Breast Pathology

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Breast Pathology: Clinical Presentation

Non-cyclical (associated with focal site)

Cyclical (with menses); if diffuse ➜ no clinical significance

❶ Pain (Mastalgia)

Causes:

- Ruptured cyst
- Prior injury
- Infection

Majority of painful masses are **benign**

10% of cancers present with pain ⇔ **All** masses should be investigated

❷ Palpable Masses

❸ Nipple Discharge

- Milky: not associated with malignancy
- Serous or bloody: associated with benign, and **rarely** malignancy

Carcinoma Clinical Presentation

Palpable mass	Mammographic density	Mammographic calcifications

Risk Factors

Age

- Highest in postmenopausal women; average age = 64yrs; rare before 25 yrs
- 70% after 55 yrs

Age at Menarche

- Younger = ↑ risk (each 2 yrs delay = 10% ↓ in risk)

First Live birth

- **Earlier =** ↓ risk; nulliparity = ↑risk; full term pregnancy before 20yrs = 1/2 risk after 35 yrs/nulliparous

First Degree relative with Breast Cancer

- **mother, sister, or daughter = x1.5 to 2.5; risk ↑ with number of affected 1st degree relatives**

Breast Biopsy

- Atypical hyperplasia = ↑ risk

Race

- Lower incidence in African American women

Estrogen Exposure

- **Later onset of menopause = ↑ risk; menopause at 55yrs = x2 the risk before 45yrs**
- **Hormone replacement =↑ risk**

Radiation exposure

Women who have had a breast cancer

- 10-fold increased risk of developing 2nd primary breast cancer

Geographic influence

- **Western industrialized countries > developing countries**

Diet

- Fatty diet

Obesity

Exercise

- Might ↓ risk

Environmental toxins e.g. pesticides

Tobacco

- Not associated with breast cancer; associated with development of subareolar abscess or peri-ductal mastitis

Breast–Feeding

- **Longer duration = ↓ risk**

Risk Factors

Major Risk Factors

Hormonal (majority of sporadic cases)

Gender

Age at menarche and menopause

Reproductive history

Breast-feeding

Exogenous estrogens

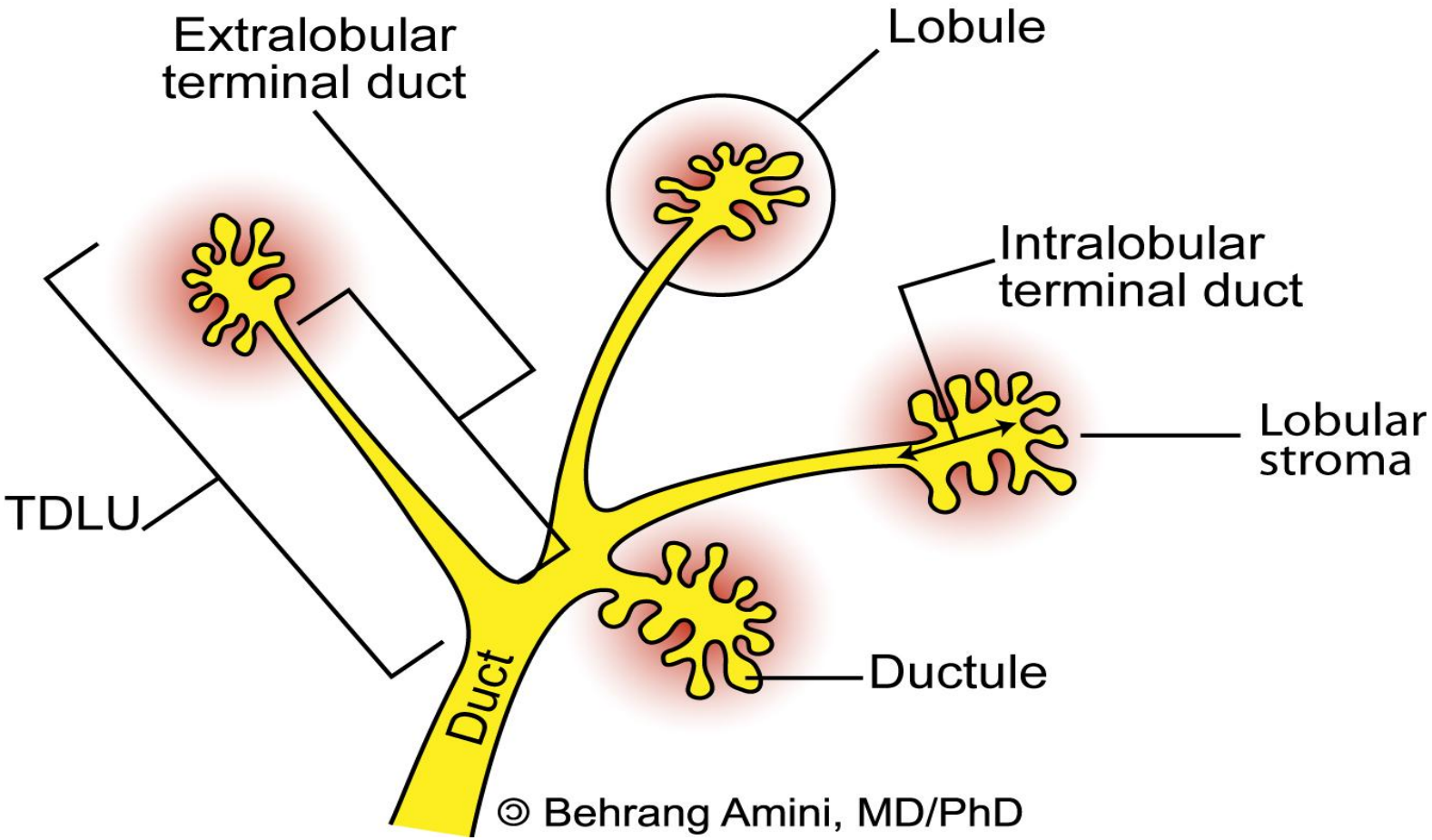
Majority occur in postmenopausal women

Genetic (family history/ germ-line mutations)

13% of cases have a family history of breast cancer in a 1st degree relative

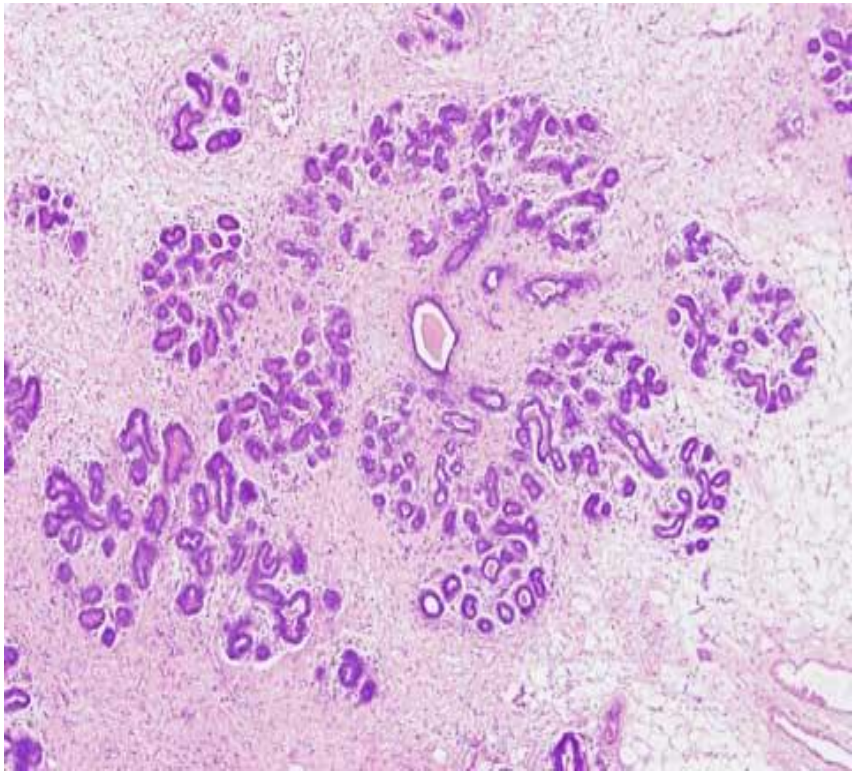
25% of familial (3% of all breast cancers) are due to BRCA1 & BRCA2 (2 highly penetrant autosomal-dominant genes)

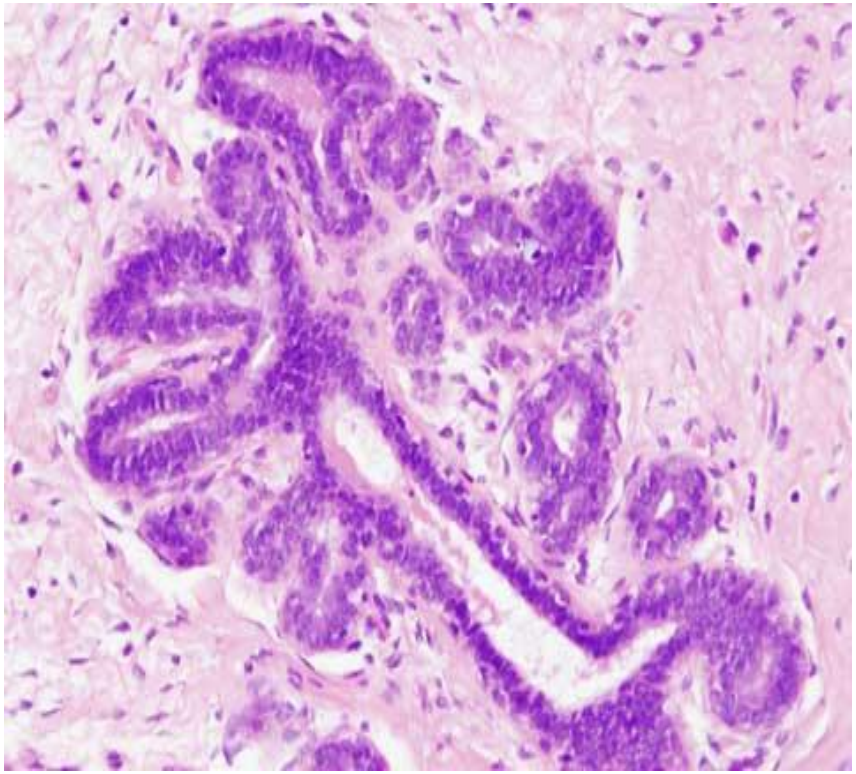
Normal TDLU★ structure



★ Terminal Ductal Lobular Unit

Normal TDLU



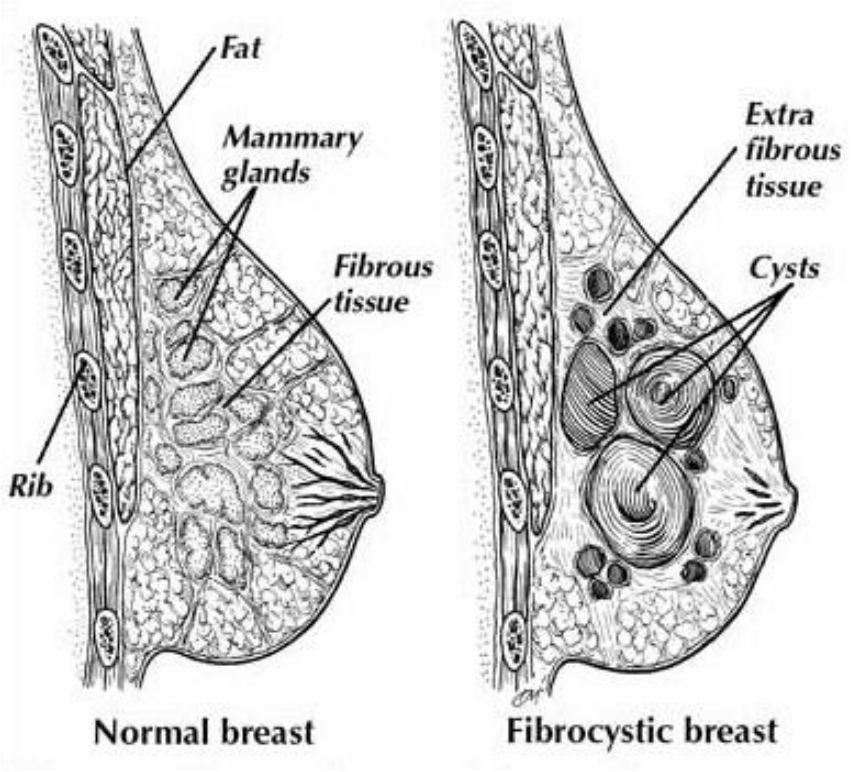


Benign Epithelial Lesions

A. Non proliferative breast changes
B. Proliferative breast disease
C. Atypical hyperplasia

Non Proliferative: Fibrocystic Changes

- **MOST COMMON** disorder of the breast
- Age: 20-55 yrs, decreases after menopause
- Cause is unknown
- Consists of various combinations of cysts, fibrous overgrowth & epithelial proliferation
- **No increased risk for cancer**

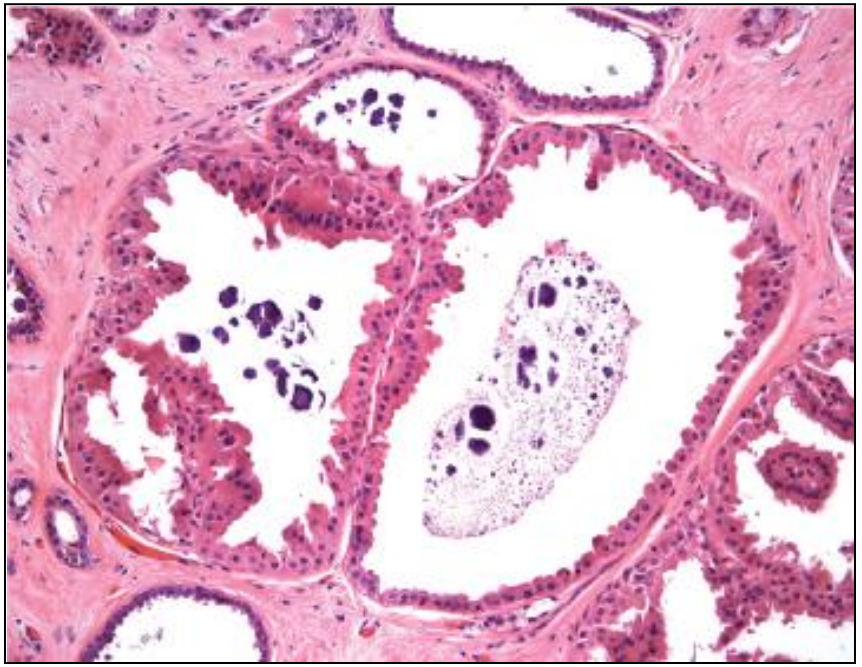


Non Proliferative: Fibrocystic Changes

- **Presentation**:
  1. Asymptomatic **palpable masses**
     - Cysts are the most common cause (alarming: if solitary and firm)
     - Vary from diffuse, small irregularities (lumpy bumpy breast) to discrete masses
  2. May produce mammographic densities ± calcifications
  3. May produce nipple discharge
  4. May produce pain
     - May be cyclical: midcycle or pre-menstrual
     - May be focal or diffuse
     - May be with or without lumps

Non Proliferative: Fibrocystic Changes

- Morphology: 3 patterns; Cystic formation, fibrosis & adenosis
  1. **Cysts**: can be big or small, contain turbid (semi-translucent) fluid
     - *Histology*: lined with flattened epithelium w/ **apocrine** features OR completely lack an epithelial lining
  2. **Fibrosis**: contribute to the palpable **firmness** of the breast
  3. **Adenosis**: Increase in the number of **acini** per lobule - *can be seen in pregnancy*



Benign Epithelial Lesions: Proliferative Disease without Atypia

Proliferation of ductal epithelium and/or stroma without cellular abnormalities that are suggestive of cancer

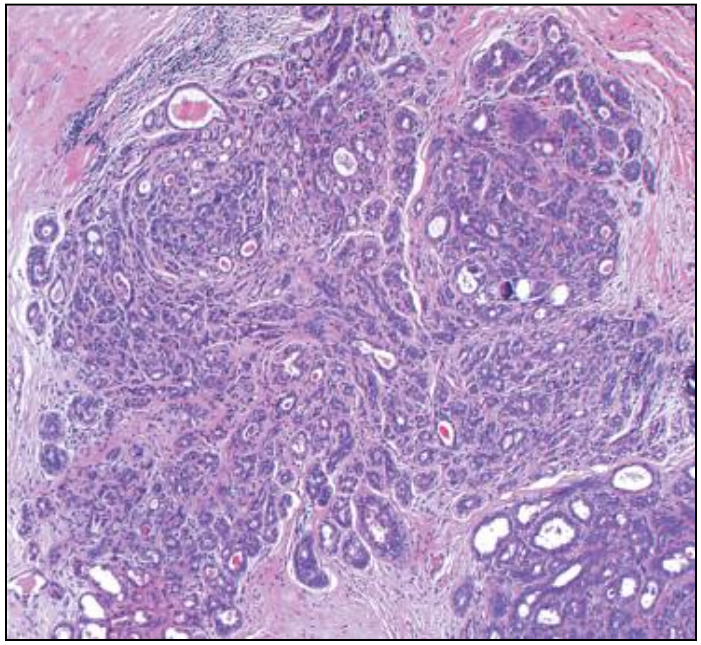
- **Rarely form palpable masses**
- **Incidental** finding
- Detected as mammographic **densities**.

e.g. Large duct papilloma present in 80% as nipple discharge.

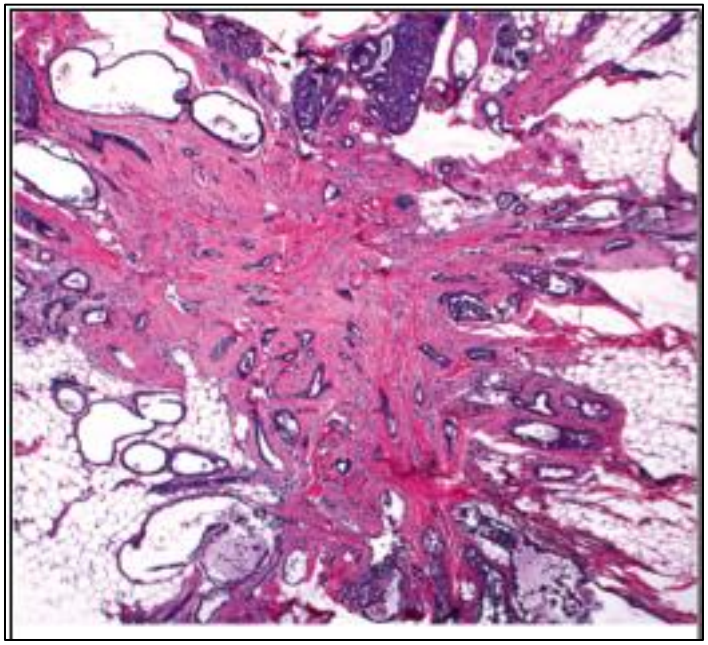
- ***Risk for cancer (slightly increased)*** is 1.5 – 2 times normal

Epithelial Hyperplasia	Sclerosing Adenosis	Complex Sclerosing Lesions/Radial Scar	Papillomas
•**Microscopic finding** •There is an increase in the cellularity of the epithelium of the TDLU •**Defined** by the presence of more than two cell layers •Ranges from mild, moderate to florid and from typical (i.e. without atypia) to atypical •**Distends** the ducts and ductules •shows two distinct cell populations, **epithelial** and **myoepithelial** cells •May **coexist** with other features of fibrocystic change; but may form the predominant pattern	•Incidental microscopic finding; may present as a mass (and can **resemble** cancer) •Diffuse **microcalcifications** are seen on mammograph •**Microscopy:** consists of proliferation of ductular structures and stroma with distortion of the TDLU •Almost always present with other forms of fibrocystic change	•"**Scar**" = morphologic appearance; not associated with prior trauma or injury •They are stellate lesions ▪Central nidus = entrapped glands ▪Hyalinized stroma •Can **resemble** irregular invasive carcinomas <u>mammographically</u> or on <u>gross</u> examination	•**Papillary tumor** that <u>arises from</u> the **duct epithelium** •Arises more often in the **central part** of the breast; lactiferous ducts (75%) but can occur in any quadrant •**Large** duct papillomas are usually **solitary** and situated in the lactiferous sinuses of the **nipple** •**Small** duct papillomas are commonly **multiple** and located **deeper** within the ductal system [more **commonly solitary**, consisting of a single tumor in one duct] •Presentation: •Nipple **discharge**; may be bloody ☞ most common in **central** papillomas •Palpable subareolar mass •Age = 30-50

Benign Epithelial Lesions: Proliferative Disease without Atypia

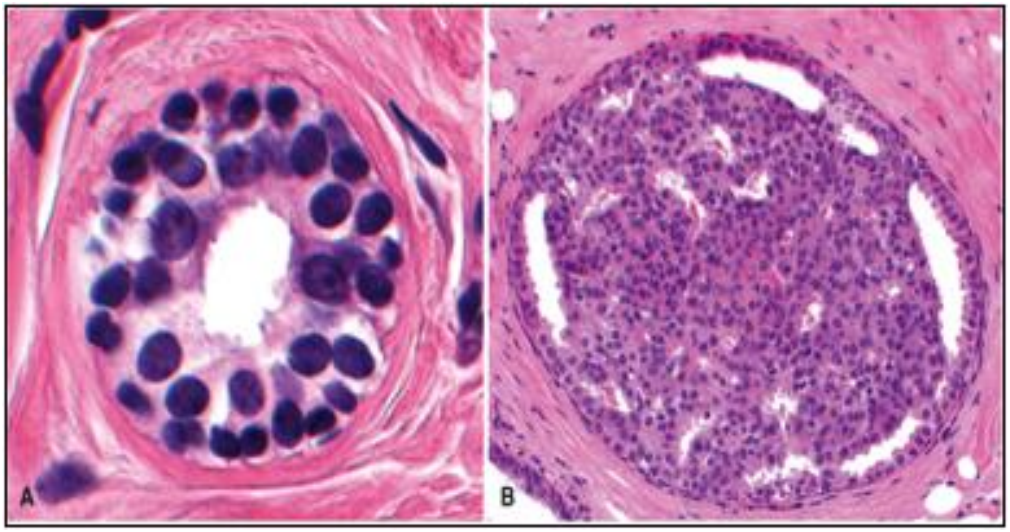


Sclerosing adenosis. The involved **TDLU** is **enlarged**, and the **acini** are compressed and **distorted** by the surrounding **dense stroma**. **Calcifications** are often present within the lumens. Although this lesion is frequently mistaken for an invasive carcinoma, unlike carcinomas, the acini are arranged in a swirling pattern, and the outer border is usually well circumscribed.

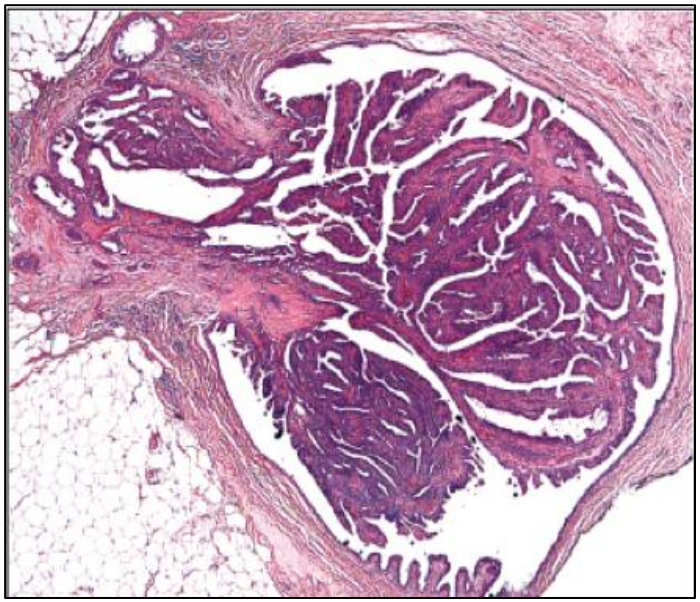


Complex sclerosing lesion (radial scar). There is a **central nidus** consisting of small tubules entrapped in a densely **fibrotic stroma** surrounded by radiating arms of epithelium with varying degrees of cyst formation and hyperplasia. These lesions typically present as an *irregular mammographic density* and closely mimic an invasive carcinoma.

Benign Epithelial Lesions: Proliferative Disease without Atypia



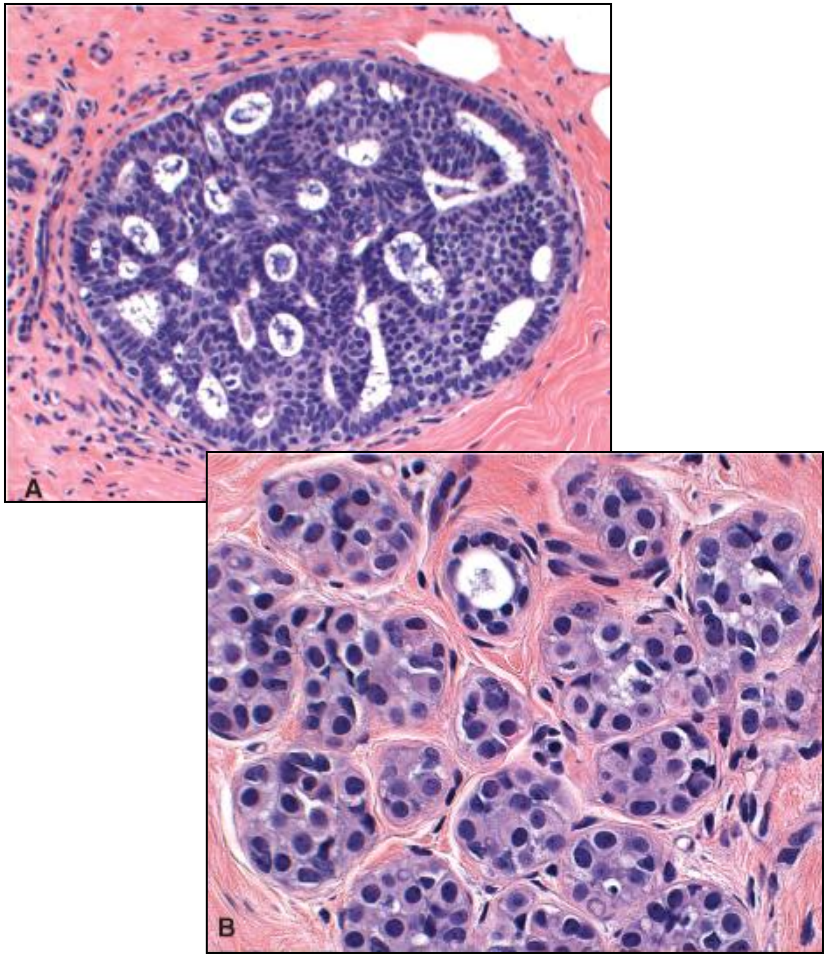
A, Normal: Acinus has a **single basally** located myoepithelial cell layer (cells with dark, compact nuclei and scant cytoplasm) and a **single luminal** cell layer (cells with larger open nuclei, small nucleoli, and more abundant cytoplasm). **B**, Epithelial hyperplasia: The lumen is filled with a **heterogeneous** population of cells of different morphologies, often including both luminal and myoepithelial cell types. Irregular slit-like **fenestrations** are prominent at the periphery.



Intra-ductal 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 w/Atypia

- **Risk for cancer is highly increased** (4-5 times)
- Cellular proliferation **resembling (**has some of the architectural and cytologic features**)** ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) but lacking sufficient qualitative or quantitative features for a diagnosis of carcinoma in situ
- **Include two entities**
  - **Atypical ductal hyperplasia**
  - **Atypical lobular hyperplasia**



Breast Cancer: Classification

Non-invasive

- Ductal Carcinoma In Situ
- Paget's Disease
- Lobular Carcinoma In Situ

Invasive

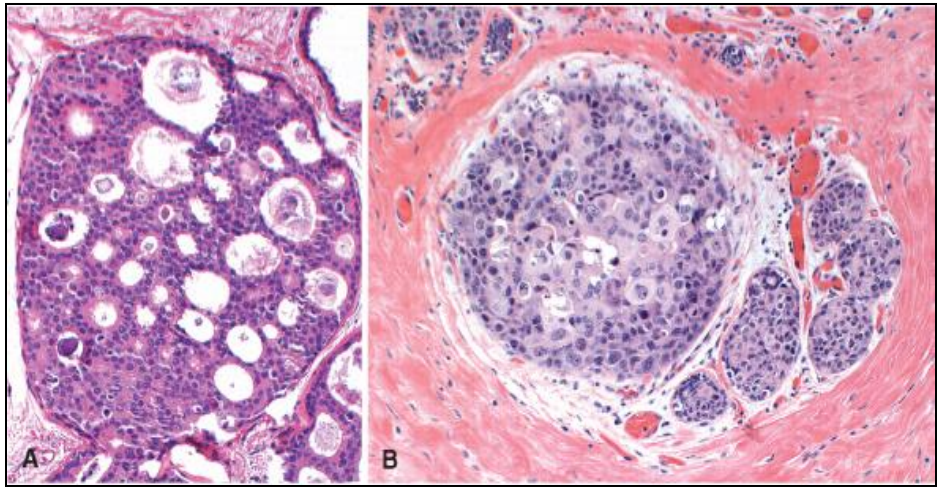
- Invasive Ductal Carcinoma, NOS
- Invasive Lobular Carcinoma
- Tubular
- Medullary
- Mucoid/Colloid

Non-Invasive: Ductal Carcinoma In Situ

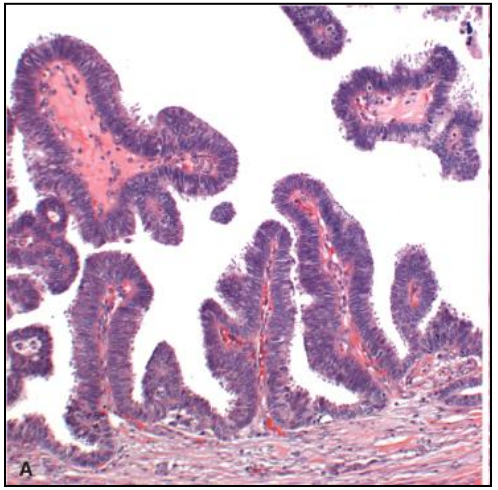
- **Heterogeneous**
- **Noninvasive neoplastic proliferation with risk of development of subsequent invasive carcinoma**
- **Distends and distorts the ducts in the TDLU so that the terminal ducts enlarge and resemble large ducts**
- **Epidemiology:**
  - **Age: between 50 & 59 (~ invasive)**
  - **50% of mammographically detected cancers**
  - **Rapidly increased in the past two decades**
- **Diagnosis: Mammography; detect microcalcifications (in 72-98% of DCIS)**
  - Because they are non-palpable
  - **Most frequently as a calcifications**
  - **Less frequently as a density or a vaguely palpable mass or nipple discharge**
- **Subtypes: Comedo, cribriform, papillary, micropapillary, solid**
- **Clinical (risk of subsequent invasive carcinoma):**
  - **Comedocarcinoma: if untreated = 100% chance**
  - **Cribriform/micropapillary: only 30% chance**

Ductal Carcinoma In Situ: Subtypes

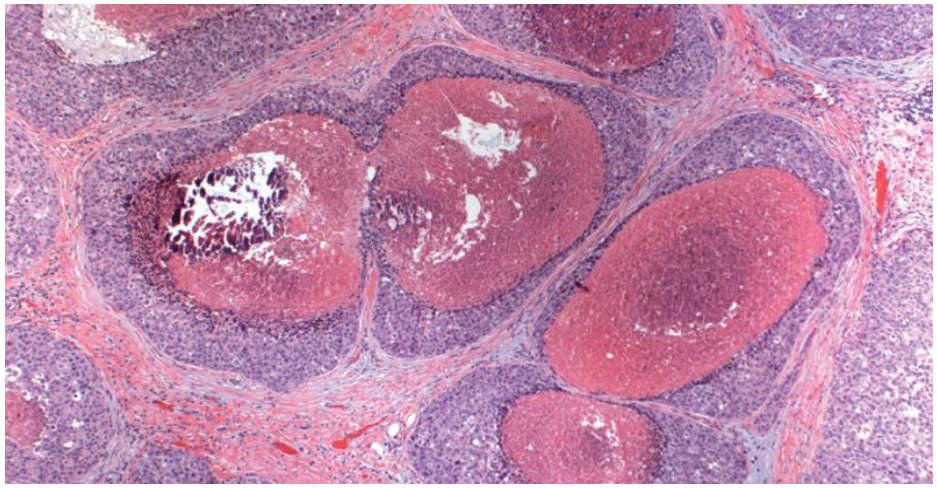
Cribriform and Solid



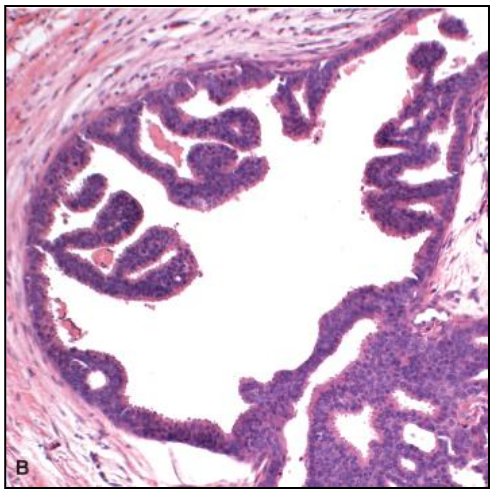
Papillary



Comedocarcinoma



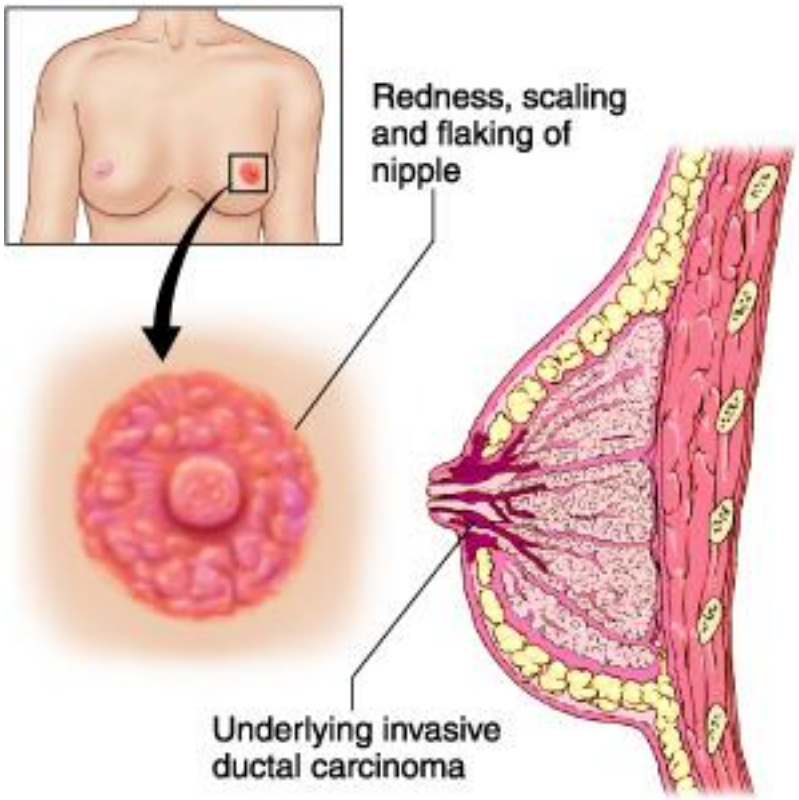
Micropapillary

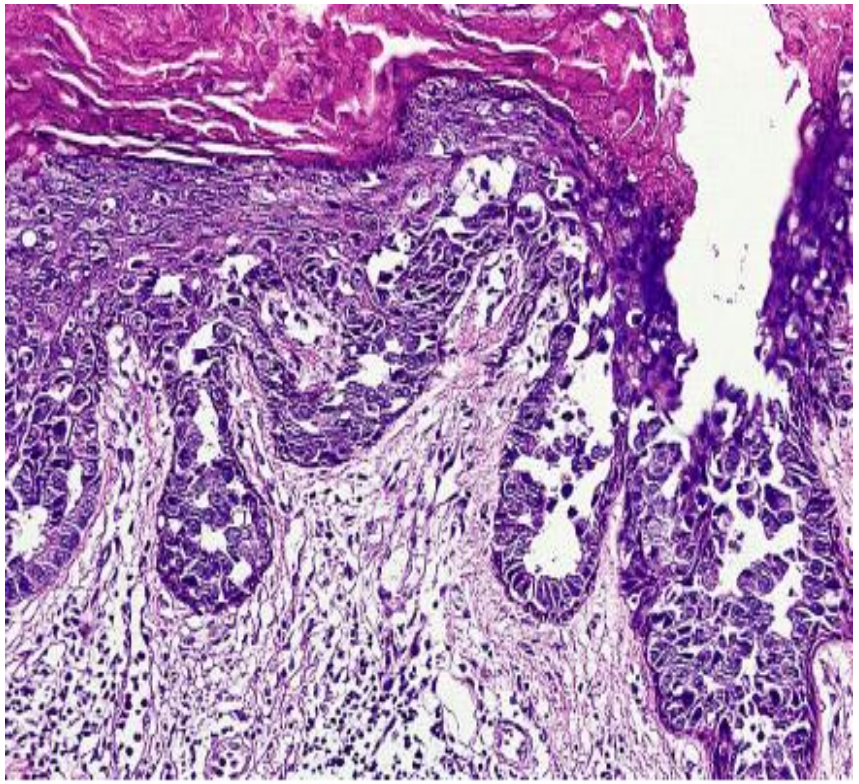


Paget's Disease

- **Rare skin manifestation of breast cancer (1-2 %)**
- Is caused by the extension of DCIS up to the lactiferous ducts and into the contiguous skin of the nipple
- **Clinical:**
  - **Presents as a unilateral erythematous eruption with a scale crust (due to exudate) of the nipple (might be mistaken for Eczema); subtle or eroded**
  - **Pruritus is common**
- **Histology: infiltration of the epidermis by large ductal neoplastic cells (malignant Paget cells)**
  - **extend from DCIS within the ductal system into nipple skin without crossing the basement membrane**
  - **abundant clear or pale cytoplasm and nuclei with prominent nucleoli**
  - **The cells usually stain positively for mucin**
- **Diagnosis: Palpable mass is present in 50 to 60%**
  - **indicates an underlying invasive carcinoma**

Paget's Disease of the Nipple

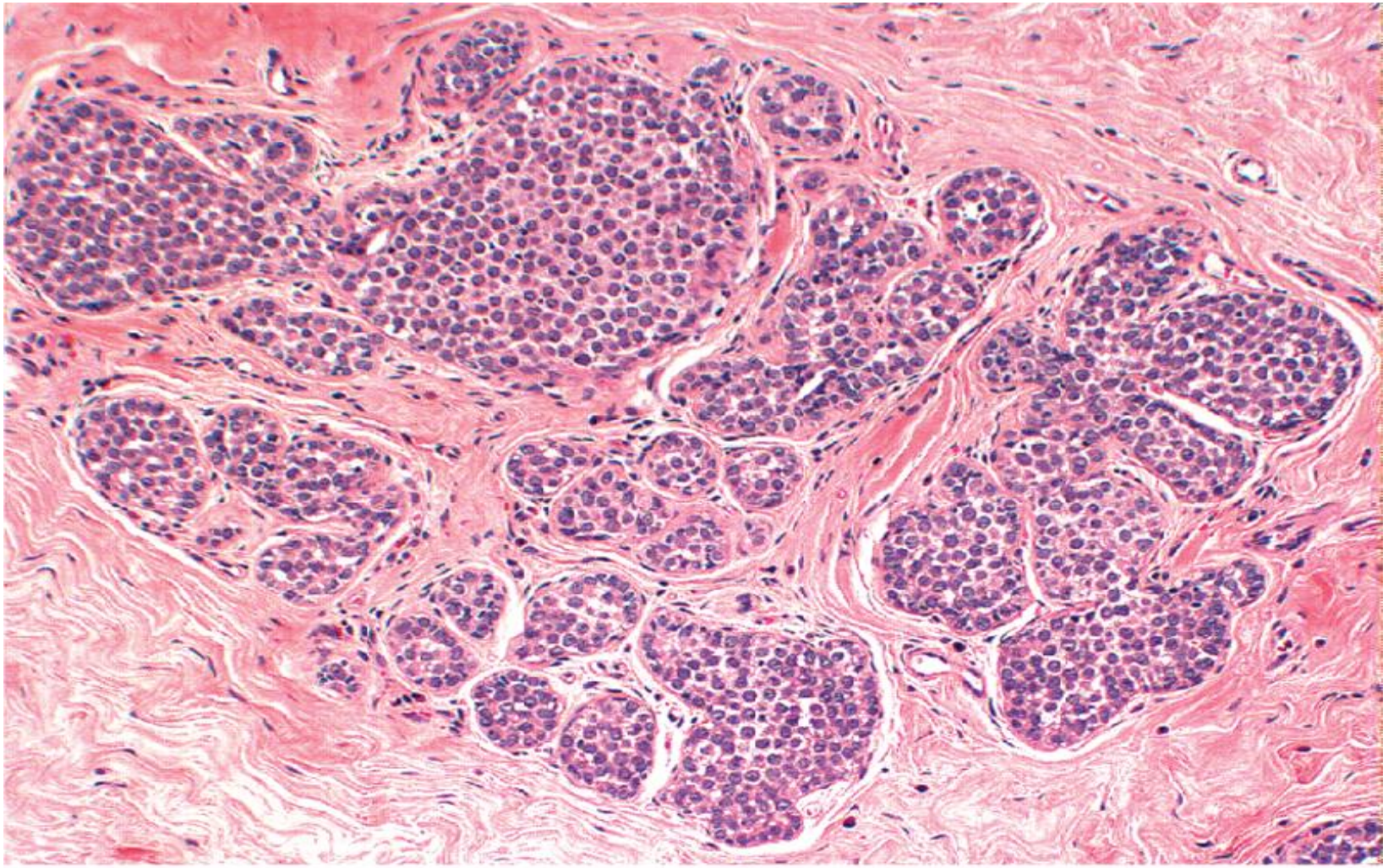




Non-Invasive: Lobular Carcinoma In Situ

- Uncommon (1-6% of carcinomas)
- Nonpalpable (no mass); always an incidental finding in a breast biopsy for other reasons; cannot be identified by mammography (no calcifications)
- **Proliferation of cells that fill and distend the Terminal Duct Lobular Unit**
- Multi-centric (multi-focal) and bilateral (in 20-40% of women)
- Clinical:
  - **If left untreated, about 30% of women develop an invasive cancer within 20 years**
  - **The cancer could be ductal or lobular**
  - **Risk is increased for both breasts**

LCIS



REMEMBER

The 2 non-invasive carcinomas are

- Non-palpable
  - But DCIS can form mass + associated w/calcifications
- A third of affected women will develop the invasive form
- DCIS: distends & distorts terminal ducts of TDLU
- LCIS: distends & distorts TDLU (the whole unit)
- LCIS is bilateral; equal risk of developing cancer for both breasts

Clinical Features of Breast Cancer

Palpable mass

Axillary lymph node metastases

- Half of patients will have ALN metastases by the time a cancer becomes palpable

Inflammatory Breast Cancer

- Dimpling of skin "peau d'orange"
- Lymphedema & thickening of the skin ; l**ymphatics may become so involved as to block the local area of skin drainage**
- **Enlarged erythematous breast**
- **Does not correlate with a specific histologic type of carcinoma**

Retraction of the nipple

- When the tumor involves the central portion of the breast

Mammographic densities

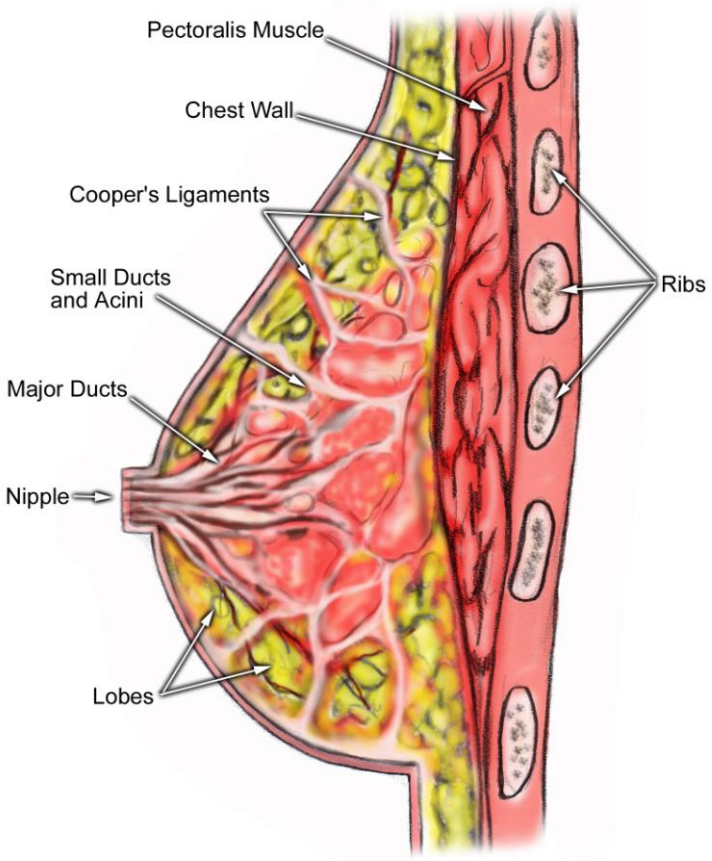
Mammographic calcifications

- In **OLDER WOMEN**, <u>invasive</u> carcinomas most commonly present as a
  - Mammographic **density**
  - Are half the size of a palpable cancer
  - *Fewer than 20% will have nodal metastases*
- <u>Invasive</u> carcinomas presenting as mammographic **calcifications *without*** *an associated density* are
  - Very small in size
  - *Metastases are unusual*.

Invasive Ductal Carcinoma ,NOS

- NOS: not otherwise specified; doesn't indicate that this tumor arises from the ductal system
- **COMMONEST** type of breast cancer (80%)
- Produce a **desmoplastic** response (fibroblastic stromal reaction to the invading tumor cells), which replaces normal breast fat (= mammographic density) and forms a hard, **palpable mass** (hence *scirrhous carcinoma*)
- The tumor shows an infiltrative attachment to the surrounding structures → dimpling of the skin (due to traction on suspensory ligaments) or nipple retraction

Invasive Ductal Carcinoma ,NOS



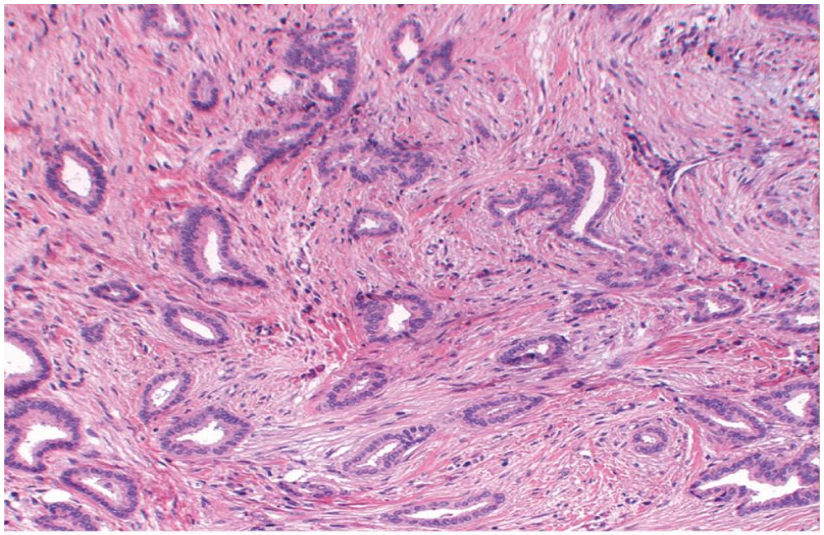
- **The tumor shows an infiltrative attachment to the surrounding structures → dimpling of the skin (due to traction on suspensory (Cooper's) ligaments) or nipple retraction**

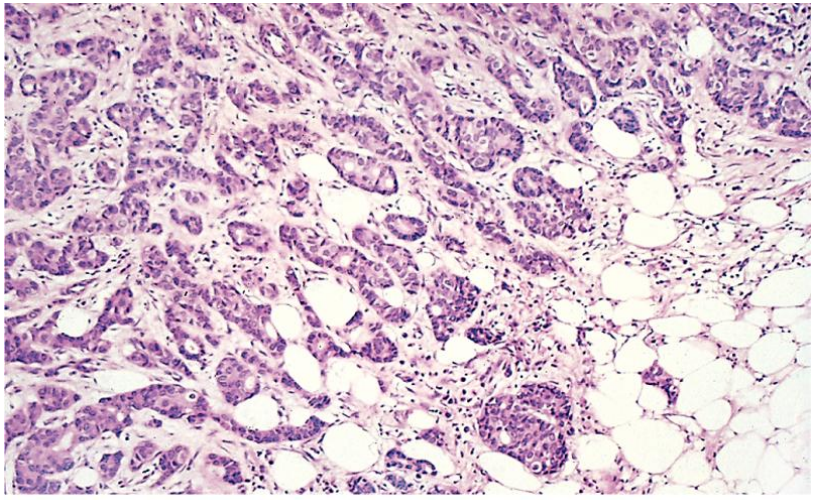
Invasive Ductal Carcinoma ,NOS

GROSS MORPHOLOGY:

- Firm ,**hard**, and have an irregular border
- Cut surface: **gritty** (grating sound when cut or scraped)
- **Irregular margins** with stellate infiltration
- Center: small foci of chalky white **stroma** & occasionally **calcifications**
- Could be soft and well demarcated
- Accompanied by varying amounts of DCIS

Invasive Ductal Carcinoma ,NOS





HISTOLOGICAL MORPHOLOGY:

- Tumor cells are larger than normal epithelium
- Patterns: **glandular** formation, **cords** of cells, broad **sheets** of cells or a mixture of all these, usually within a **dense stroma**
- Range from well differentiated, in which there is glandular formation, to poorly differentiated, containing solid sheets of pleomorphic neoplastic cells
- When associated with a large amount of DCIS require large excisions with wide margins to reduce local recurrences

Invasive Ductal Carcinoma ,NOS

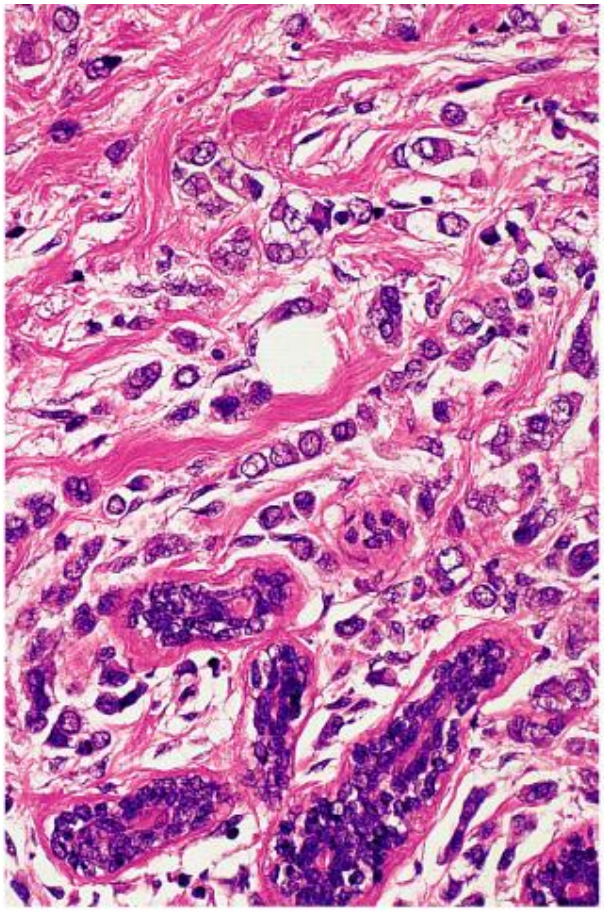
SUMMARY

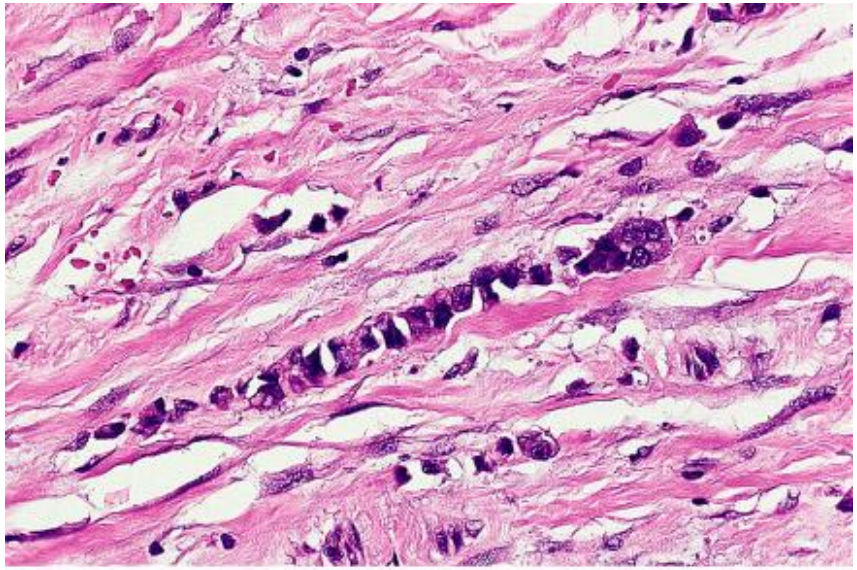
- Commonest type
- Produce desmoplasia (abundant fibrous stroma)
- Forms a hard palpable mass
- Could cause dimpling of the skin/nipple retraction
- Gross: hard, gritty cut surface with irregular margins
- Histology:
  - Large tumor cells, in glandular formations, cell cords, broad sheets or a mixture; within dense stroma
  - Ranges from well differentiated to poorly differentiated

Invasive Lobular Carcinoma

- 2nd most **COMMON** (10% of breast cancers)
- Alone or in combination with ductal carcinoma
- Bilateral & multi-centric
- Amount of desmoplasia varies from dense to very little → presentation varies from discrete mass to subtle, diffuse indurated (hardened) area
- Morphology:
  - Most are firm to hard with irregular margins
  - Single infiltrating cells ,often one cell width
  - No tubules or papillary formation
  - 10% of cases have mixed features of invasive ductal and lobular carcinomas.

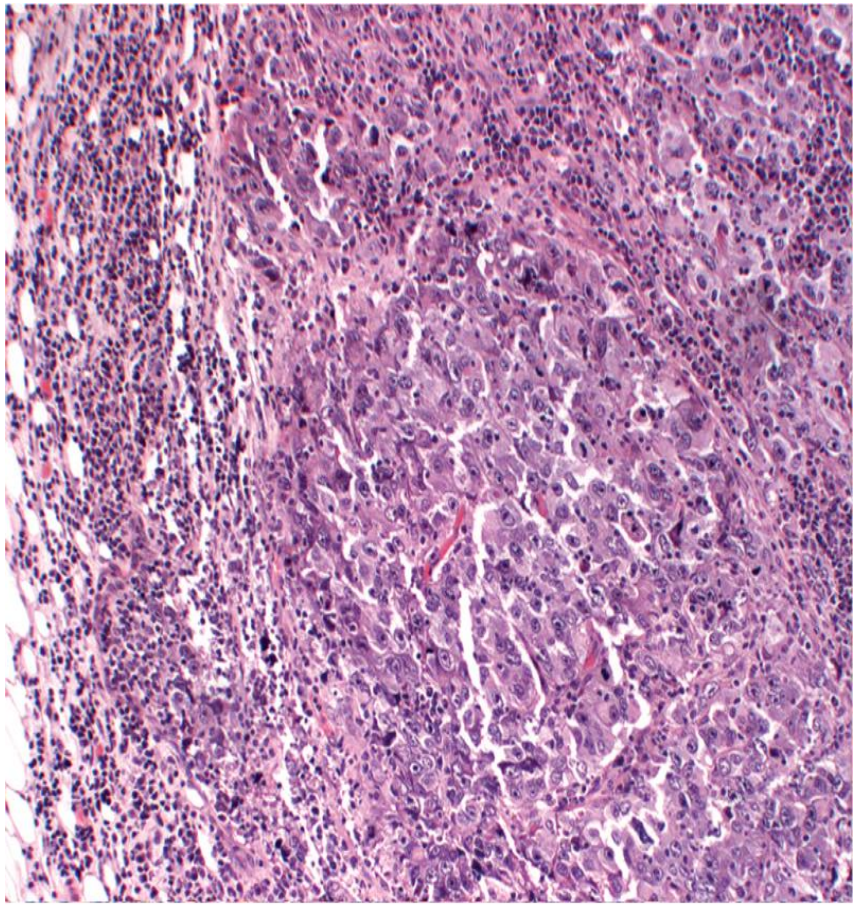
Invasive Lobular Carcinoma





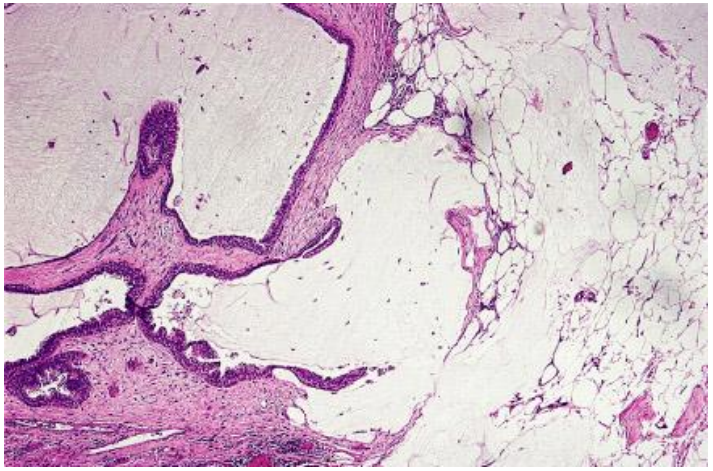
Invasive Medullary Carcinoma

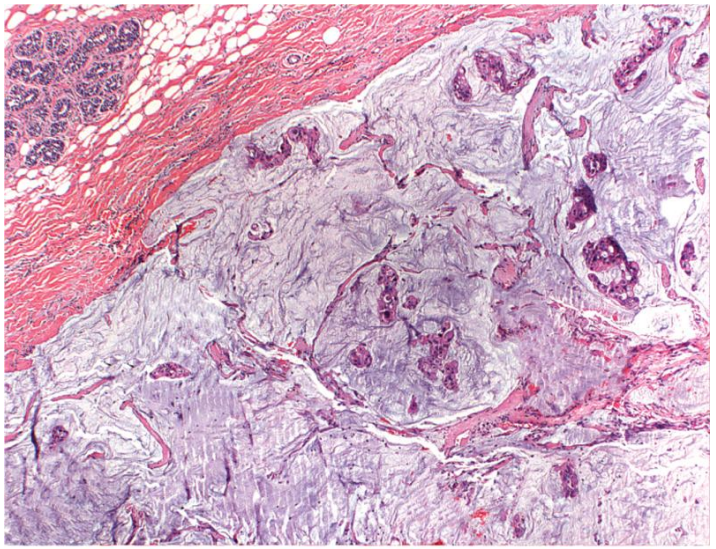
- Presents as a well circumscribed **mass**
- *May be mistaken clinically and radiologically for fibroadenoma*
- **No desmoplastic** reaction → is **soft** and **fleshy** (encephaloid)
- Gross: **hemorrhage** & **necrosis**
- Microscopically:
  - **Solid sheets** of malignant cells and frequent mitoses
  - **Scant fibrous stroma**
  - **Lymphocytes and plasma cells** surround the tumor cells



Colloid Carcinoma/Mucinous Carcinoma

- Occur in **OLDER WOMEN**
- Sharply **circumscribed**
- Lacks fibrous stroma (**no desmoplasia**) → **soft** and gelatinous
- May be in pure mucinous or mixed
- Gross: **glistening** cut surface
- Histologically: composed of small **islands**, occasionally forming **glands**, and isolated tumor cells floating in pools of **extracellular mucin**



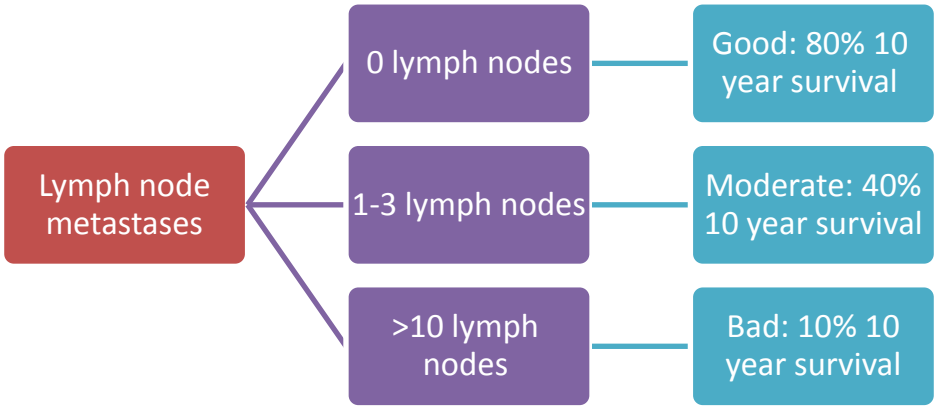


Invasive Ductal Carcinoma ,NOS	Invasive Lobular Carcinoma	Invasive Medullary Carcinoma	Colloid Carcinoma/Mucinous Carcinoma
•**Commonest** type •Produce desmoplasia (abundant fibrous stroma) •Forms a hard palpable mass •Could cause dimpling of the skin/nipple retraction •GROSS: hard, gritty cut surface with irregular margins •HISTOLOGY: •Large tumor cells, in glandular formations, cell cords, broad sheets or a mixture; within dense stroma •Ranges from well differentiated to poorly differentiated	•2nd most **COMMON** •Alone / in combination •Bilateral & multi-centric •desmoplasia varies → presentation varies (mass or no mass) •MORPHOLOGY: •Firm/hard w/ irregular margins •Single infiltrating cell •No tubules or papillary formation •10% have mixed features of ductal & lobular	•Well-circumscribed mass •No desmoplasia → soft & fleshy (encephaloid) •GROSS: **hemorrhage** & **necrosis** •MICROSCOPICALLY: •**Solid sheets** of malignant cells and frequent mitoses •**Scant fibrous stroma** •**Lymphocytes and plasma cells** surround the tumor cells	•Occur in **OLDER WOMEN** •Well-circumscribed mass •No desmoplasia → soft & gelatinous •May be in pure mucinous or mixed •GROSS: **glistening** cut surface •HISTOLOGICALLY: composed of small **islands**, occasionally forming **glands**, and isolated tumor cells floating in pools of **extracellular mucin**

Prognosis

Major prognostic factors:

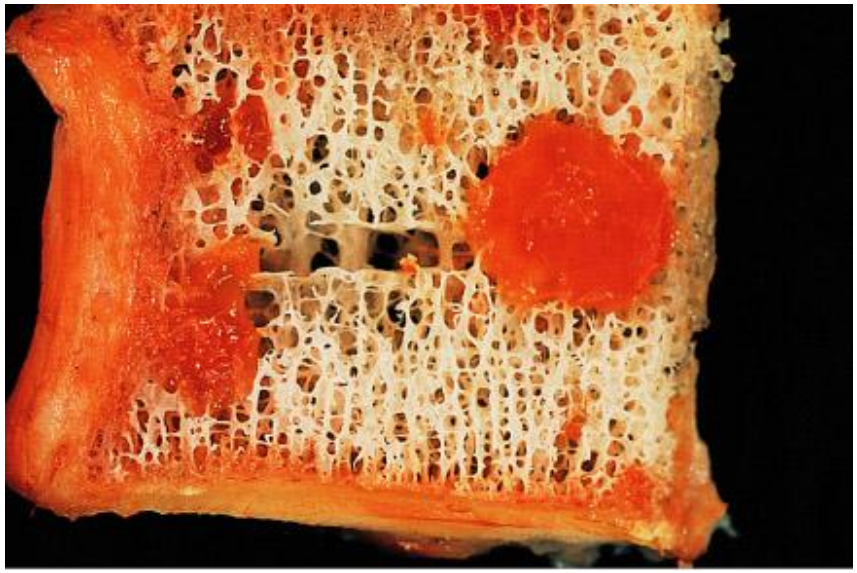
1. Invasive or in situ disease
   - Majority of women with DCIS will be cured
   - ~50% of invasive will metastasize
     - Non-invasive has better prognosis
     - Distant metastases = worse prognosis
2. Lymph node metastases
   - if we cant find distant metastases the most important prognostic factor for metastases is axillary lymph node metastases
   - Remember the bigger the tumor the more risk it might reach the axillary lymph nodes



Prognosis

3. Tumor size
   - Bigger → reaches axillary node → metastases
   - <2 cm → good prognosis
4. Local invasion
   - Invasion of muscles and skin is associated with later distant metastases
   - Rare nowadays
5. Inflammatory carcinoma = bad prognosis

Metastasis to vertebra



Prognosis

Minor prognostic factors

1. Histological Subtype
   - Invading Infiltrating ductal and lobular carcinomas > worse prognosis
   - medullary and mucinous > intermediate
   - tubular and cribriform > most favourable prognoses
2. Tumour grade
   - name of grading : bloom Richardson
   - Grading separates tumors into three categories
     - according to the amount of well formed tubules,
     - the degree of nuclear pleomorphism
     - mitotic rate
3. Estrogen and progesterone receptors
   - **Good prognosis** (better than cancers without receptors. Why? they respond to **tamoxifen**
4. HER2/neu .
   - Associated with a **poor prognosis** but responds well to **Trastuzumab (Herceptin)**
3. Lymphovascular invasion: Tumor cells may be seen within vascular spaces (either lymphatics or small capillaries) surrounding tumors
   - **associated with lymph node metastases = poor prognosis**
4. Proliferative rates

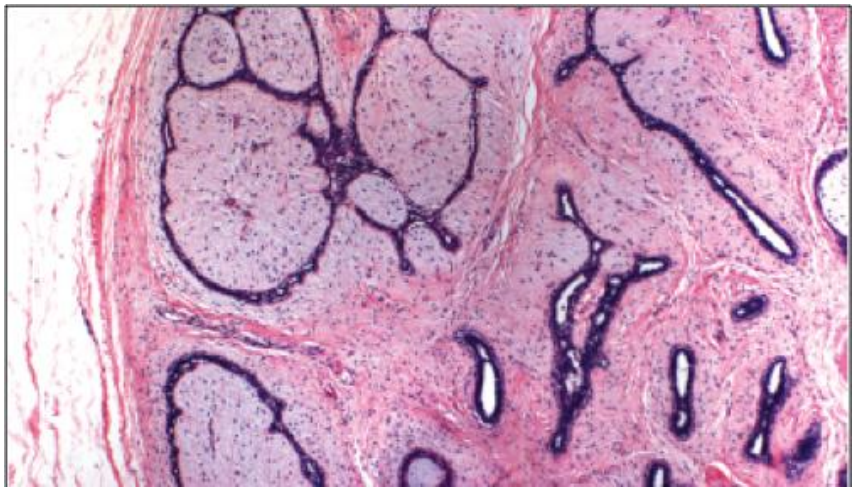
Breast Cancer:

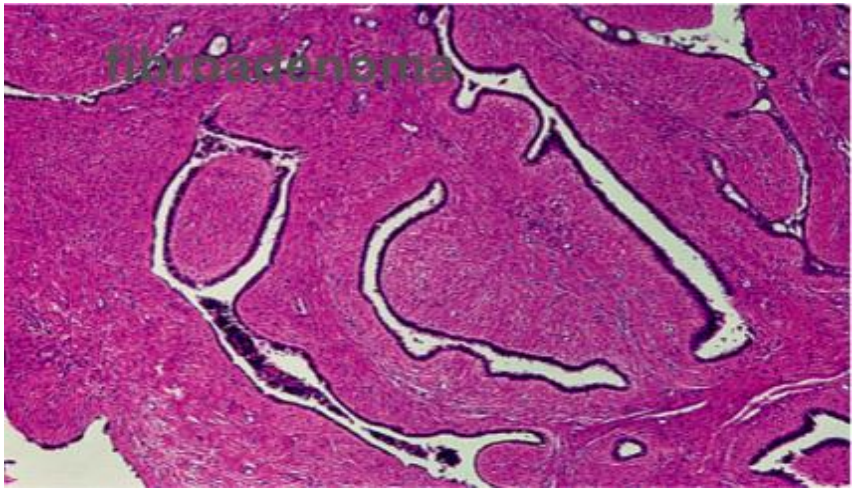
STROMAL TUMORS

❶ Fibroadenoma

Presentation	Most common benign tumor of the breast •Age: <30years •Palpable mass; •Spherical, rubbery nodule •Sharply circumscribed •Freely movable; can be shelled out •May increase in size during pregnancy, and cease to grow after menopause
Course	Completely benign; carcinoma may arise within a fibroadenoma; predominant type has been *lobular carcinoma*
Morphology	•Usually solitary; but may be multiple & involve both breasts •Cut-surface: pearl white •Histologically •mixture of ducts and fibrous connective tissue
Treatment	•Lumpectomy

❶ Fibroadenoma





❷ Phylloides Tumor

Presentation	•Any age; but most commonly 6th decade (10-20 yrs later than fibroadenoma) •Palpable mass
Morphology	Arise from intralobular stroma
Course	•Majority: low-grade •May recur locally •Rarely metastasize •Rarely: high-grade; behave aggressively •Local recurrences •Distant hematogenous metastases
Treatment	Excised with wide margins to avoid local recurrences