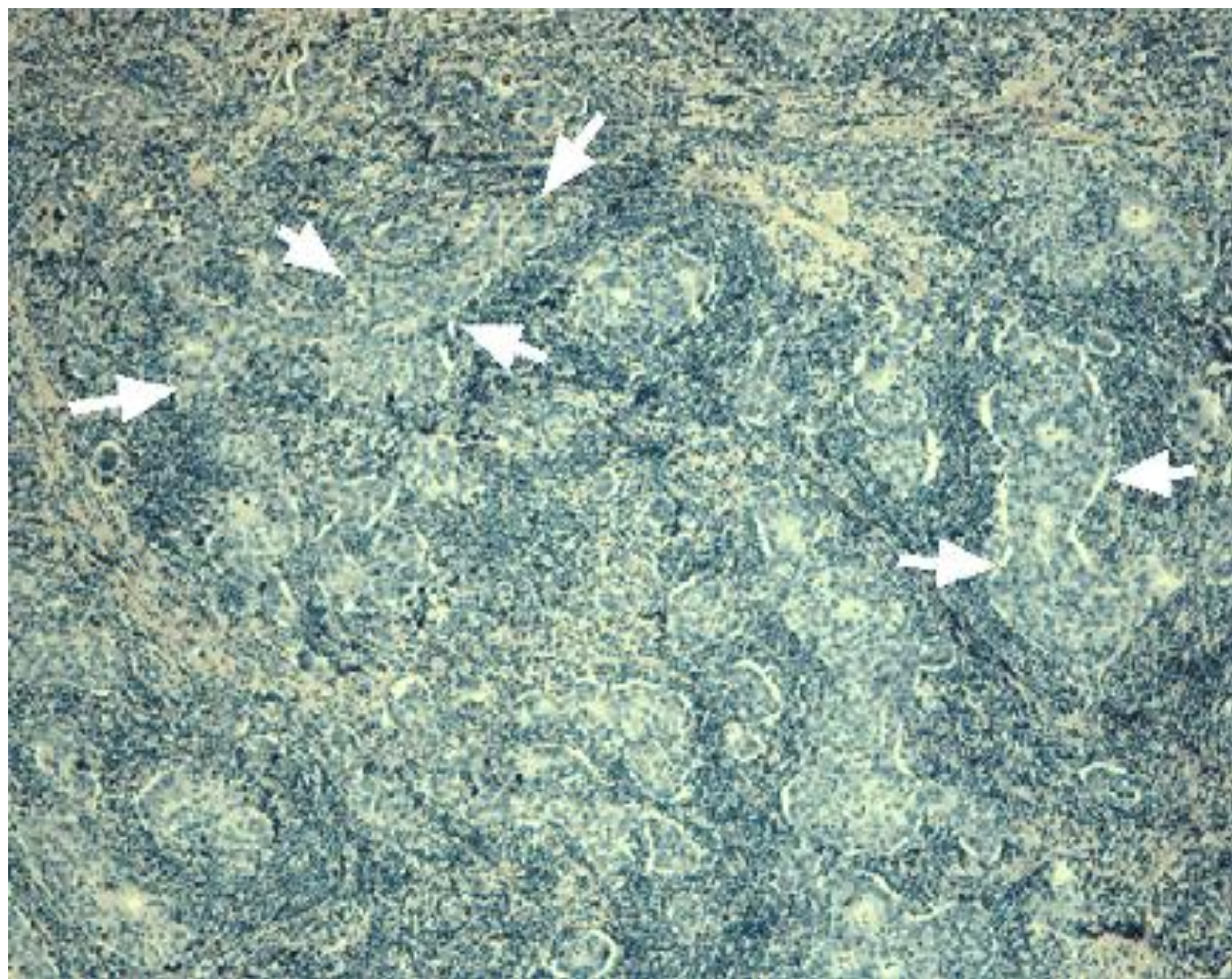


Invasive ductal carcinoma



Medullary carcinoma

- Big, bulky, and soft.
- Lymphocytes are plentiful among the tumor cells.
- The prognosis is slightly better than that of other types.
- This type of cancer is much-overrepresented among women with mutated BRCA1 syndrome.



Mucinous (colloid, gelatinous) carcinoma

- Clumps of cells in lakes of mucin.
- Grossly, the tumor is a gelatinous mass.

Adenoid cystic carcinoma

- Very low aggressiveness in the breast.

Papillary carcinoma

- Arises from the large ducts.

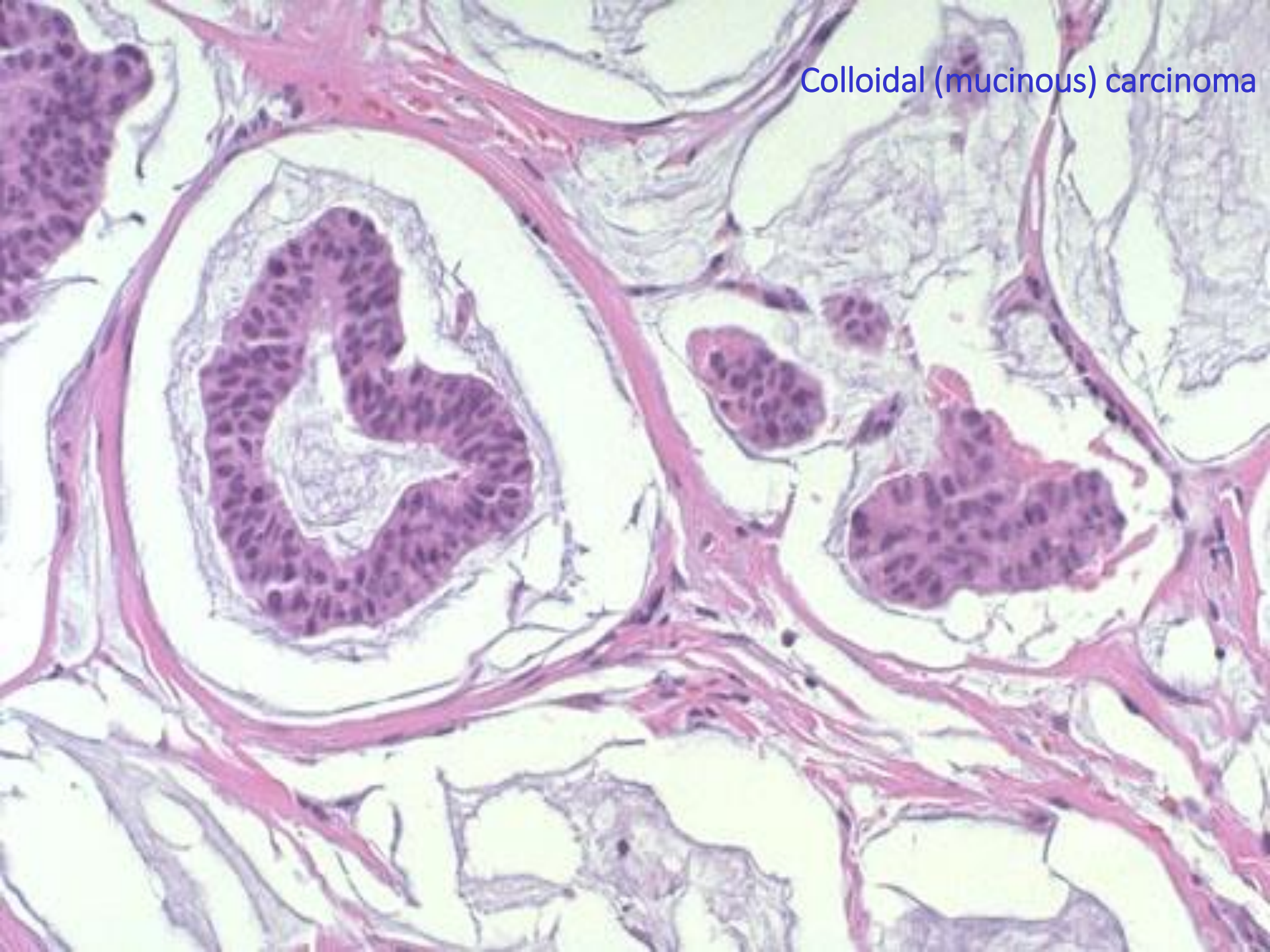
Tubular carcinoma

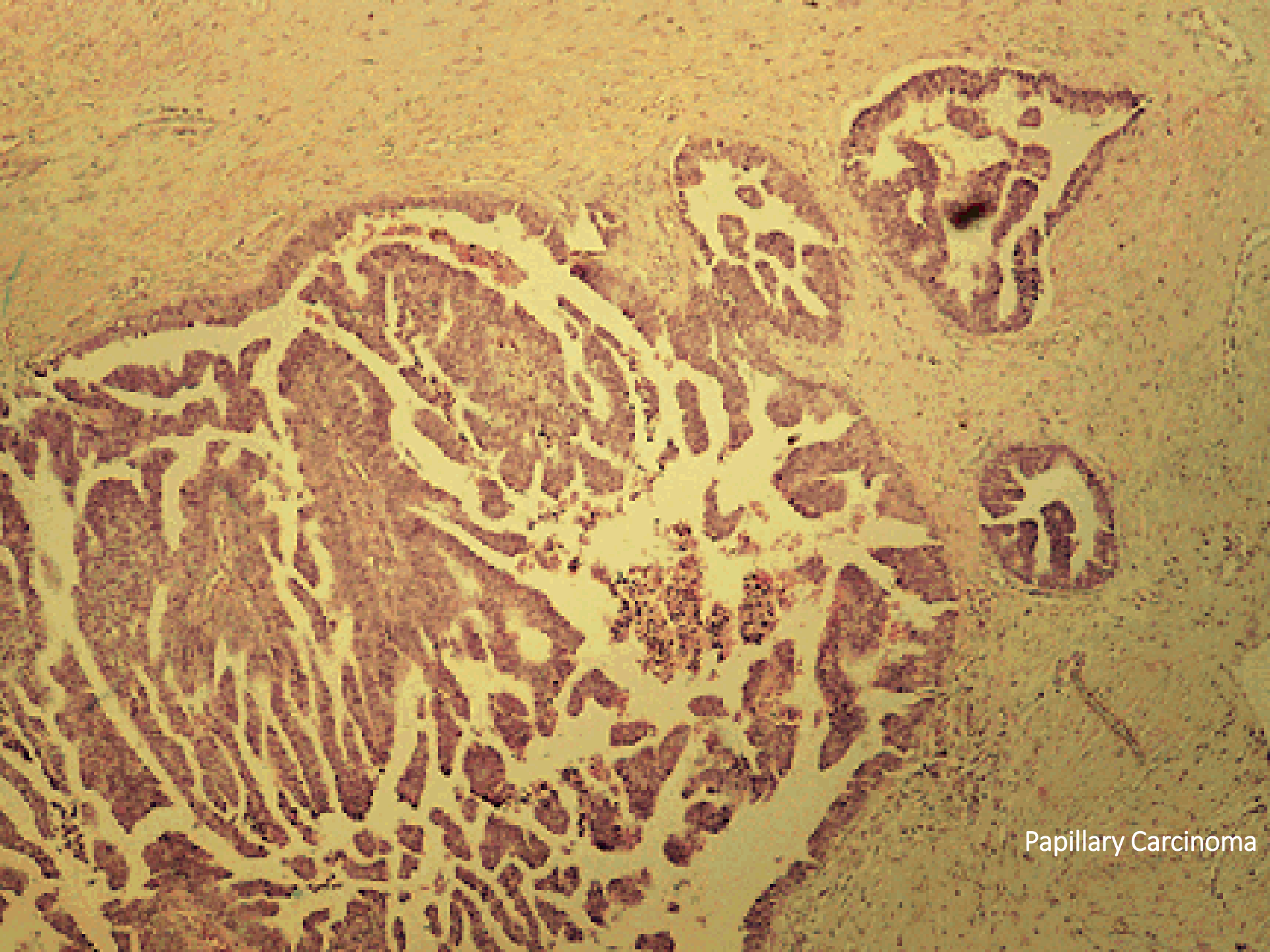
- Best prognosis for any breast carcinoma
- Grossly: star-shaped
- Microscopy: microglandular structures plus impressive desmoplasia

Metaplastic cancers

- Usually with cartilage
- The cell of origin is myoepithelium.

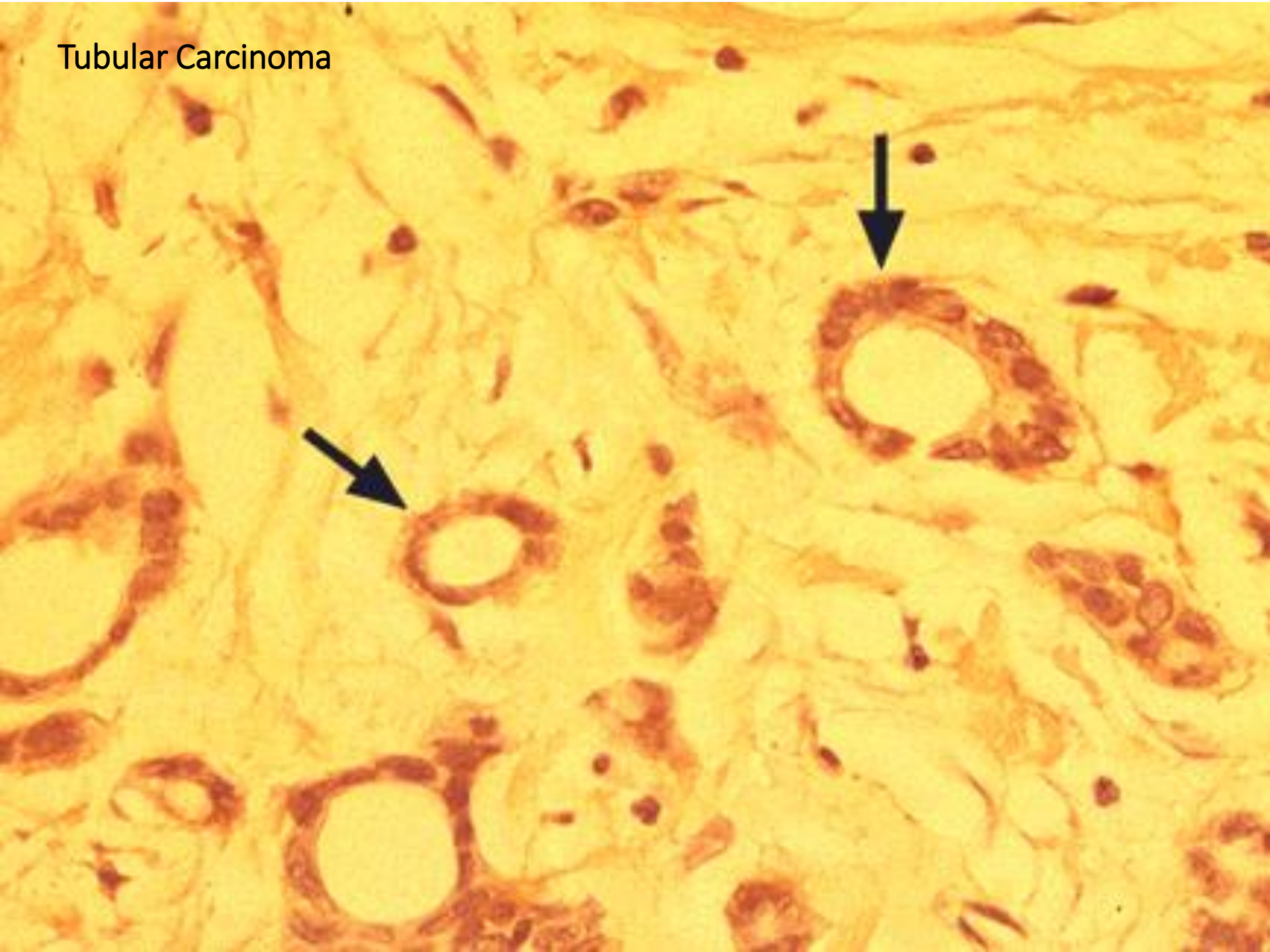
Colloidal (mucinous) carcinoma





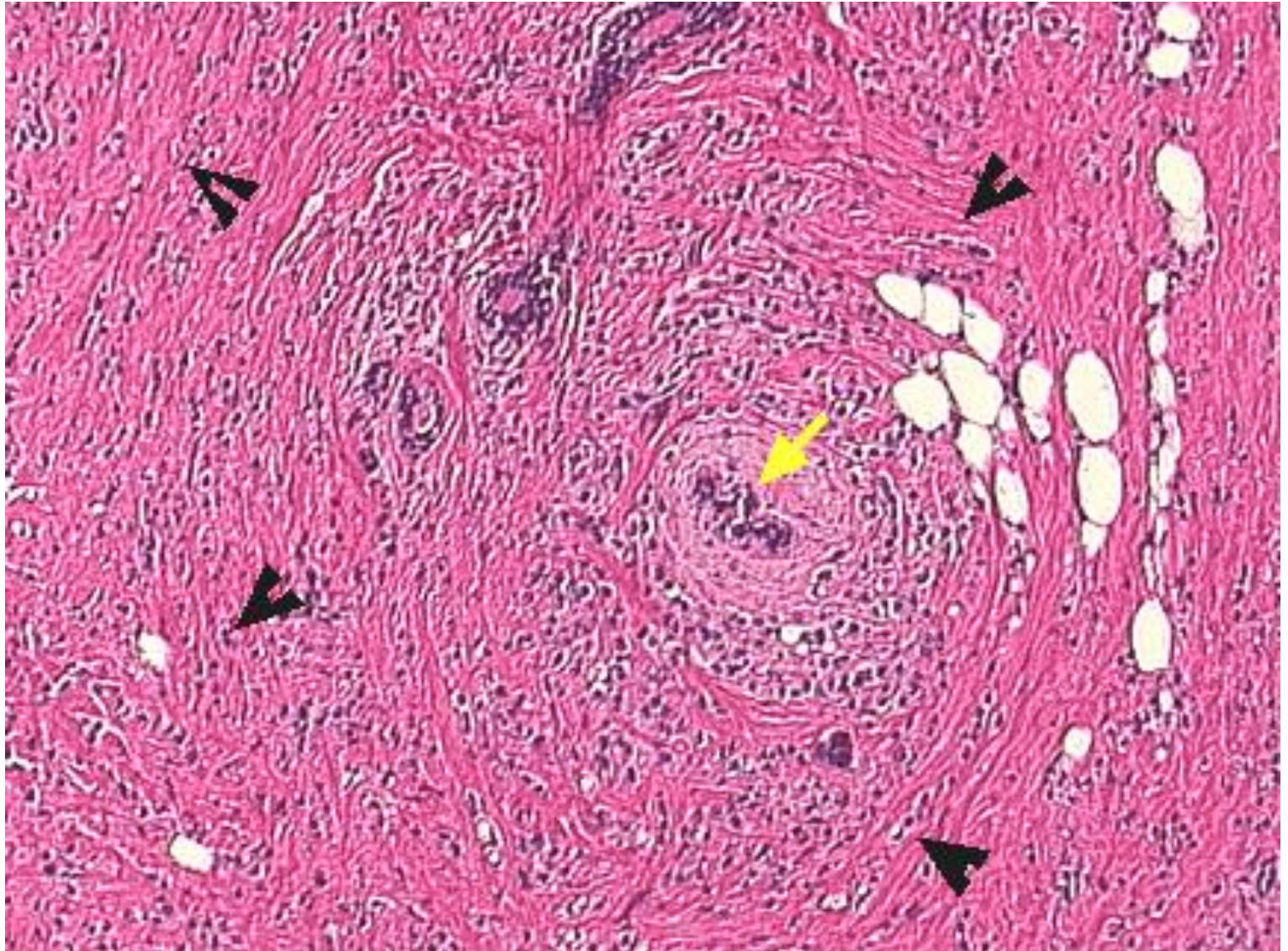
Papillary Carcinoma

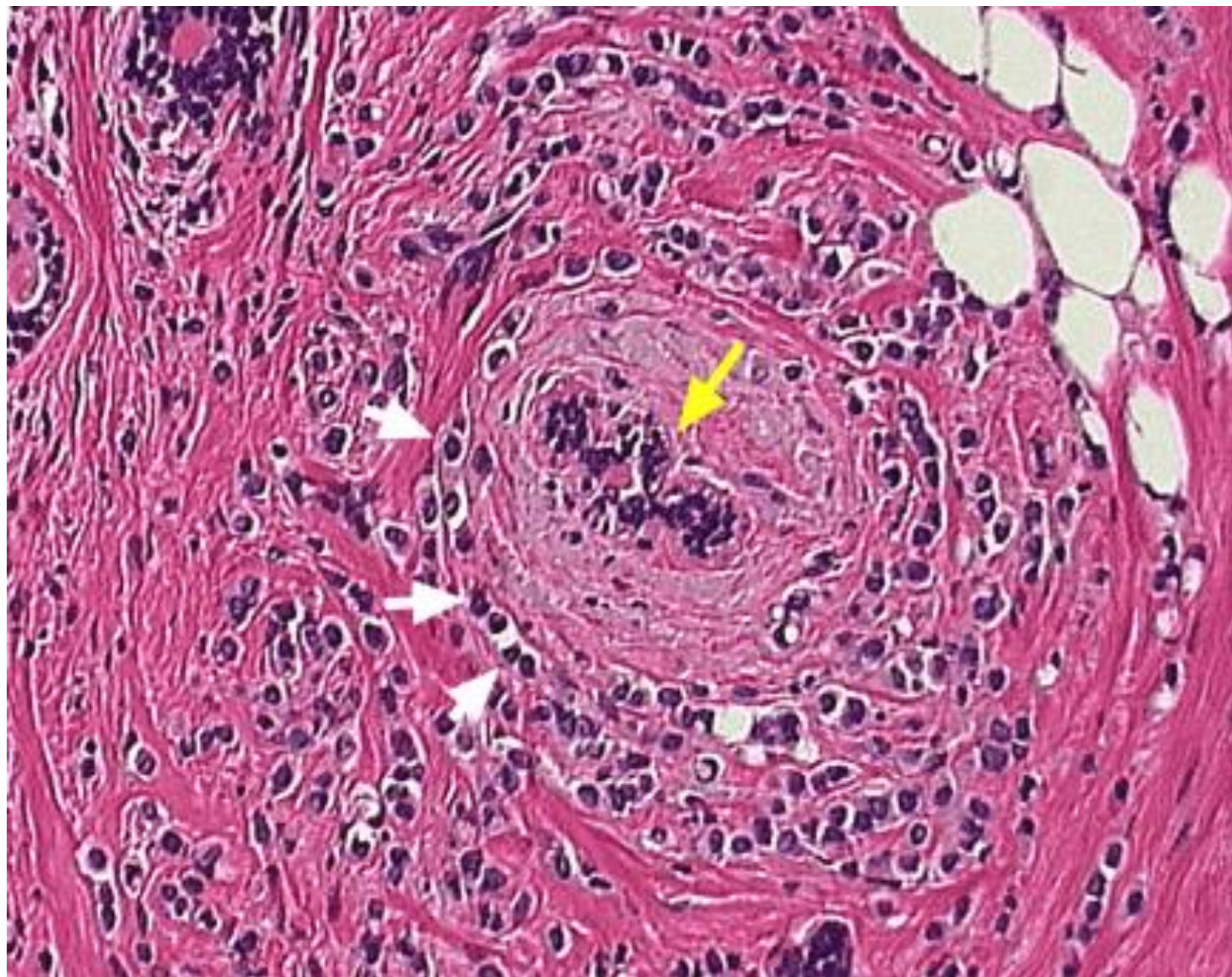
Tubular Carcinoma

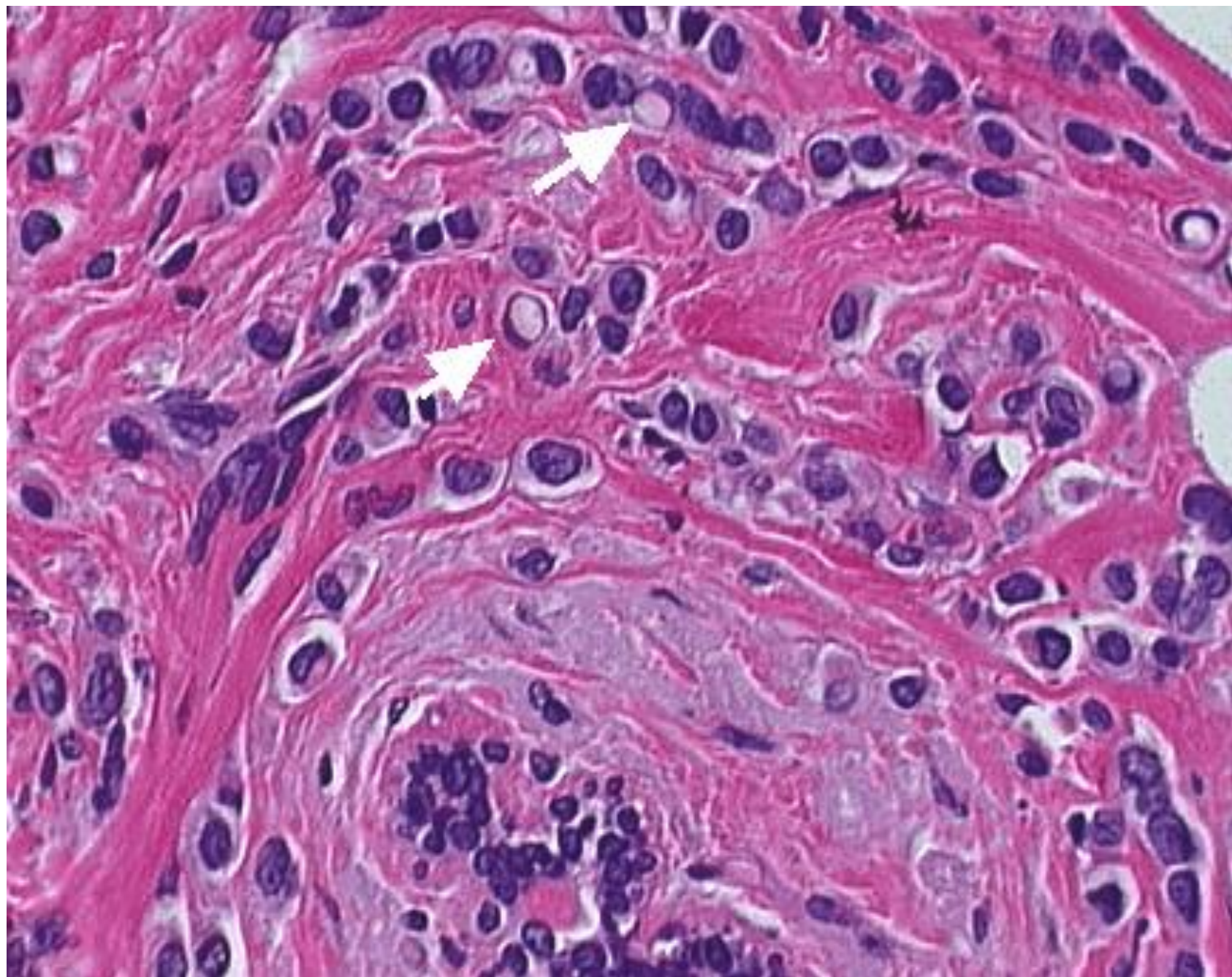


Infiltrating lobular carcinoma

- 10% of infiltrating breast cancer.
- The cells tend to be very small and to lack much anaplasia:
 - often include signet-ring cells
 - making circles around the ducts.
- Such tumors are often multifocal within a breast, and are often bilateral.
- is the subtype with the clearest association of phenotype and genotype. Like LCIS, most cases show biallelic loss of expression of CDH1, the gene that encodes E-cadherin. Lobular carcinomas are dyscohesive, typically infiltrate as single cells, and sometimes fail to produce a desmoplastic response, making it difficult to detect these cancers by palpation and imaging.
- Lobular carcinoma is infamous for spreading to the arachnoid and to bone.







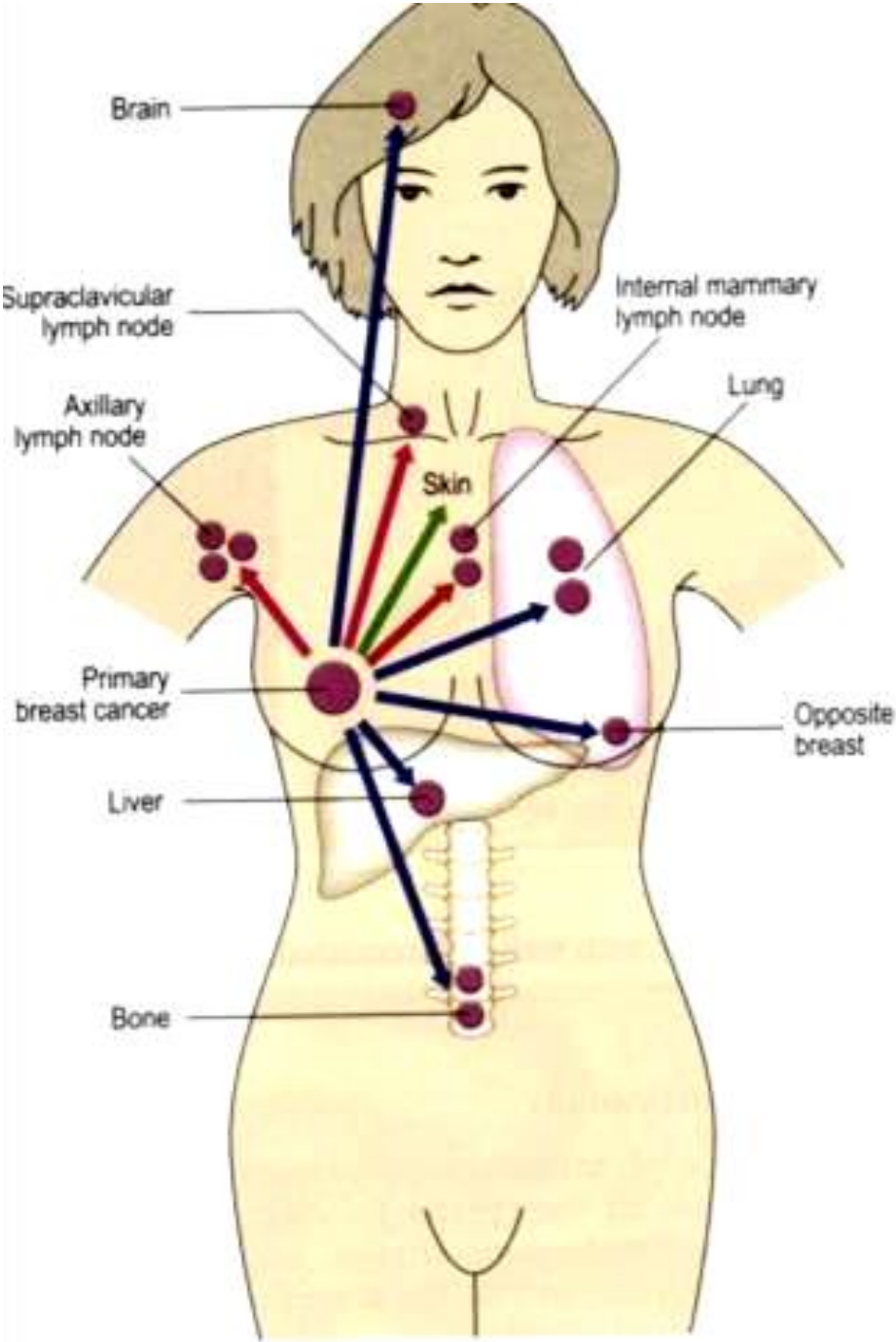
Localization of Breast Cancers

- A majority of breast cancers arise in the outer quadrants, particularly the upper outer quadrant,
- Left breast is slightly more often affected than the right one.
- The single most important prognostic indicator in a case of breast cancer is the size of the tumor at presentation.
- The presence or absence of metastatic tumor in the axillary lymph nodes is even more important.

Prognosis & Metastases

- Cancers detected by self examination (very good prognostic indicator, but very few women perform self-examination properly)
- Tiny cancers found only on mammography, with no palpable mass.
- Clinical course: The disease is likely to metastasize, but is often indolent, and late recurrences are common.
- Metastases:
 - Regional lymph nodes
 - Brain
 - Bone
 - Other organs (lung, liver, opposite breast, skin).

Spread of Breast Carcinoma



Tis-	Carcinoma-in-situ
T1 -	Gross size of tumor is less than 2.0 cm diameter
T2 -	Gross size of tumor is between 2-5 cm diameter
T3 -	Gross size of tumor is above 5 cm diameter
T4 -	Tumor of any size involving chest wall or skin
N0 -	No axillary node involved
N1 -	Metastases to axillary nodes that are freely mobile
N2 -	Metastases to fixed (immobile) axillary nodes
N3 -	Metastases to internal mammary nodes
M0-	No metastases outside of local nodes
M1-	Metastases present

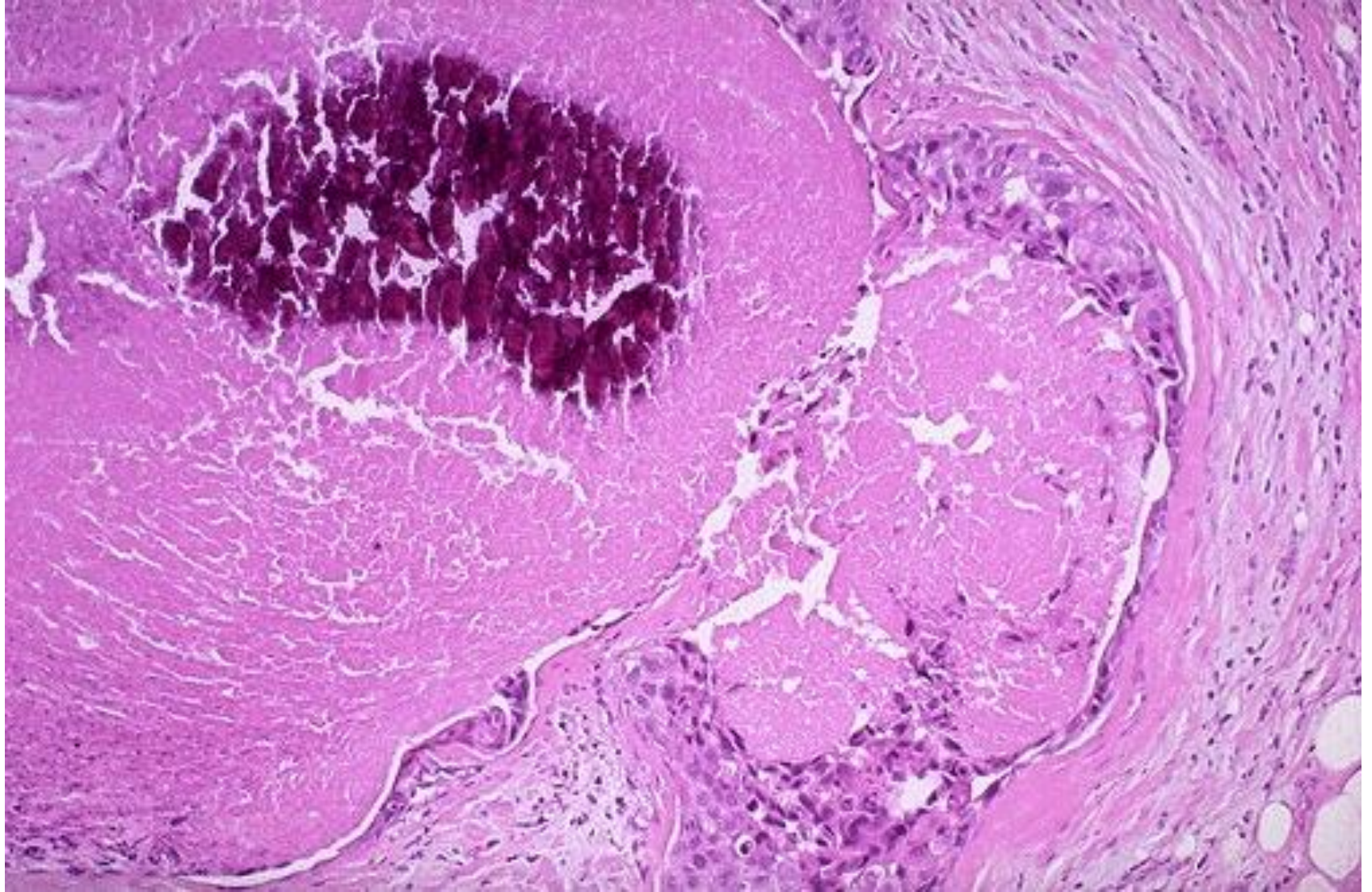
Table 23.6 American Joint Committee on Cancer 8th Edition: Anatomic Stage^a

Stage ^b	T: Primary Cancer (Tumor)	N: Lymph Nodes	M: Distant Metastasis	10-Year Survival (%)
0	Ductal carcinoma in situ	No metastases	Absent	97
I	Invasive carcinoma ≤2 cm	No metastases or only micrometastases	Absent	87
II	Invasive carcinoma >2 cm	1–3 positive LNs	Absent	65
	Invasive carcinoma >5 cm but ≤5 cm	0–3 positive LNs	Absent	
III	Invasive carcinoma >5 cm	Negative or positive LNs	Absent	40
	Any size invasive carcinoma	≥4 positive LNs	Absent	
	Invasive carcinoma with skin or chest wall involvement or inflammatory carcinoma	Negative or positive LNs	Absent	
IV	Any size invasive carcinoma	Negative or positive LNs	Present	5

Diagnosis

- **nipple retraction**
- **calcification** (around 60% calcify to some extent; many benign lesions also calcify)
- retraction and dimpling of skin
- edema of overlying skin or arm
- **lymphedema of breast**
(lymphangiitis carcinomatosa;
peau d'orange, orange-peel)
- **fixation** to chest wall or overlying skin
- ulceration of overlying skin
- **satellite nodules** in overlying skin
- **"inflammatory carcinoma"**
(heavy invasion of breast skin veins, causing congestion).

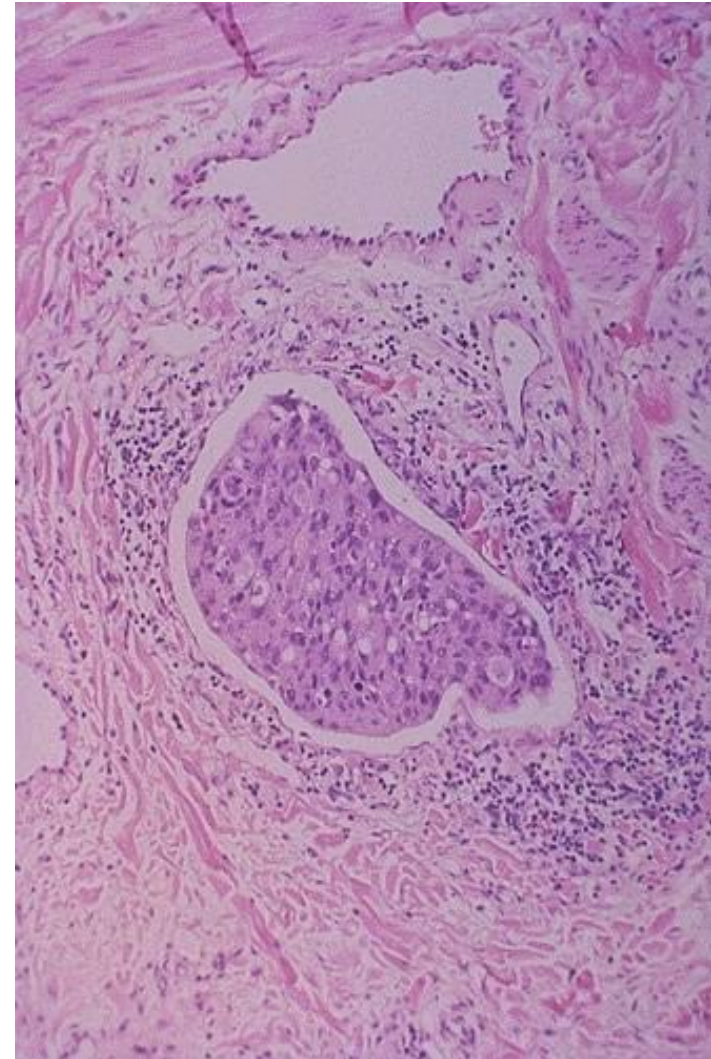
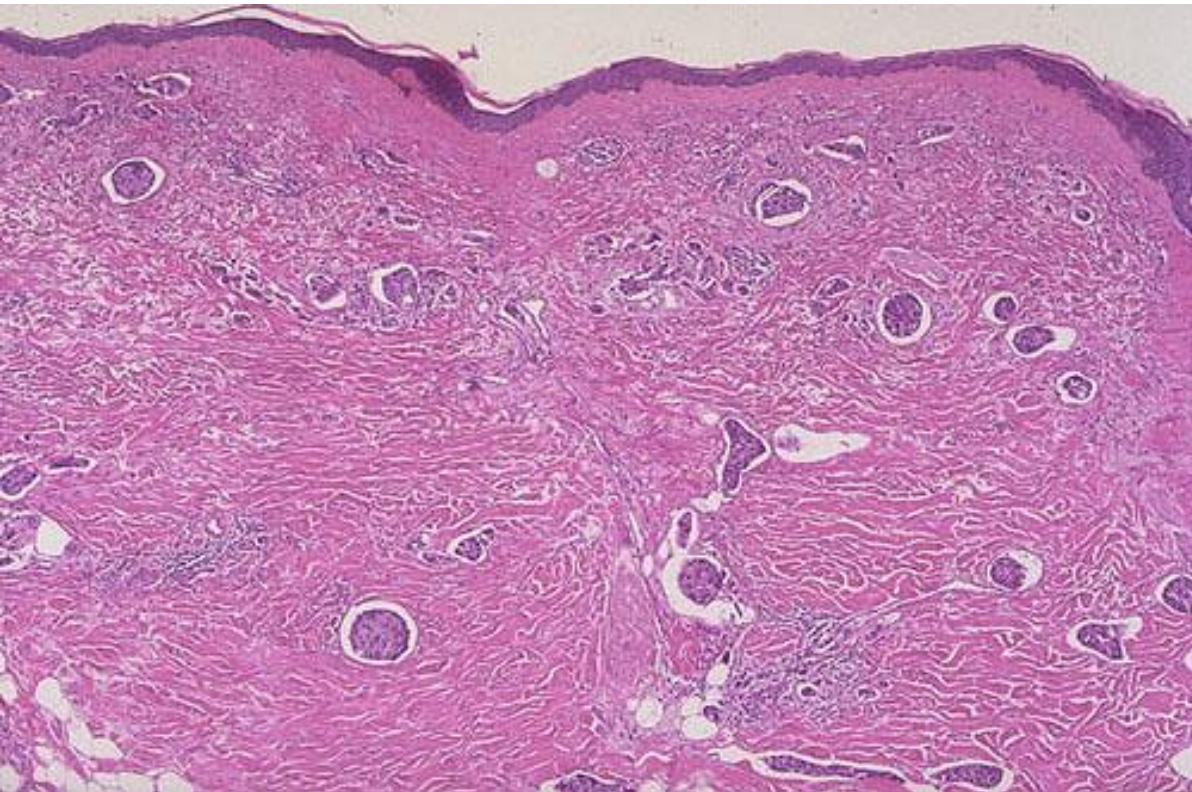
Calcification



Inflammatory carcinoma (*peau d'orange*)



Lymphovascular invasion



	<u>Luminal A</u>	<u>Luminal B</u>	<u>Her-2/neu</u>	<u>Basal-like</u>
Gene expression pattern	Expression(LMW) cytokeratins, and high expression of HR's and associated genes	Expression (LMW) cytokeratins, and moderate to weak expression of HR's and associated genes.	High expression of Her-2/neu . Low expression of ER and associated genes.	High expression of basal epithelial genes, basal cytokeratins. Low expression of ER and Her-2/neu associated genes.
Clinical	~ 50% of invasive breast cancer	~ 20% of invasive breast cancers	~15% of invasive breast cancers	~15% of invasive breast cancers
ER/PR status	ER/PR positive	ER/PR positive	ER/PR negative	Most ER/PR negative
Her-2/neu status	Her-2/neu negative	Her-2/neu expression variable (+/-)	Her-2/neu positive (by definition)	Her-2/neu negative("triple negative")
Biological features		High proliferation than luminal A	High proliferation	High proliferation

Defining Features	Luminal (ER-Positive/HER2-Negative)		HER2 (HER2 Positive)	TNBC (ER-Negative/HER2-Negative) ^a
Percent of breast cancers	~40%–55% (low to moderate proliferation)	~10% (high proliferation)	~20%	~15%
Most similar group defined by mRNA profiling ^b	Luminal A	Luminal B	HER2-enriched (ER-negative), luminal B (ER-positive)	Basal-like
Most common gene mutations	<i>PIK3CA</i> (45%), <i>TP53</i> (12%)	<i>PIK3CA</i> (29%), <i>TP53</i> (29%)	<i>PIK3CA</i> (39%), <i>TP53</i> (70%–80%)	<i>PIK3CA</i> (9%), <i>TP53</i> (70%–80%)
Typical special histologic types	Tubular, grade 1 or 2 lobular, mucinous, papillary	Grade 3 lobular	Some apocrine, some micropapillary	Medullary features, metaplastic ^c
Typical patient groups	Older women, men, cancers detected by mammographic screening	<i>BRCA2</i> mutation carriers	Young women, <i>TP53</i> mutation carriers (ER positive)	Young women, women of African heritage, <i>BRCA1</i> mutation carriers
Complete response to chemotherapy	<10%	~10%	ER positive ~15%; ER negative ~30%–60%	~30%
Metastatic pattern	Bone (70%), more common than viscera (25%) or brain (<10%)	Bone (80%) more common than viscera (30%) or brain (10%)	Bone (70%), viscera (45%), and brain (30%) all are common	Bone (40%), viscera (35%), and brain (25%) all are common
Relapse pattern	Low rate over many years, long survival possible with bone metastases	Early peak at <10 years, late recurrence possible	Bimodal with early and late (10 years) peaks	Early peak at <8 years, late recurrence rare, survival with metastases rare

Molecular testing in breast cancer is used to

- Classify tumor types,
- recognize hereditary implications (eg, BRCA1 mutations)
- identify appropriate therapeutic agents (eg, HER2+ disease or ER/PR + disease).

determine the prognosis of the disease by giving the risk score,

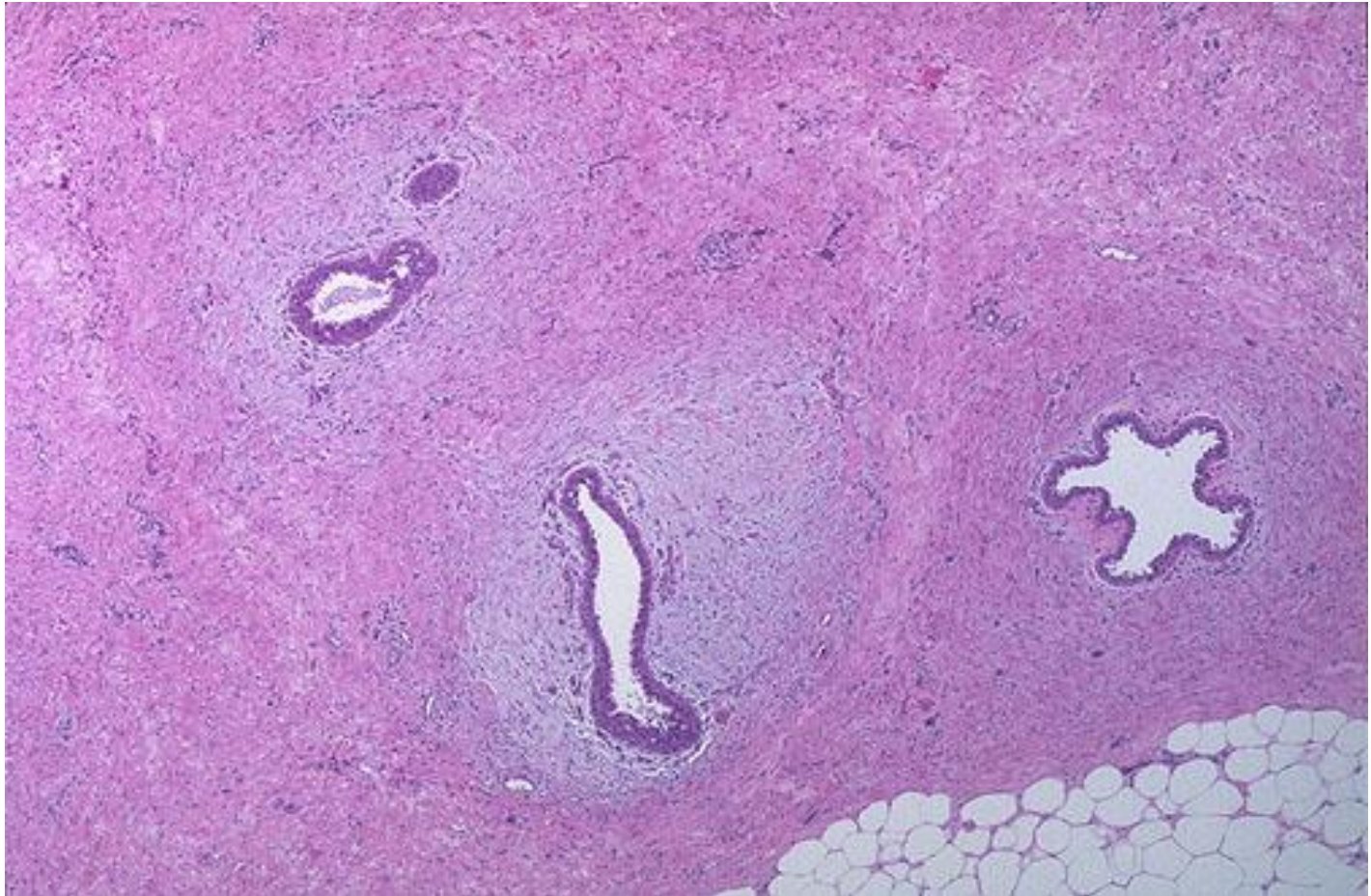
- identify biomarkers that can predict or monitor the response to treatment
- To avoid unnecessary treatment to all cancer patients

DISEASES OF THE MALE BREAST

Gynecomastia

- ▶ Men's breast doesn't contain lobules!!!
- ▶ Proliferation of a man's ducts and stroma, unilateral or bilateral.
- ▶ Causes:
 - ▶ Idiopathic (adolescents or older men; due to XXY)
 - ▶ Hyperestrinism (liver cirrhosis, tumors, iatrogenic, female impersonators, guys using anabolic steroids to look more masculine).
 - ▶ Other drugs
 - ▶ digitalis
 - ▶ spironolactone;
 - ▶ soy products (contain natural estrogens).
- ▶ Idiopathic gynecomastia has no risk for cancer
 - ▶ XXY's and female impersonators (trans-sexuality) on estrogens are at increased risk.
- ▶ The severity is widely variable.

Gynecomastia in male breast



Carcinoma of the male breast

- Uncommon
 - 100x less common than in women,
 - XXY's and female impersonators (trans-sexuality) on estrogens are at increased risk (20X).
- It is almost always an **infiltrating ductal carcinoma**, usually without much desmoplasia.
- Remember: men's breast doesn't contain lobules!!!

THANK YOU FOR YOUR
ATTENTION