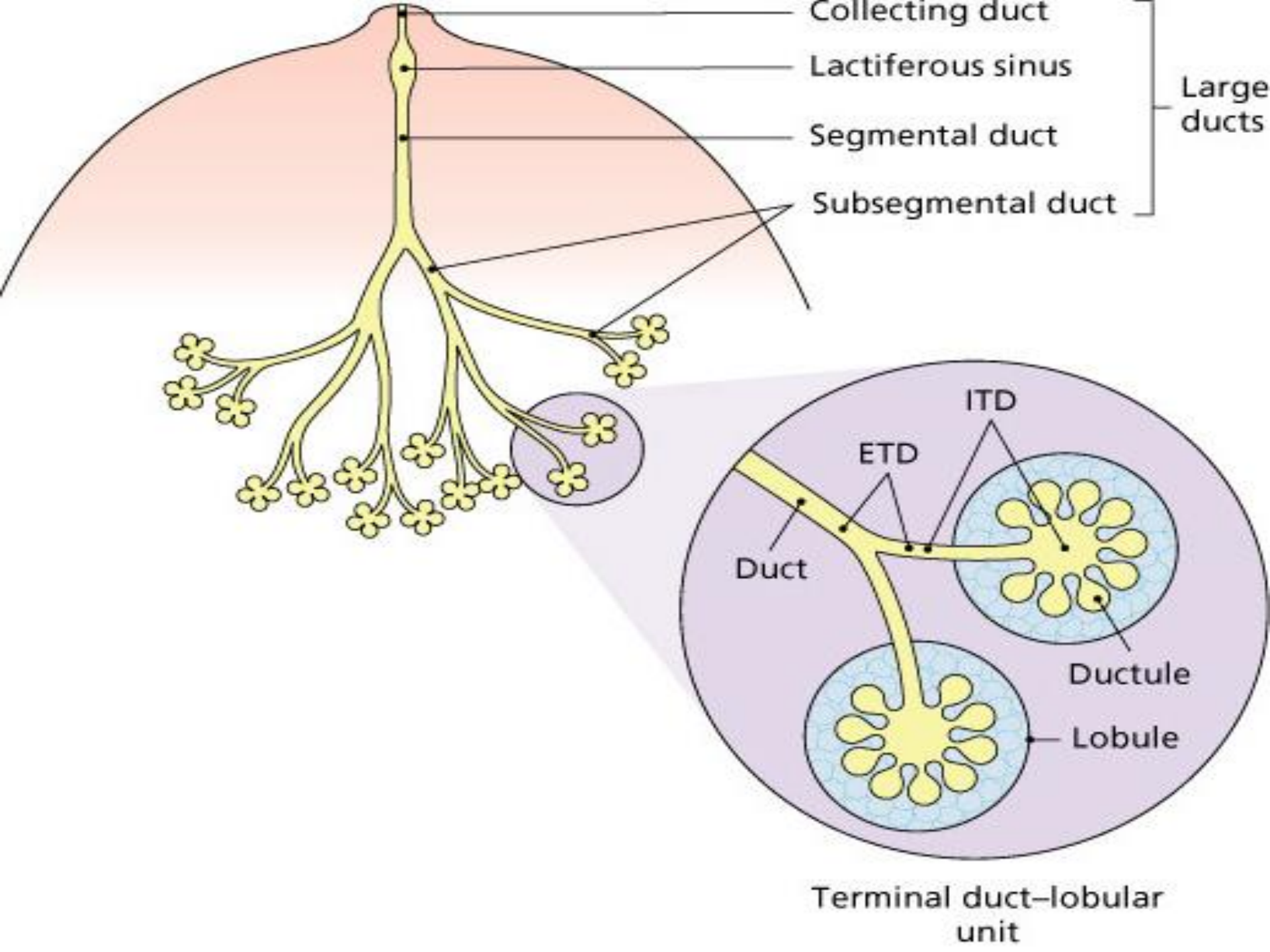
Breast pathology

Outline

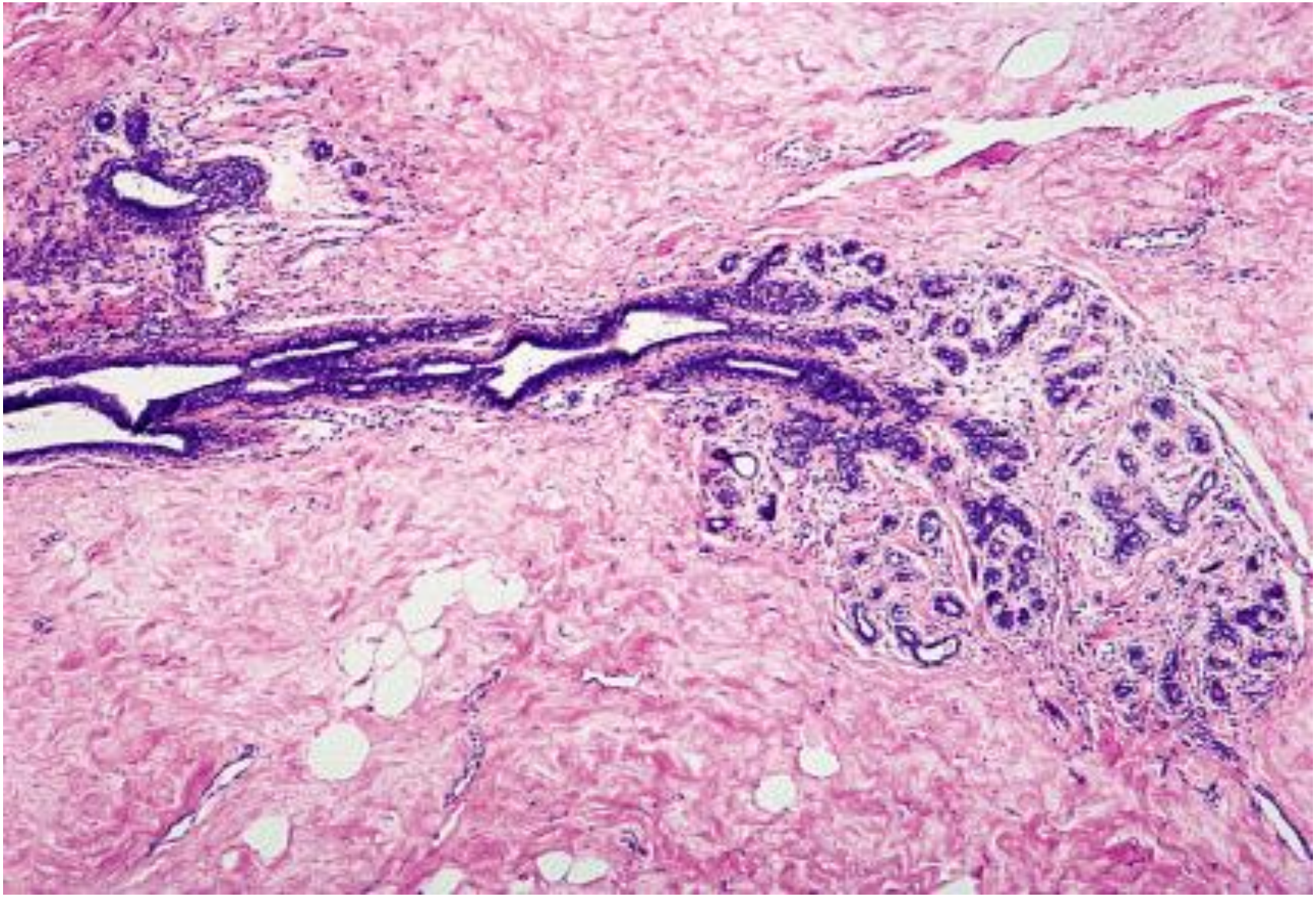
- Developmental disorders
- Inflammation
- Non-proliferative breast changes
- Proliferative breast disease

- **Tumors**
  - Epithelial tumors
  - Connective tissue tumors



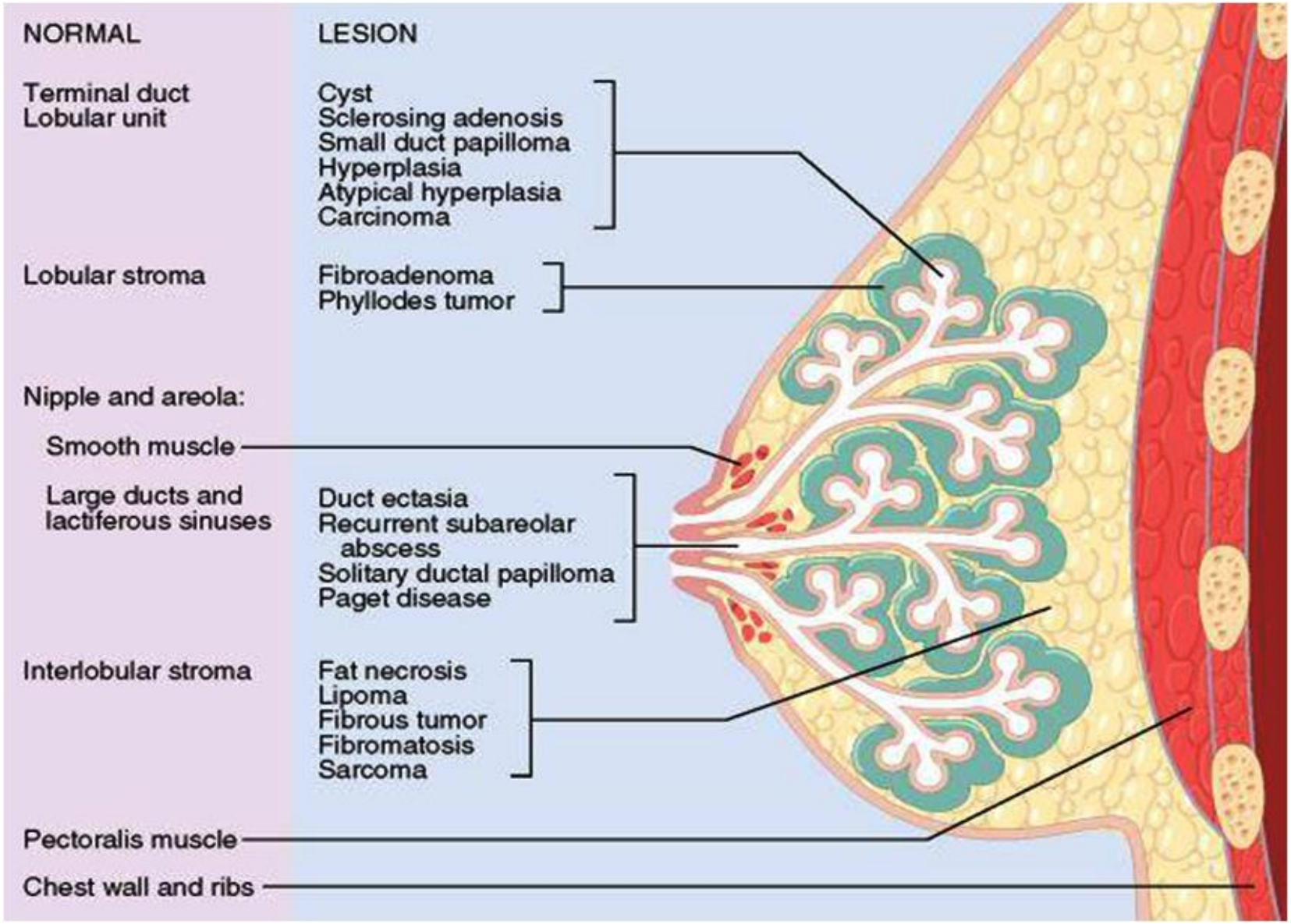
Terminal duct–lobular unit

TDLU

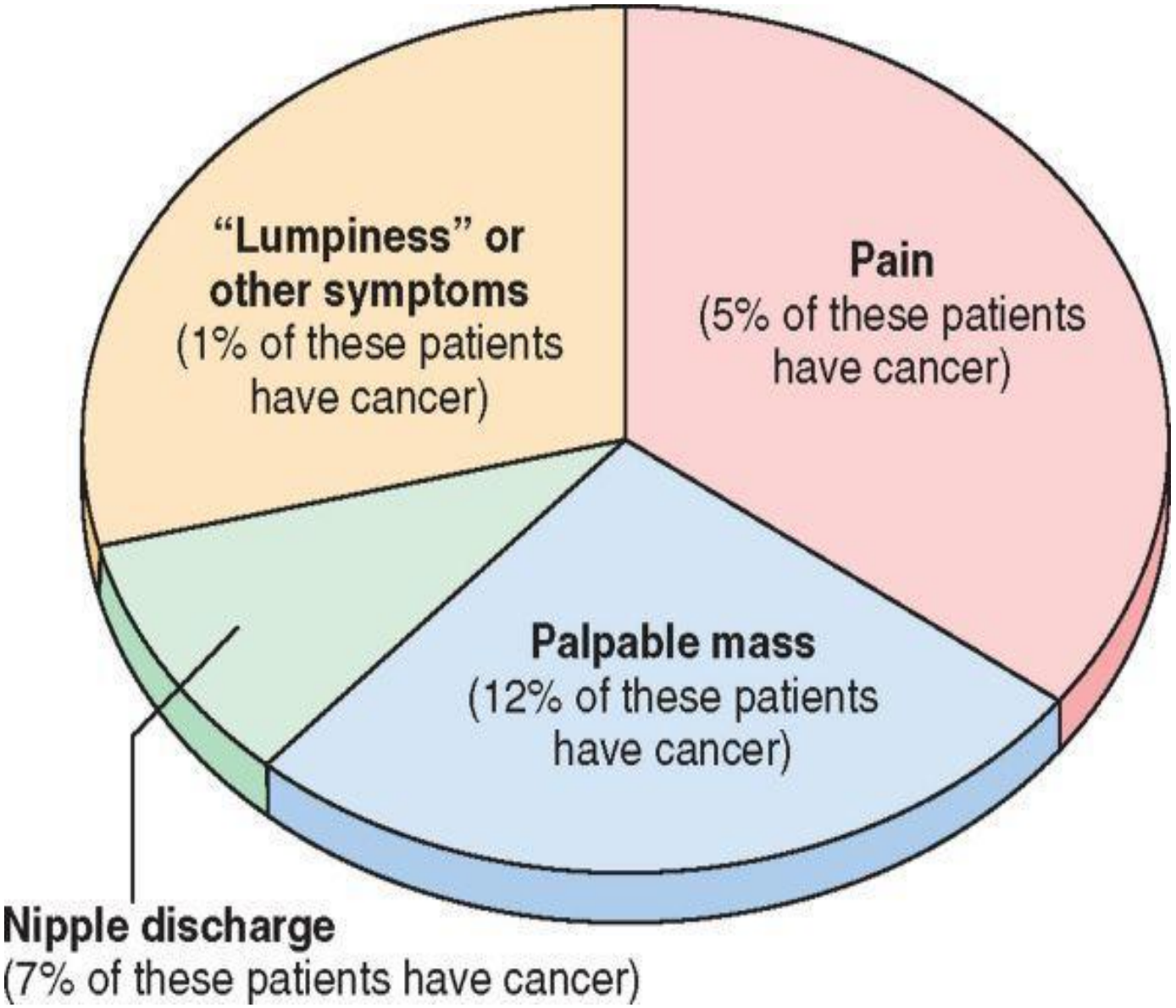


Epithelial (luminal cells) and myoepithelial cells

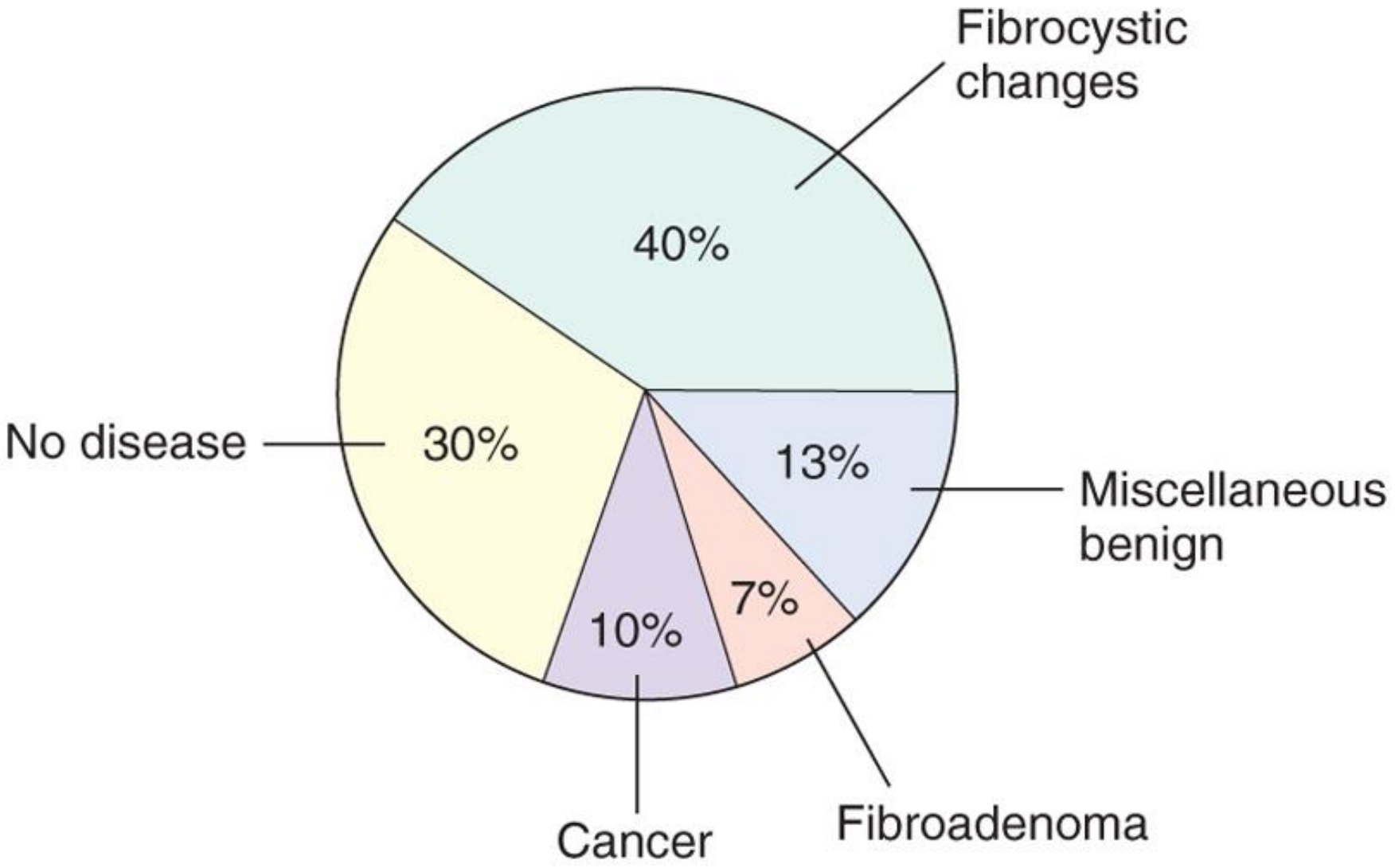
Anatomic origins of common breast lesions



Common clinical symptoms of breast disease



The findings of women seeking evaluation of apparent breast "lumps"



INFLAMMATIONS

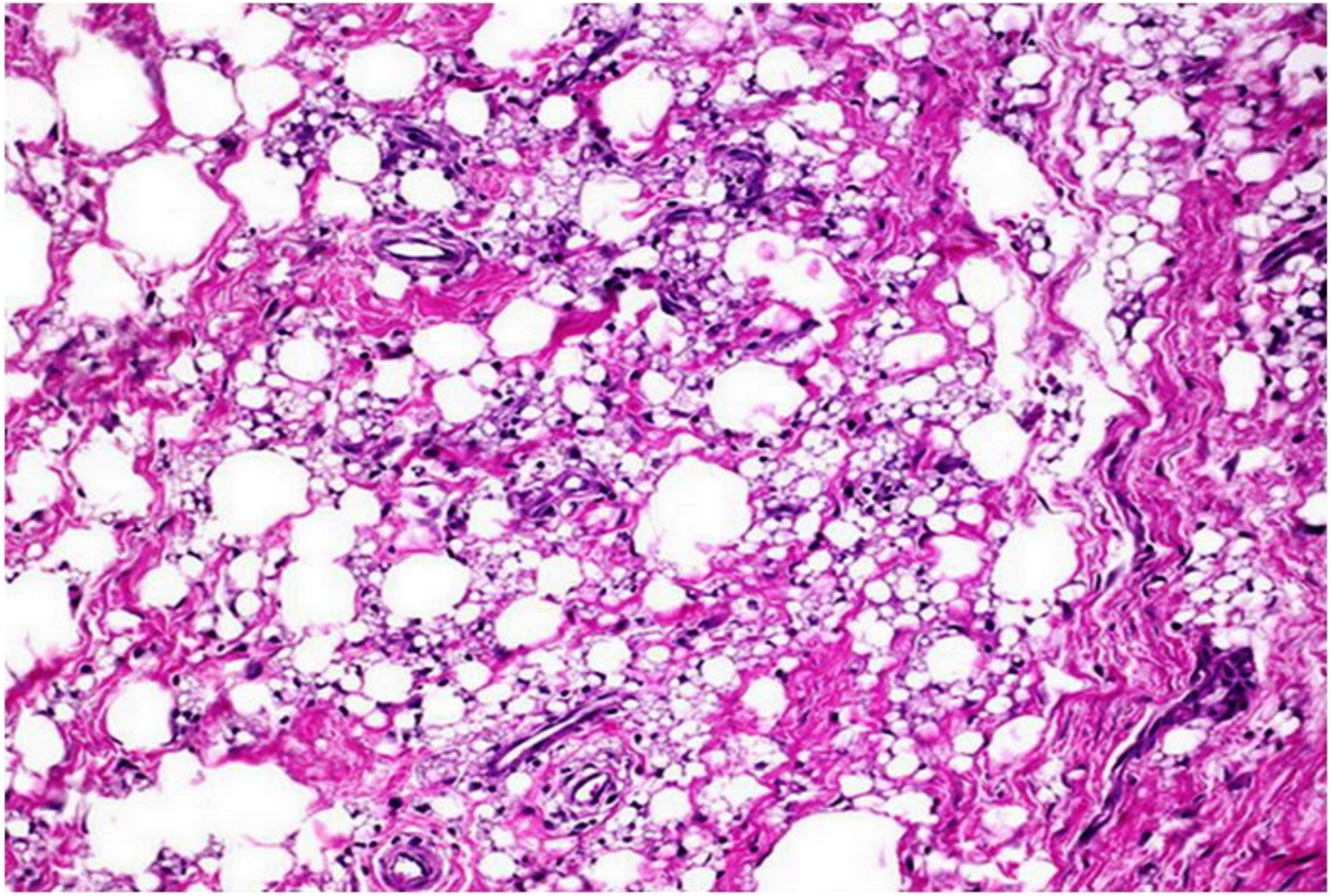
- Uncommon
- Pain & tenderness in during the acute stages
- Not associated with increased risk of cancer
  - Acute mastitis
  - Duct ectasia
  - Recurrent subareolar abscess
  - Fat necrosis

Traumatic fat necrosis

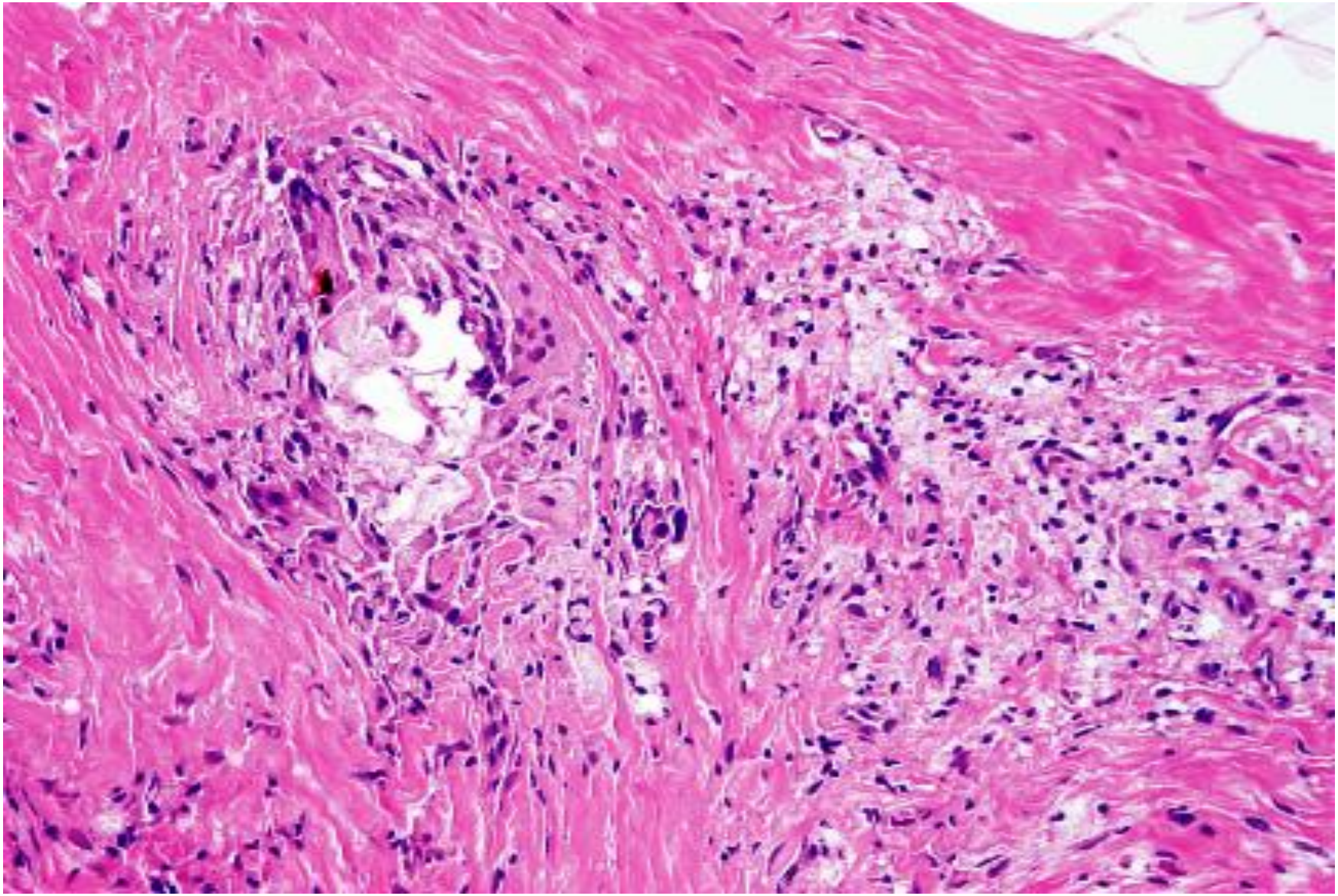
- An uncommon lesion
- May produce a palpable mass
- Most women have history of trauma

- **Morphology:**
  - A focus of necrotic fat cells surrounded by neutrophils and lipid-filled macrophages
  - Later it becomes enclosed by fibrous tissue and mononuclear leukocytes
  - Calcifications may occur

Traumatic fat necrosis



Traumatic fat necrosis



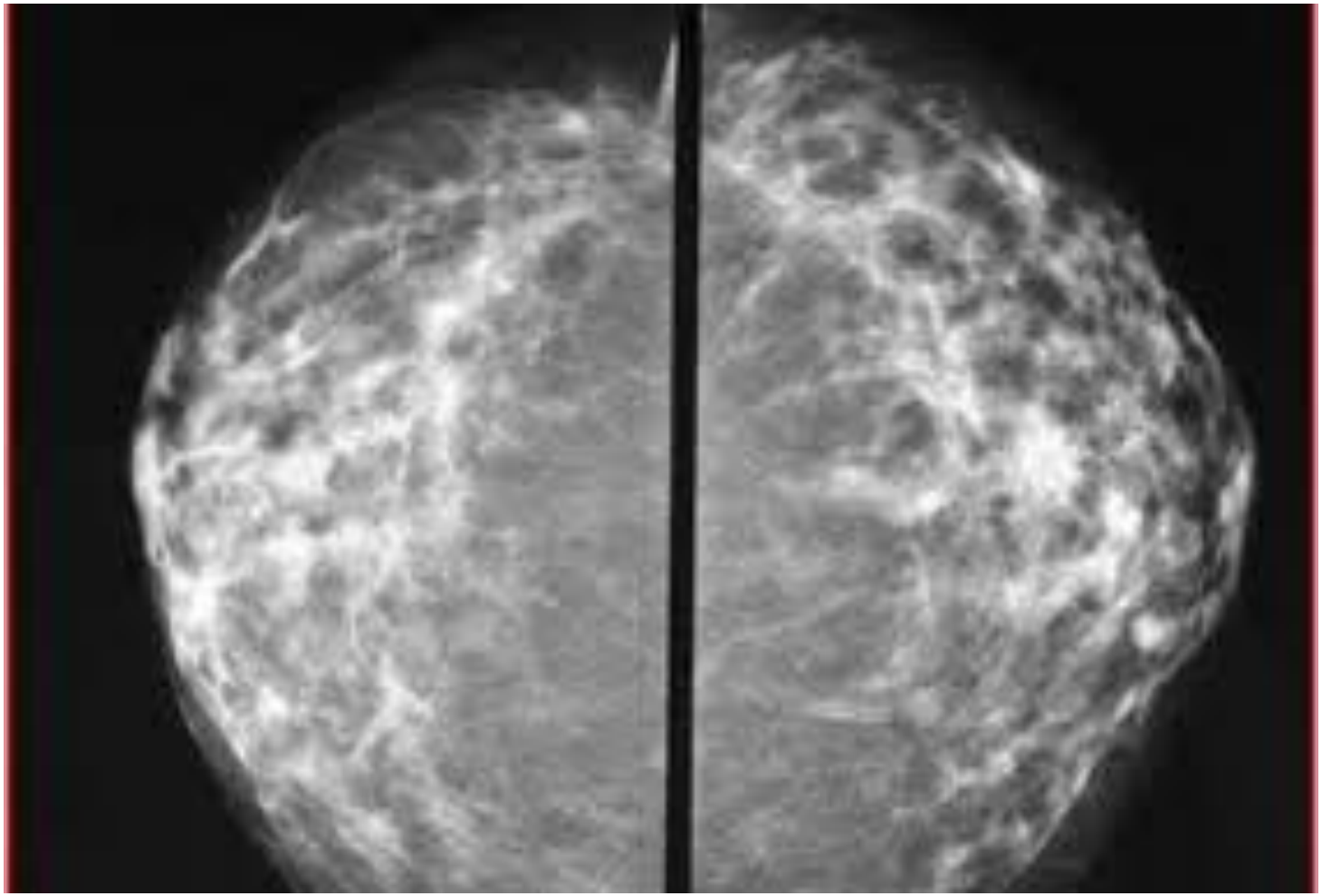
NONPROLIFERATIVE BREAST CHANGES (FIBROCYSTIC CHANGES)

- Extremely common, 60–80% at autopsy
- Estrogenic therapy and OCPs do NOT increase the incidence
- Doesn't increase the risk of breast CA, RR=1

Clinical features

- **Age**: 3rd. to 5th.decade
- Nodular “lumpy” breasts
- May present as a palpable mass
- Nipple discharge
- **Mammogram**:
- Dense breasts with cysts ± calcification

Mammogram



Fibrocystic changes in both breasts

Gross appearance

- Usually multifocal and bilateral
- ill-defined diffusely increased density
- Discrete nodularities
- The cysts vary from < 1 cm to 5 cm
  Brown to blue **(blue dome cysts)**
  Filled with serous turbid fluid

Fibrocystic changes

Fibrocystic changes

Microscopic appearance

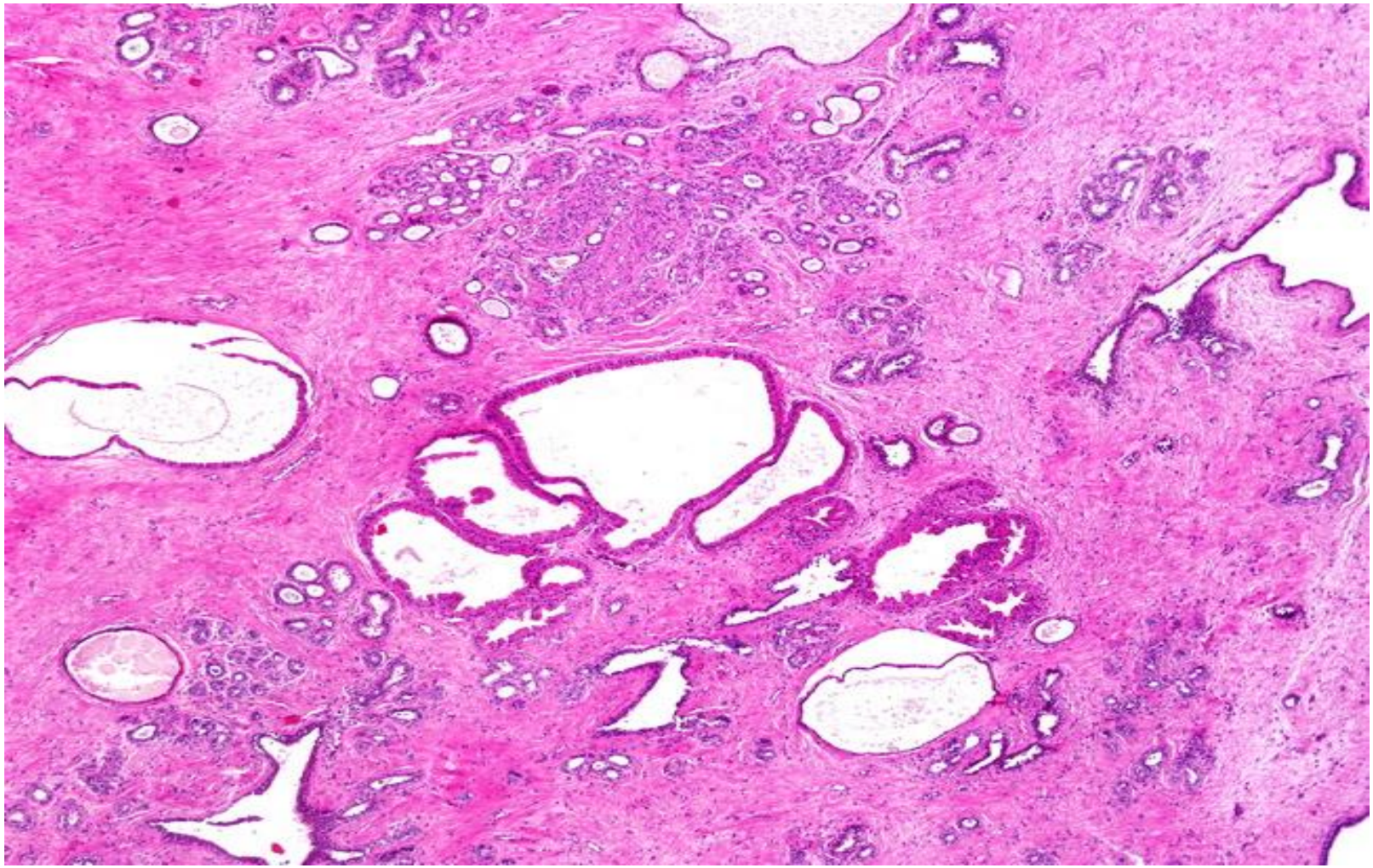
- **Cyst** lined by:
- Flattened, cuboidal or columnar epithelium
- May show mild epithelial hyperplasia
- Frequently show apocrine metaplasia; large polygonal cells with abundant granular eosinophilic cytoplasm and small, round nuclei

- **Fibrosis** ± lymphocytic infiltrate

- **Adenosis**

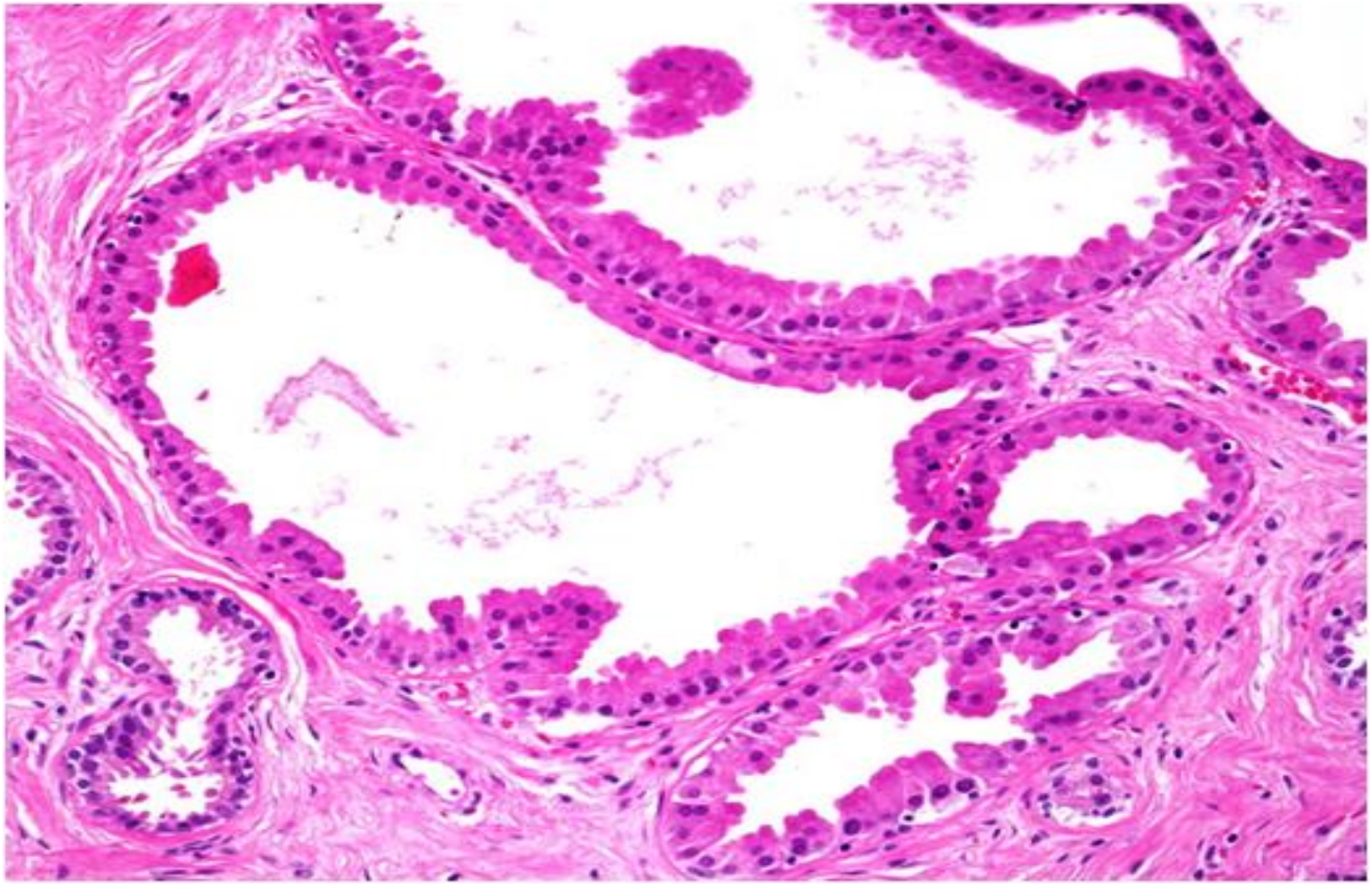
" An increase in number of acini per lobule"

Fibrocystic changes



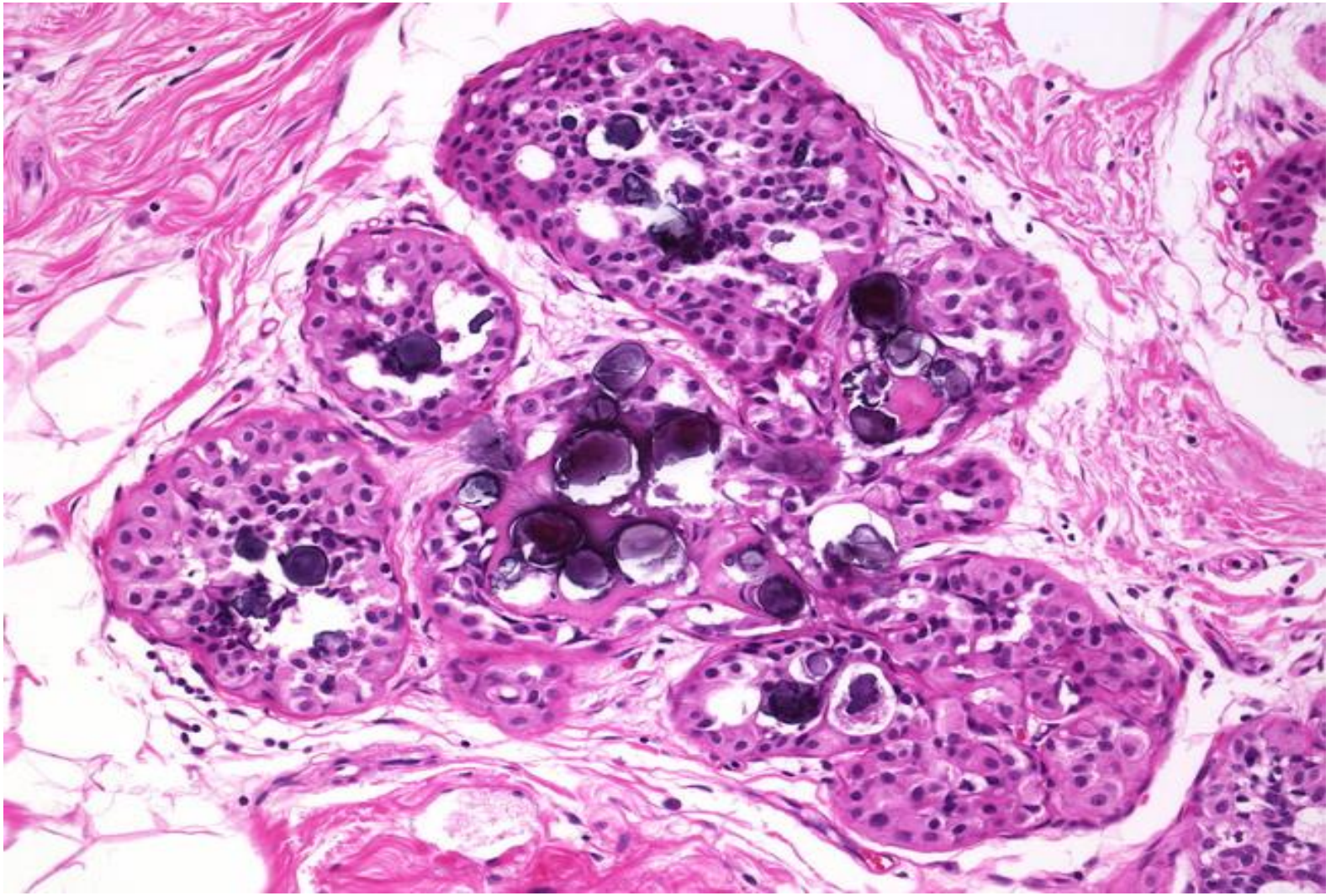
Adenosis, fibrosis, apocrine metaplasia and cyst formation

Fibrocystic changes



Cyst formation and apocrine metaplasia

Fibrocystic change



Adenosis and calcification

TUMORS OF THE BREAST

- **Epithelial neoplasms**
- Papilloma
- Breast carcinoma

- **Connective tissue tumors:**
- Fibroadenoma
- Phyllodes tumor

} arise from periductal stroma

Breast Lesions and Relative Risk of Developing Invasive Carcinoma

Pathologic lesion	RR	Comment
Non-proliferative breast changes Cyst, Fibrosis, Adenosis Apocine metaplasia Mild epithelial hyperplasia Fibroadenoma without complex features	1 Minimal or No risk	
Proliferative disease without atypia Moderate or florid hyperplasia Sclerosing adenosis Small duct papillomas Comples sclerosing lesion Fibroadenoma with complex features	1.5-2 Mild	**Both breasts** ↑risk if + FH ↓ risk 10 years after Bx
Proliferative disease with atypia ADH & ALH	4-5 Moderate	**Both breasts** ↑ risk if + FH ↑ risk if premenopausal ↓ risk 10 y after Bx for ALH
Lobular carcinoma in-situ (LCIS)	8-10 Severe	**Both breasts**
Ductal carcinoma in-situ		**Ipsilateral breast**

Fibroadenoma

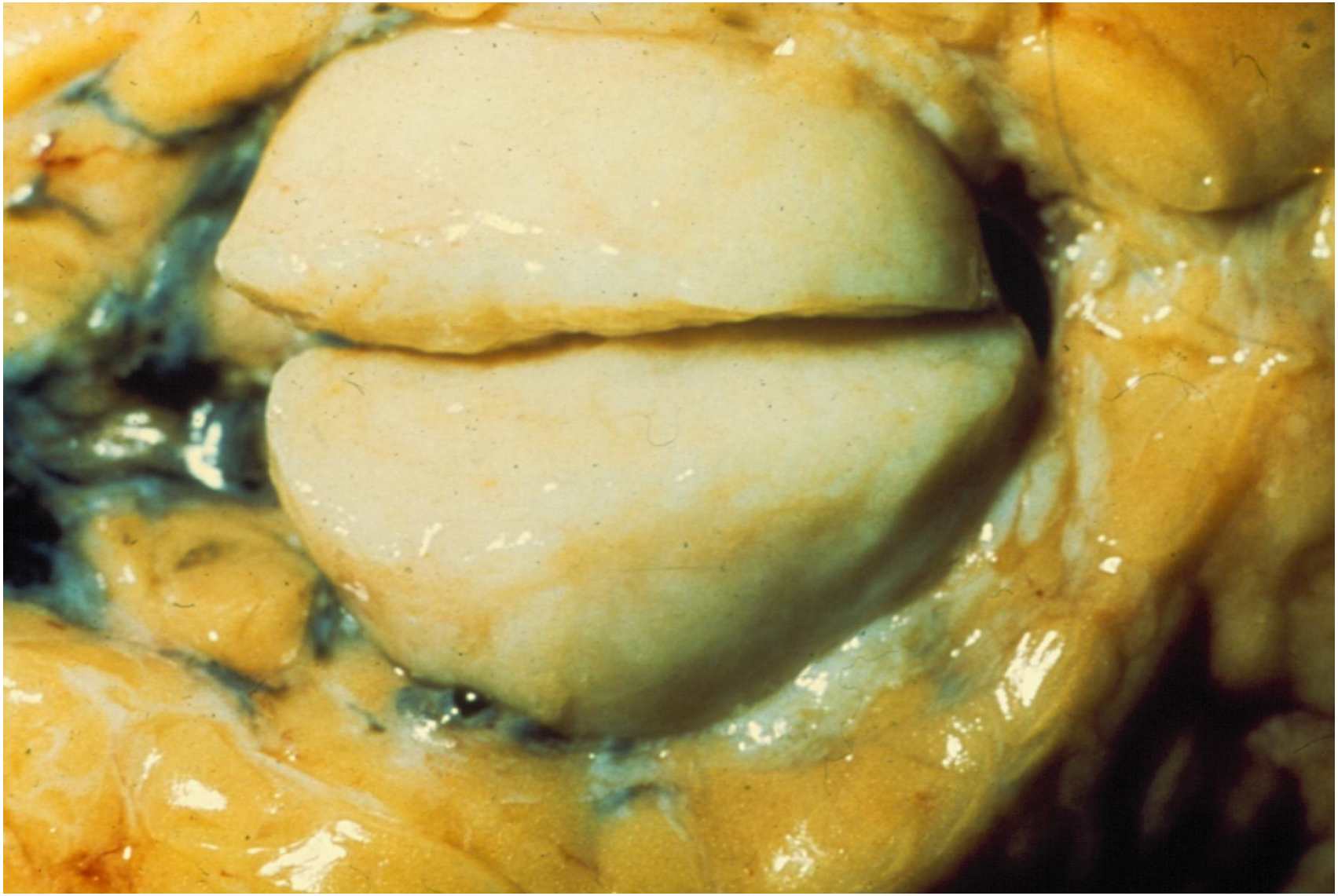
- The most common benign neoplasm of the female breast
- An absolute or relative increase in estrogen activity is important in pathogenesis
- Usually young women, peak incidence in 20s
- Not associated with ↑ risk of malignancy

Gross appearance

- Usually discrete & solitary
- Freely movable (mouse of the breast)
- May be multiple
- Variable in size

- Well circumscribed and firm
- Tan-white cut section with slit-like spaces

Fibroadenoma



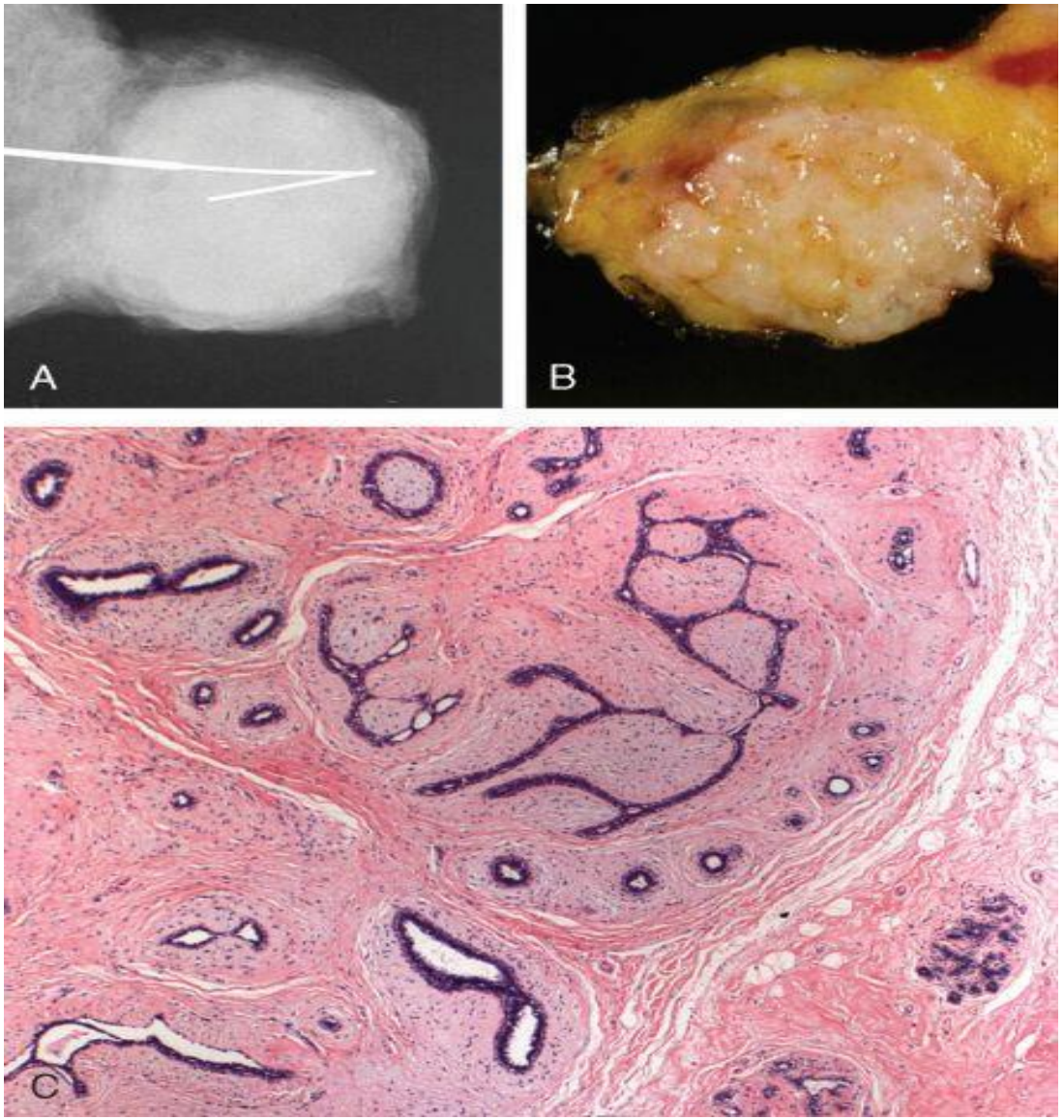
Fibroadenoma

Microscopic appearance

- Loose fibrous or myxoid stroma
- Monoclonal; the neoplastic elements

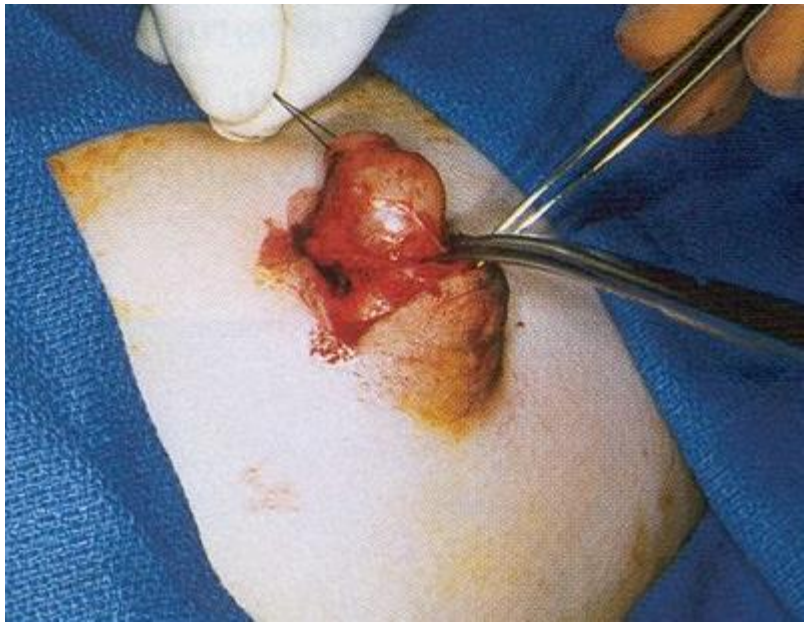
- Duct-like or glandular spaces:
- lined with uniform cuboidal or low columnar cells resting on myoepithelial cells

Fibroadenoma



Clinical features

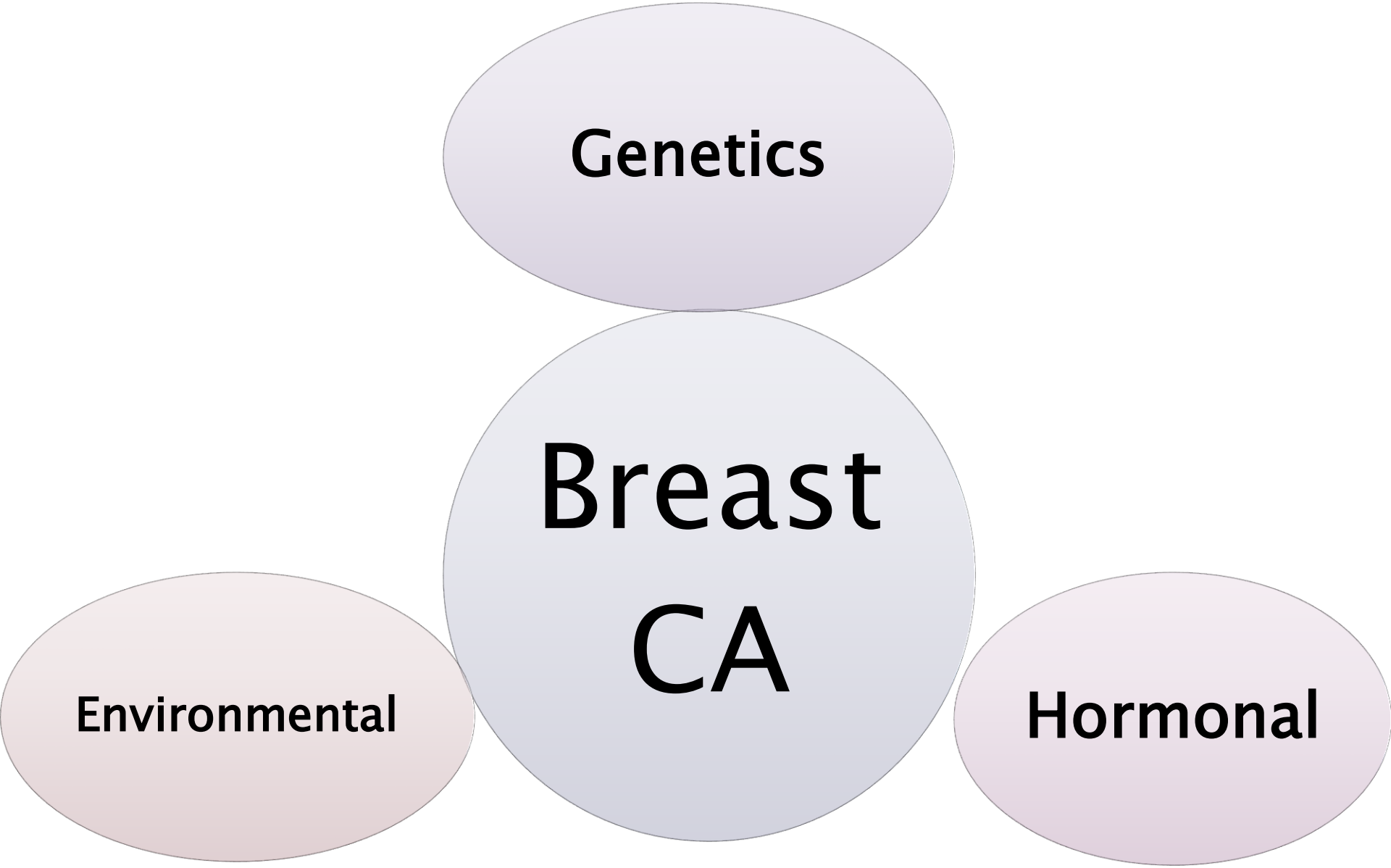
- Solitary, discrete, movable masses
- They may enlarge late in the menstrual cycle and during pregnancy
- After menopause they may regress and calcify



Breast carcinoma

- The most common cancer and the 2nd most common cause of cancer related deaths in ♀
- The lifetime risk is 1 in 8 for women in the US
- Age: 75% are older than age 50
  5% are younger than the age of 40

Pathogenesis



Risk factors

Well-established risk factors	Less well-established risk factors
Geographic factors Age Family history Menstrual history Pregnancy Benign breast disease •Proliferative breast •Proliferative breast disease with atypia •LCIS	Exogenous estrogen Radiation exposure Obesity Diet rich in animal fat Alcohol consumption

Geographic variation and age

- **Geographic Variations:**
- Higher incidence in North America and northern Europe than in Asia and Africa
- Environmental rather than genetic differences

- **Age:**
- Breast cancer is uncommon in women < 30 y
- The risk steadily increases throughout life

Family History and genetics

- **5% to 10% of breast cancers are familial**
- Young age (premenopause)
- Bilateral cancer
- First degree relatives with breast cancer
- Have other associated cancers (e.g., ovarian)
- Certain ethnic groups

- **Genes:**
- BRCA1 and BRCA2
- Other genes: P53, PTEN, CHEK2, LKB1, ATM

	BRCA1	BRCA2
Chromosome	17q21	13q12.3
Function	Tumor suppressor gene Transcriptional regulation DNA repair by homologous recombination	
Mutations	> 500	> 300
Risk of breast CA	60–80%	60–80%
Age of onset	Younger (40s to 50s)	50 years
Ovarian cancer	20–40% risk	10–20% risk
Male breast cancer	<20%	76%
Other cancers	Prostate, colon, pancreas	Prostate, colon, pancreas, stomach, melanoma
Pathology of breast cancer	Medullary carcinoma Poorly differentiated (Basal-like) ER–, PR–, Her2/neu– P53 mutation	Similar to sporadic breast CA

Other genes

Gene	Syndrome
p53	Li-Fraumeni syndrome
CHEK2	Li-Fraumeni variant
PTEN	Cowden syndrome
ATM	Ataxia-telangiectasia
LKB1	Peutz Jeghers syndrome

Genes associated with sporadic breast cancer

Gene	Comment
HER2/NEU	A proto-oncogene A member of EGFR family Amplified in 30% Poor prognosis
RAS MYC	Proto-oncogenes
P53 RB	Tumor suppressor genes

Menstrual history and pregnancy

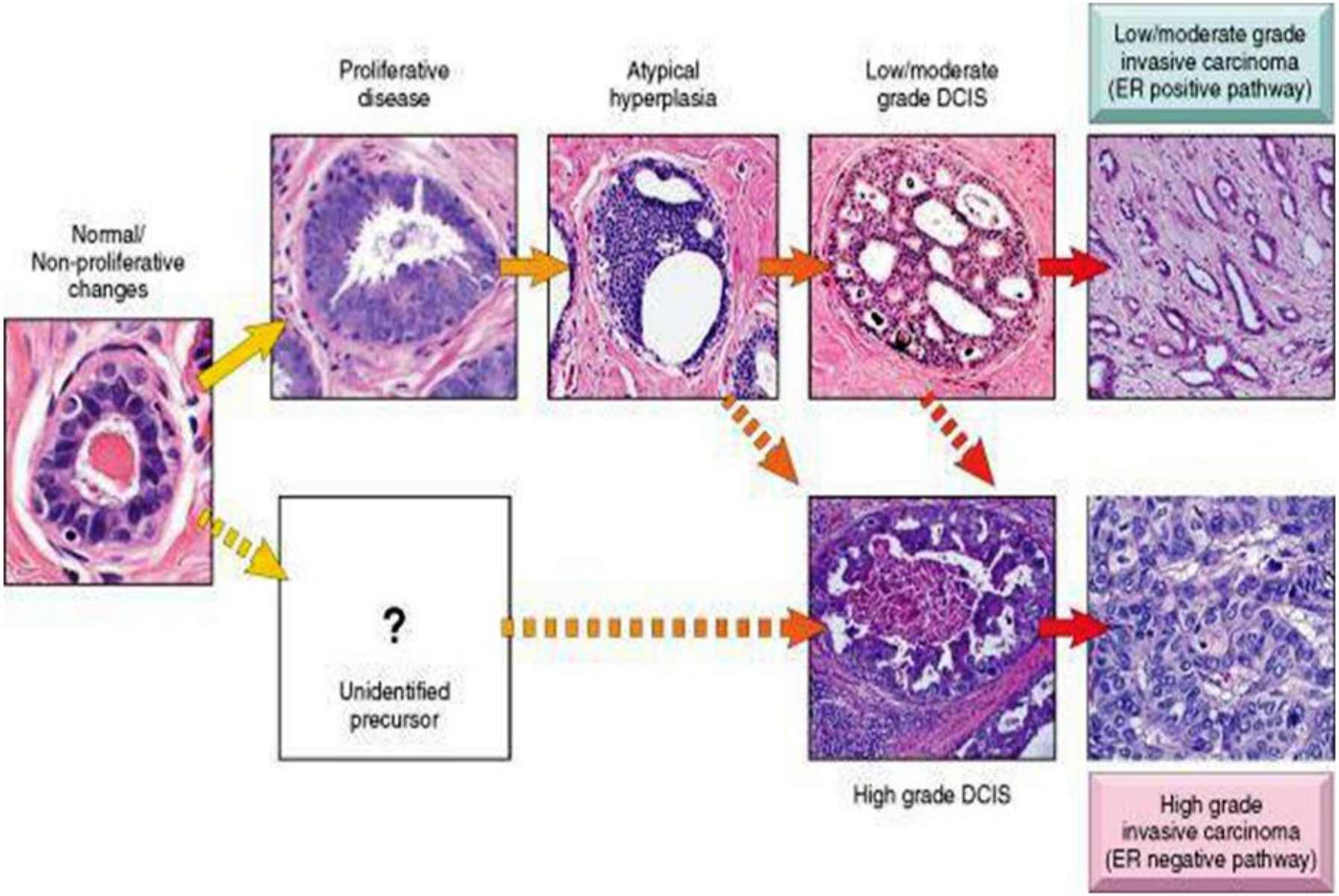
- **Menstrual history**
- Early menarche < 11 years
- Late menopause

- **Pregnancy**
- First live birth over age of 35
- Nulliparous

Estrogen exposure

- **Hormone replacement therapy (HRT)**
  - Combined estrogen plus progestin hormone
  - Increased risk of breast cancer
  - Diagnosis at a more advanced stage
- **OCPs don't increase the risk**
- **Functioning ovarian tumors elaborating estrogens**
- **Obesity:**
  - ↓ risk in obese women < 40 y
  - ↑ risk in postmenopausal obese women

Carcinogenesis



Morphology

- **Site:**
- The left breast slightly more than the right
- 4% bilateral or multicentric

The locations within the breast	
Upper outer quadrant	50%
Central portion	20%
Lower outer quadrant	10%
Upper inner quadrant	10%
Lower inner quadrant	10%

Classification of breast cancer

- **Noninvasive (in-situ) 15-30%**
  - Ductal carcinoma in situ (DCIS) 80%
  - Lobular carcinoma in situ (LCIS) 20%
- **Invasive (infiltrating) 70-85%**
  - Invasive ductal carcinoma ~90%
  - Invasive lobular carcinoma 10%
  - Mixed ductal and lobular carcinoma
- Both arise from **TDLU** and the diagnosis depends on the cytoarchitecture

DCIS

- **The incidence of DCIS:**
- $<$ 5% of breast cancers in unscreened women
- $\sim$ 40% of those screened by mammography

- Rarely presents as mass
- 1/3 of untreated DCIS become invasive

- **Treatment:**
- Excision or mastectomy $\pm$ RTX $\pm$ tamoxifen
- Excellent prognosis

DCIS- morphology

- **Architectural Patterns**:
- Solid, comedo, cribriform, papillary, micropapillary, and clinging types
- Necrosis &/or calcification may be present

- **Nuclear Grade**:
- Grade I (low grade)
- Grade II (Intermediate grade)
- Grade III (High grade)

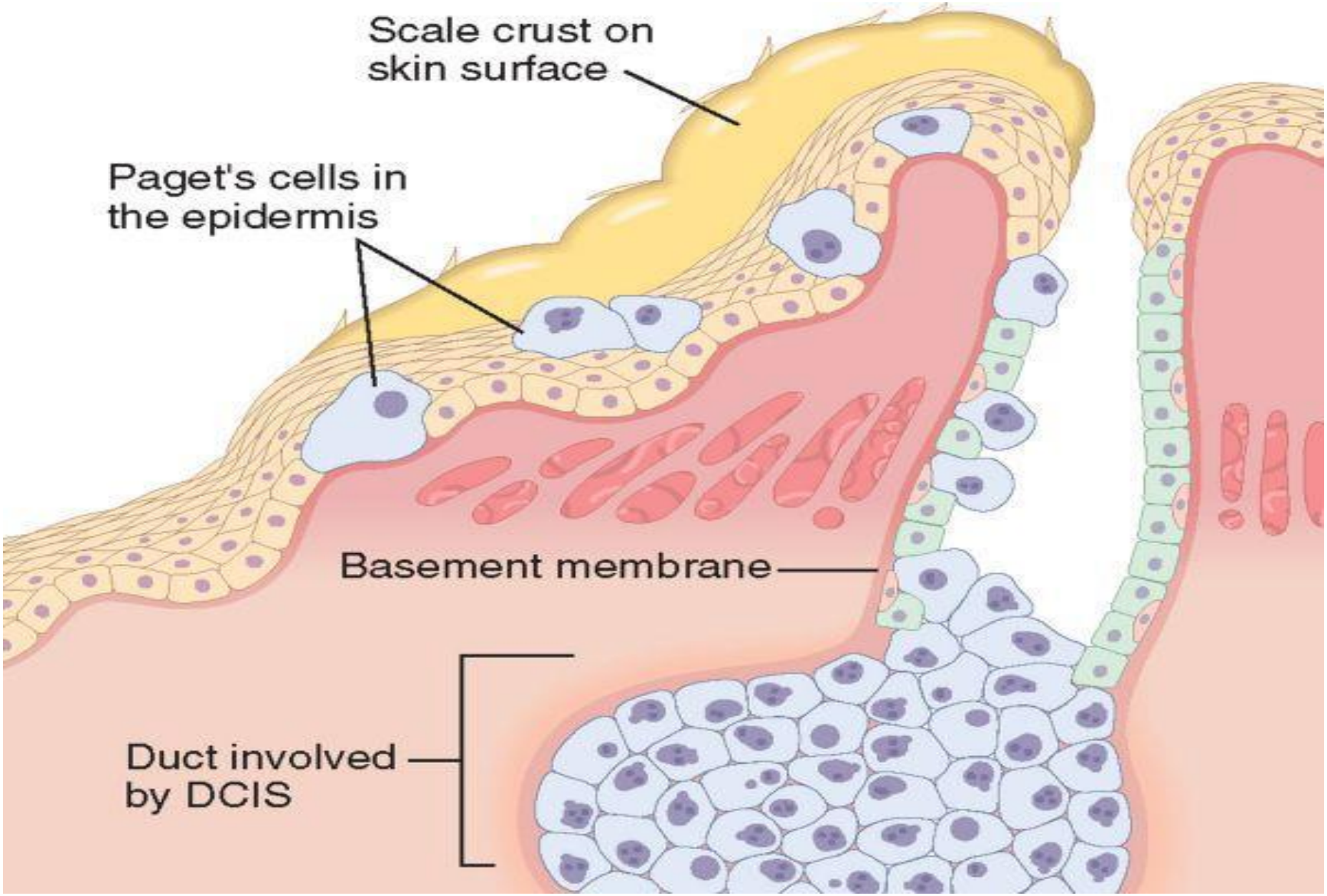
- Low grade DCIC are ER+, PR+

Paget disease of the nipple

- Caused by the extension of DCIS up to the lactiferous ducts and skin of the nipple

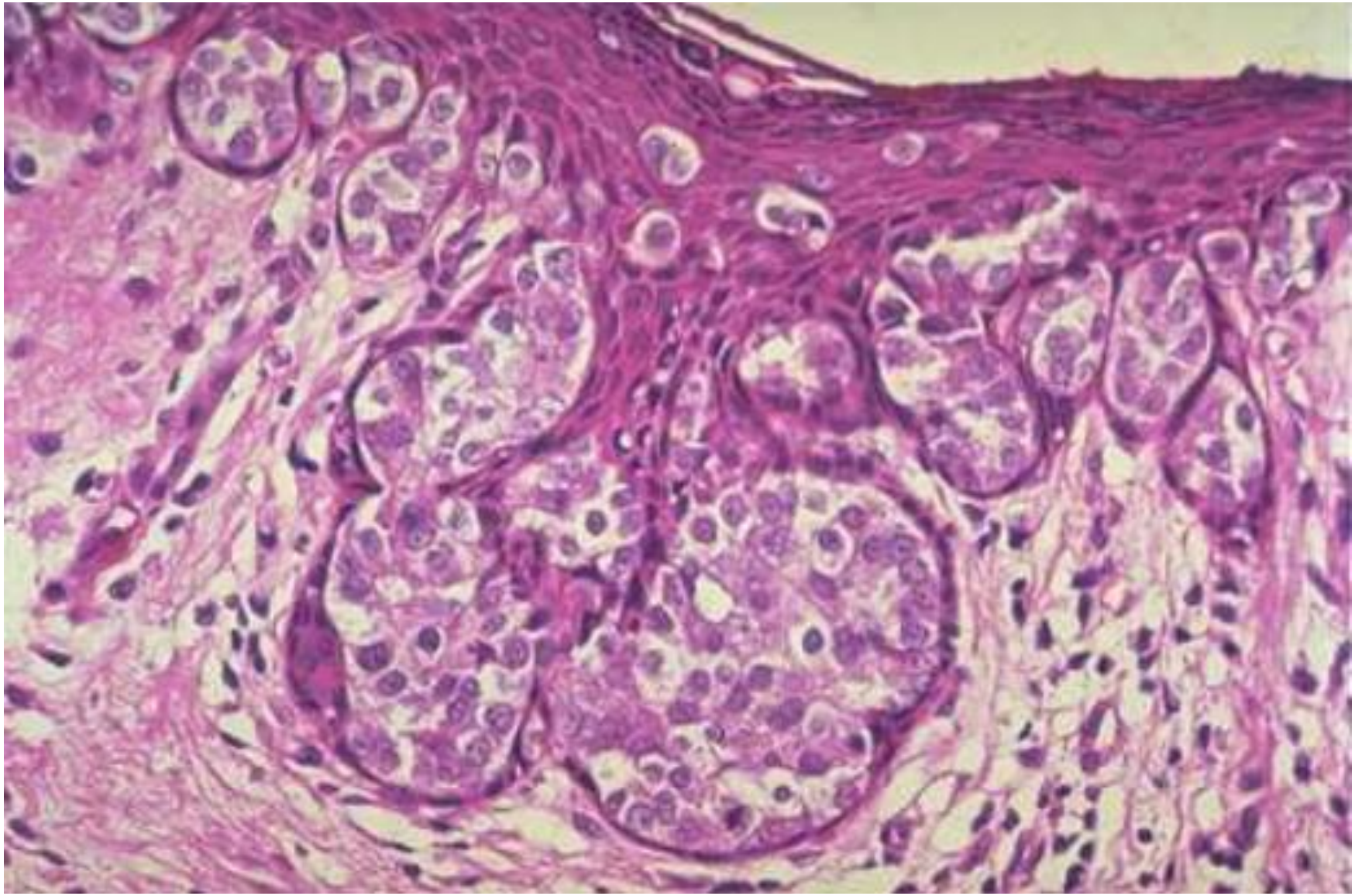
- **Clinical picture**:
- Unilateral crusting exudate over the nipple and areolar skin (eczema-like).
- An underlying invasive carcinoma n 50%
- Prognosis is based on the underlying carcinoma

Paget disease of the nipple



Paget disease of nipple

Paget disease of nipple



Invasive ductal carcinoma (IDC)

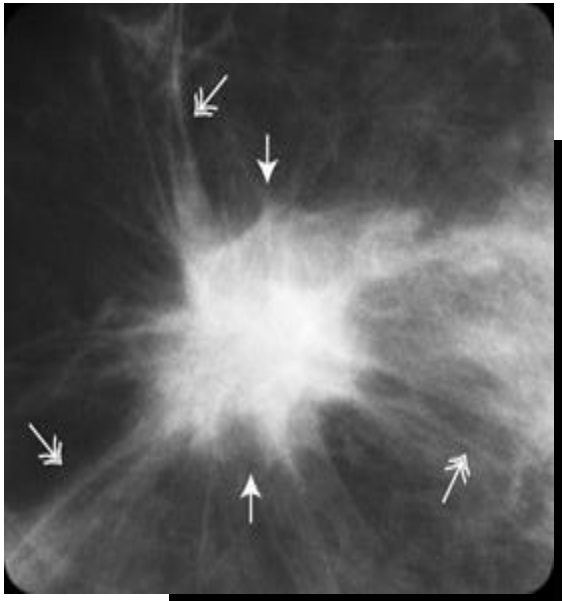
- A term used for all carcinomas that cannot be subclassified into one of the specialized types
  - Invasive ductal carcinoma NOS, the most common 80%
  - Medullary carcinoma 1%
  - Colloid (mucinous) carcinoma 2%
  - Tubular carcinoma 2%
  - Invasive papillary carcinoma 1%
  - Metaplastic carcinoma < 1%

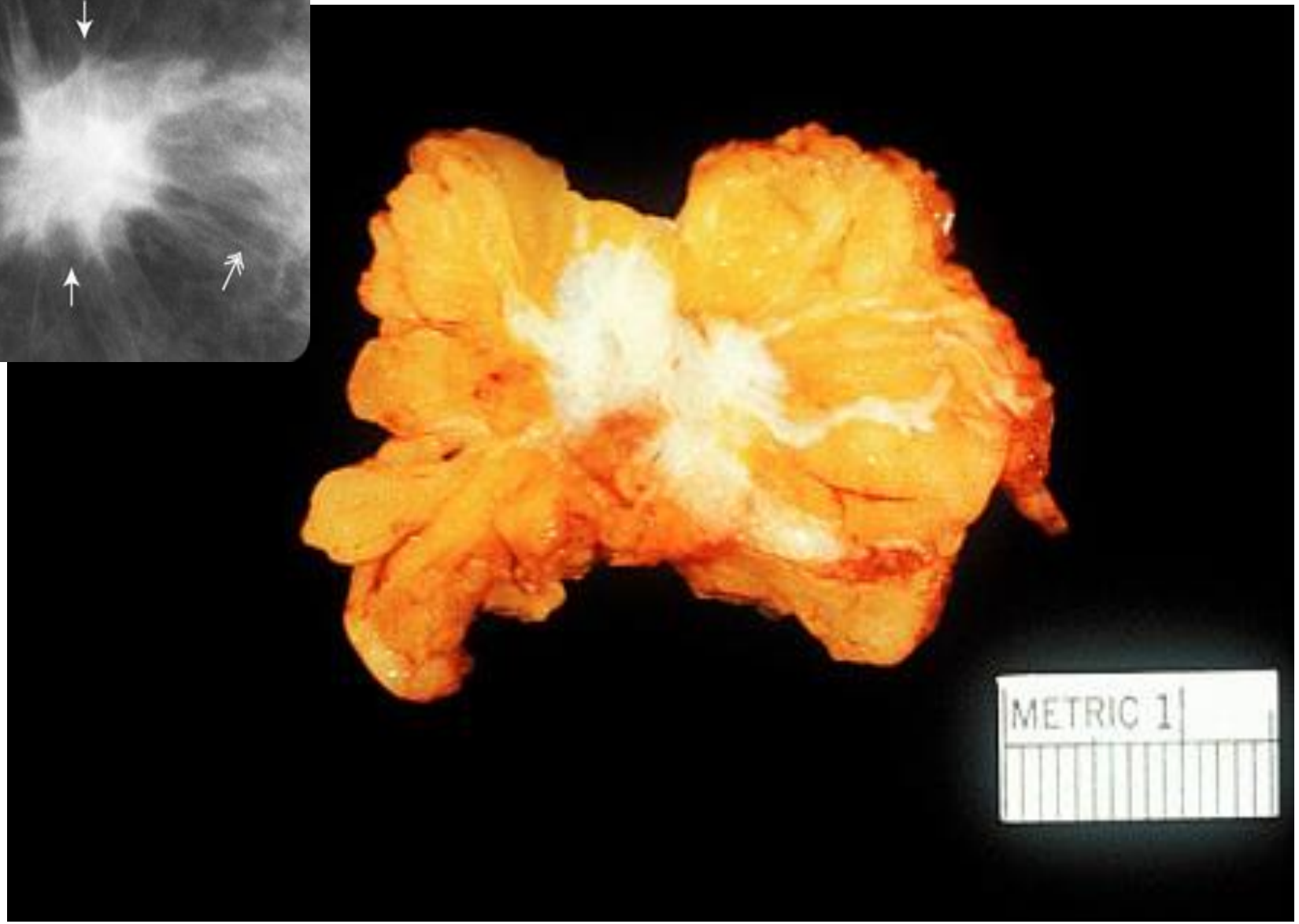
IDC, NOS

- 70% to 80% of cancers fall into this group
- Usually associated with DCIS, & rarely LCIS
- Bilateral or multicentric in 4 %

- **Clinical features**:
- Most IDC produce a desmoplastic response resulting in a mammographic density
- Forms a hard palpable mass

IDC





IDC

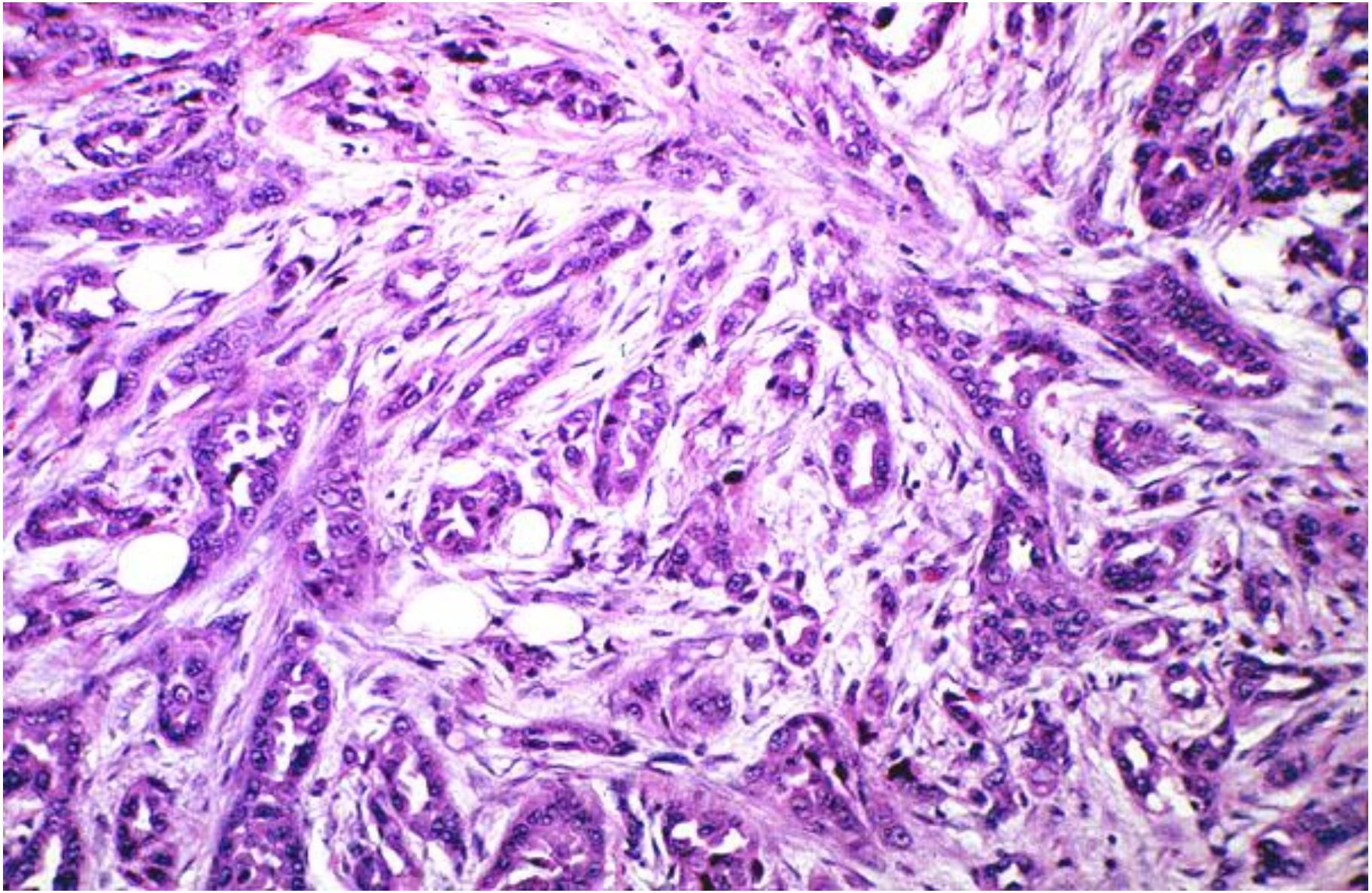
Microscopic appearance

- Heterogeneous, ranging from:
- Well formed tubules and low grade nuclei
- Sheets of anaplastic cells

- Tumor margins are infiltrative or pushing
- LVI & perineural invasion

- 2/3 express estrogen or progestron receptors
- 1/3 overexpress HER2/NEU

IDC



Microscopic grading of breast carcinoma

Notingham modification of Bloom-Richardson score

Tubule formation

1 point: tubule formation in > 75% of the tumor
2 poinst: tubule formation in 10 - 75% of the tumor
3 points: tubule formation in < 10% of the tumor

Nuclear pleomorphism

1 point: nuclei with minimal variation in size & shape
2 points: nuclei with moderate variation in size & shape
3 points: nuclei with marked variation in size & shape

Mitotic count

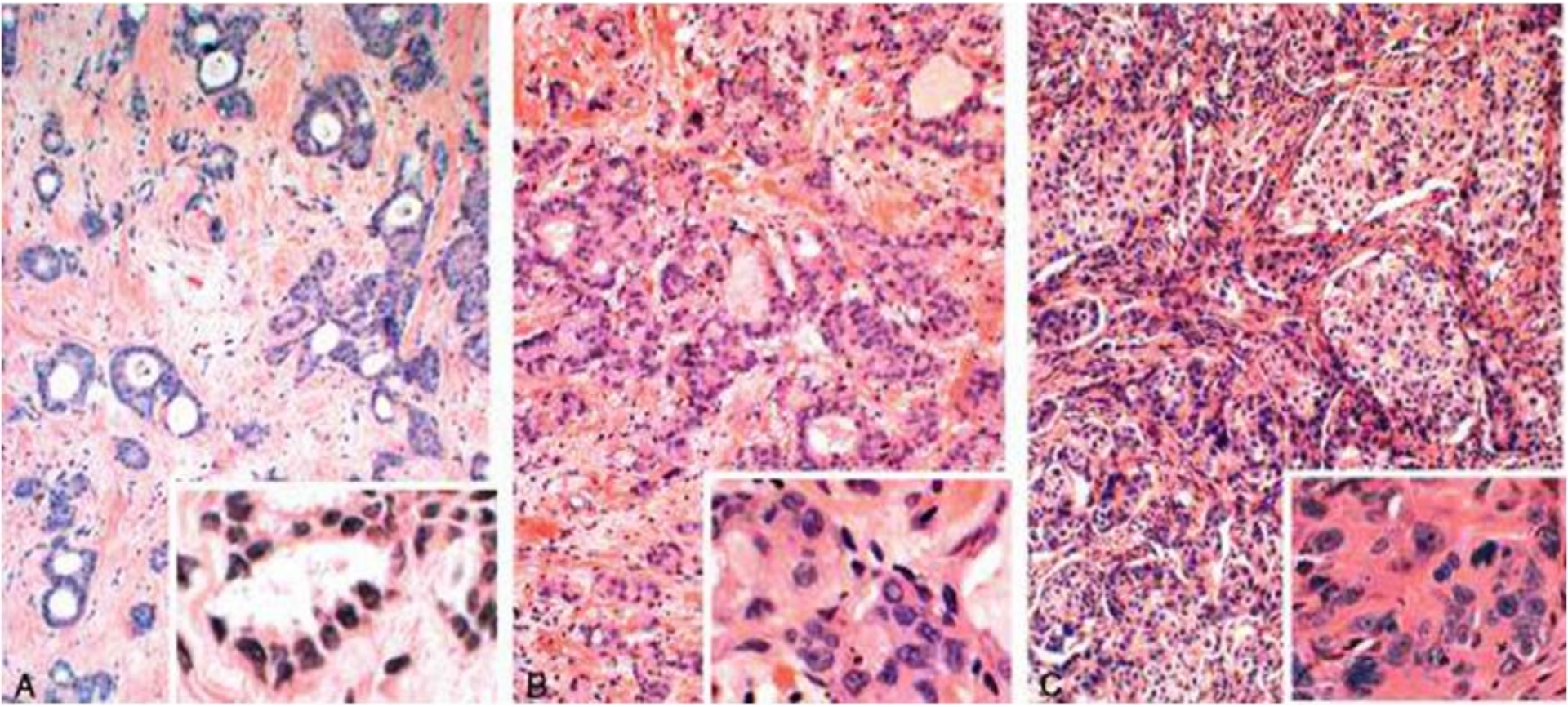
1 point: 0-5/ 10 HPF
2 points: 6-10/ 10 HPF
3 points:>11/ 10 HPF

Overall Grade

Grade 1(well-differentiated): score 3-5
Grade 2(moderately-differentiated): score 6-7
Grade 3(poorly-differentiated): score 8-9

Can be applied to all breast carcinoma subtypes

Microscopic grading of breast carcinoma



Grade 1

Grade 2

Grade 3

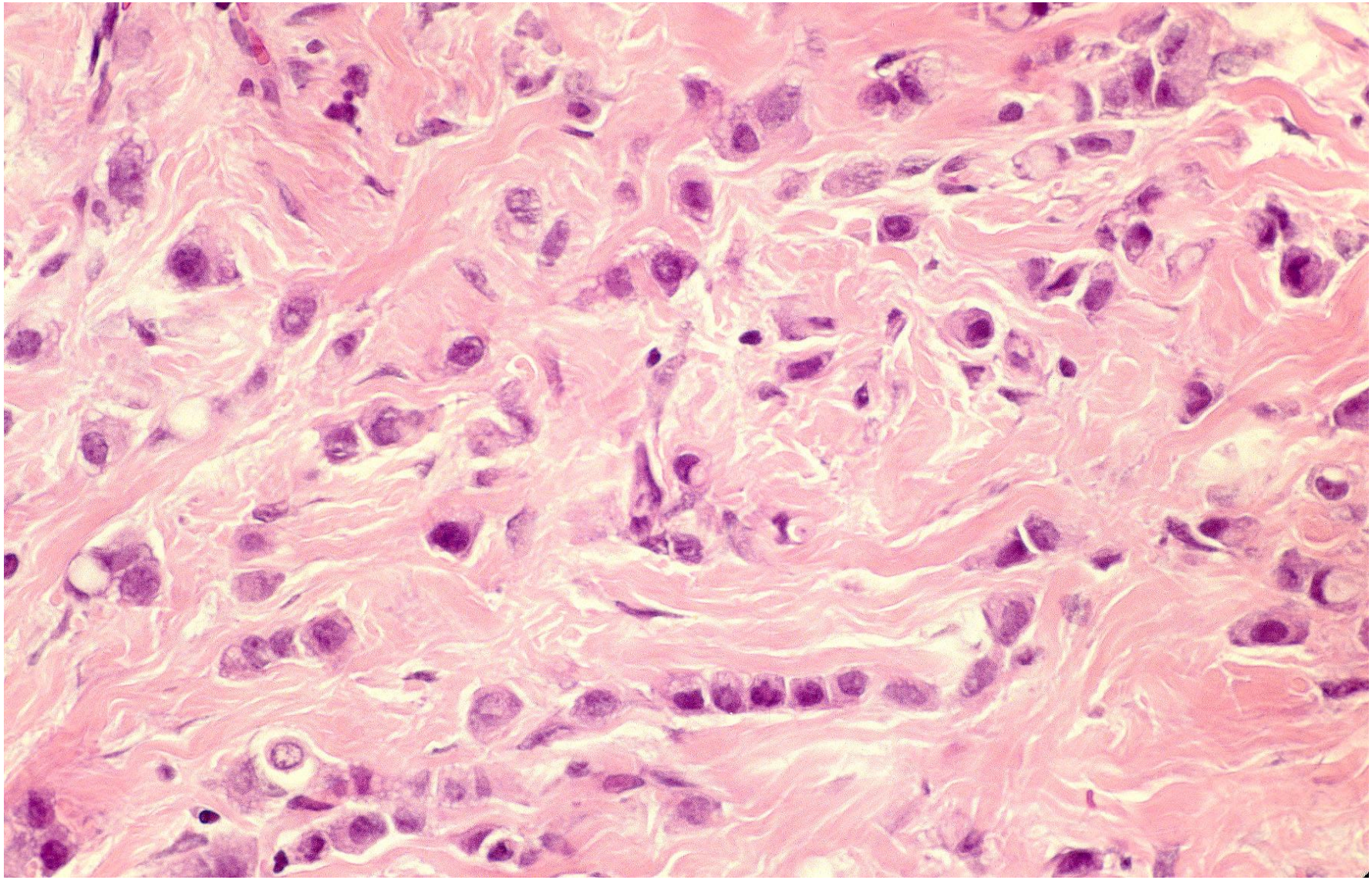
Invasive lobular carcinoma, ILC

- 10% of breast carcinoma
- 10-20% bilateral & more frequently multicentric
- In 2/3 adjacent LCIS present
- Present as palpable masses, mammographic densities or may be clinically occult
- ILC metastasize to CSF, serosal surfaces, GIT, ovary and uterus, and BM more than IDC
- Prognosis is similar to IDC,NOS

Morphology

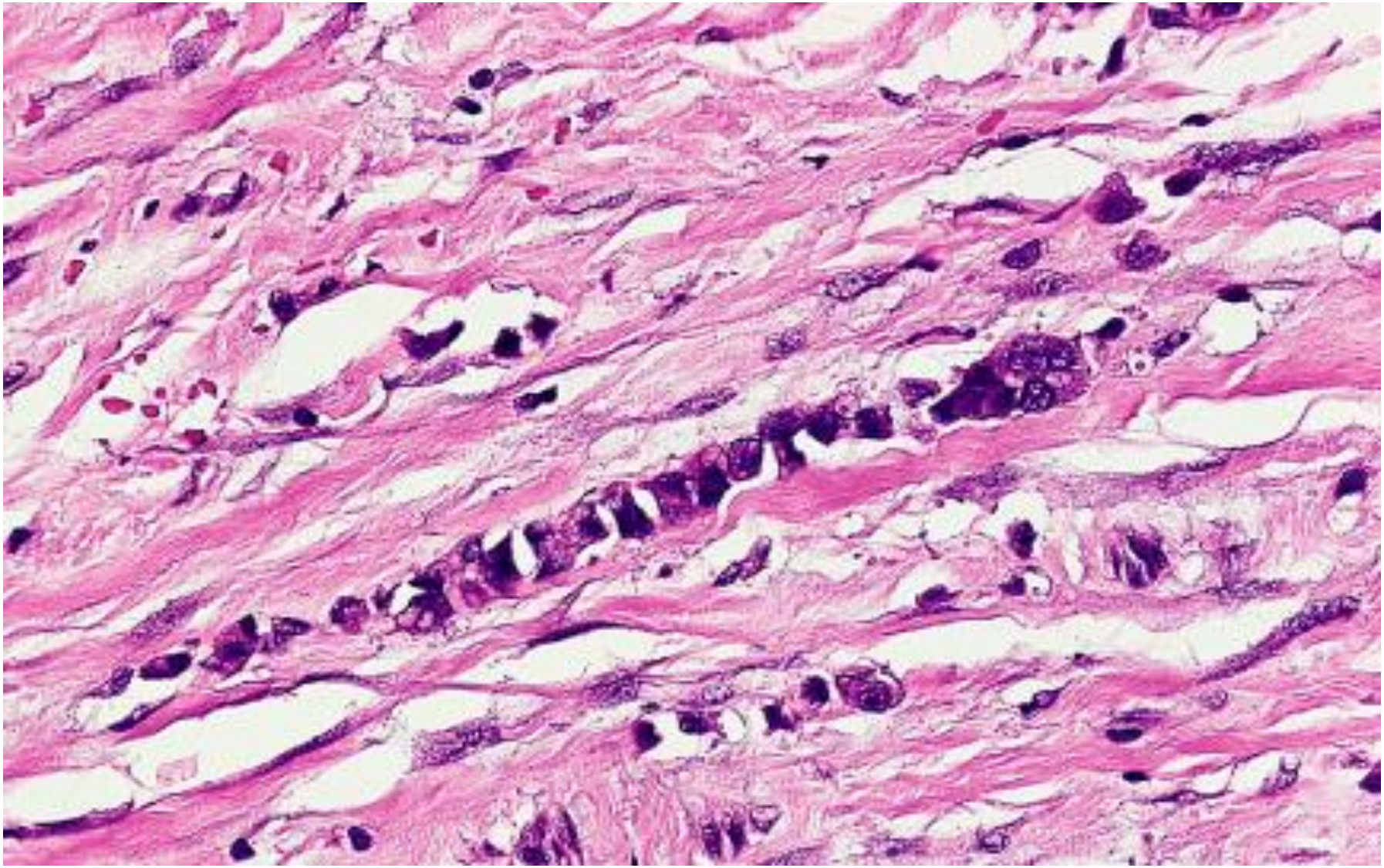
- Consists of cells morphologically identical to LCIS (small and uniform)
- Single cells or in indian file
- Target-like growth around ducts or lobules
- Gland formation is NOT a feature
- Abundant fibrous stroma
- Almost all express ER and PR
- HER2/NEU overexpression is very rare or absent

ILC



Single cells, Indian file, and mucin vacuoles

ILC



Indian file pattern of ILC

Staging of breast cancer

Primary Tumor (pT)	
pTis (DCIS)	Ductal carcinoma in situ
pTis (LCIS)	Lobular carcinoma in situ
pTis (Paget)	Paget disease of the nipple *not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS)*
pT1	Tumor ≤2 cm in greatest dimension
pT2	Tumor >2 cm but≤5 cm in greatest dimension
pT3	Tumor >5 cm in greatest dimension
pT4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
pT4a	Extension to chest wall (not only pectoralis m)
pT4b	Skin ulceration and/or ipsilateral satellite nodules and/or edema (peau d'orange)
pT4c	Both T4a and T4b
pT4d	Inflammatory carcinoma

Staging of breast cancer

Regional LNs (pN) and distant metastasis (M)
Regional lymph nodes pN0: No regional lymph nodes metastasis pN1: 1–3 axillary lymph nodes metastasis pN2: 4–9 axillary lymph nodes metastasis pN3: ≥ 10 axillary lymph nodes metastasis
Distant metastasis M0: No distant metastasis pM1: distant metastasis

Clinical Course

- A discrete, solitary, painless mass
- Regional LNs involved in 50%

- Screening:
- Mammographic screening detect carcinomas before being palpable & 15% have LNs mets
- In many women DCIS is detected
- MRI can be used in screening of young high risk patients or in case of breast implants

Prognosis

- Is determined by the pathologic examination of the breast carcinoma and axillary LNs
- **Major prognostic factors**
- The strongest predictors of death from breast CA and are incorporated in staging
- **Minor prognostic (predictive) factors**
- Determine the likehood of response to particular therapy (CTX, hormonal, Trastuzumab)

Prognosis

Major prognostic factors	Minor prognostic factors
Invasive or in-situ Distant metastasis Lymph node involvement: Presence of LNs The number of LNs Tumor size Locally advanced disease Inflammatory carcinoma Poor prognosis	Histologic subtypes Special subtypes better Tumor grade ER & PR HER2/NEU Lymphovascular invasion Proliferative rate Mitosis, IHC (Ki67) flowcytometry DNA content (aneuploidy) Slightly worse