BREAST DISEASES

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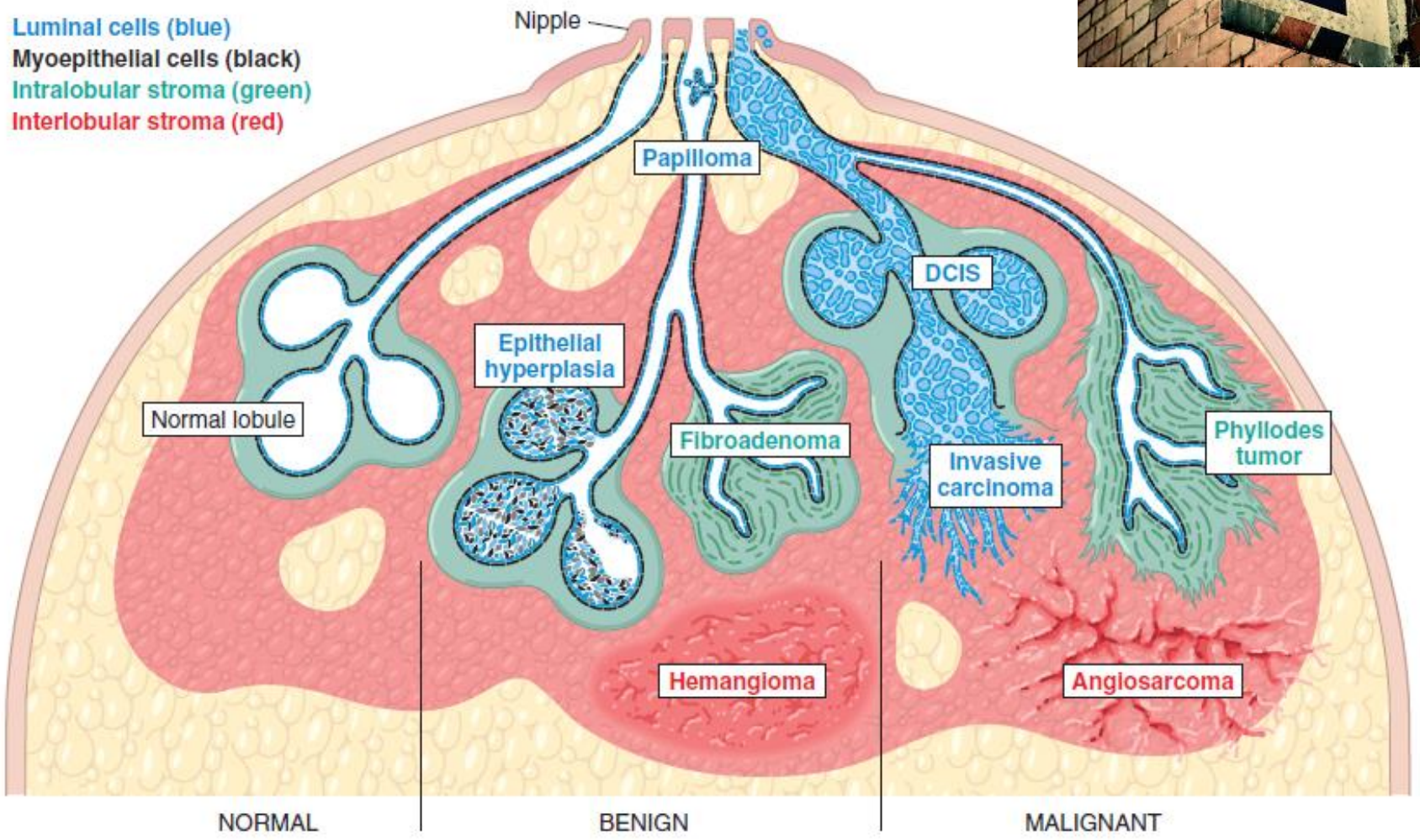
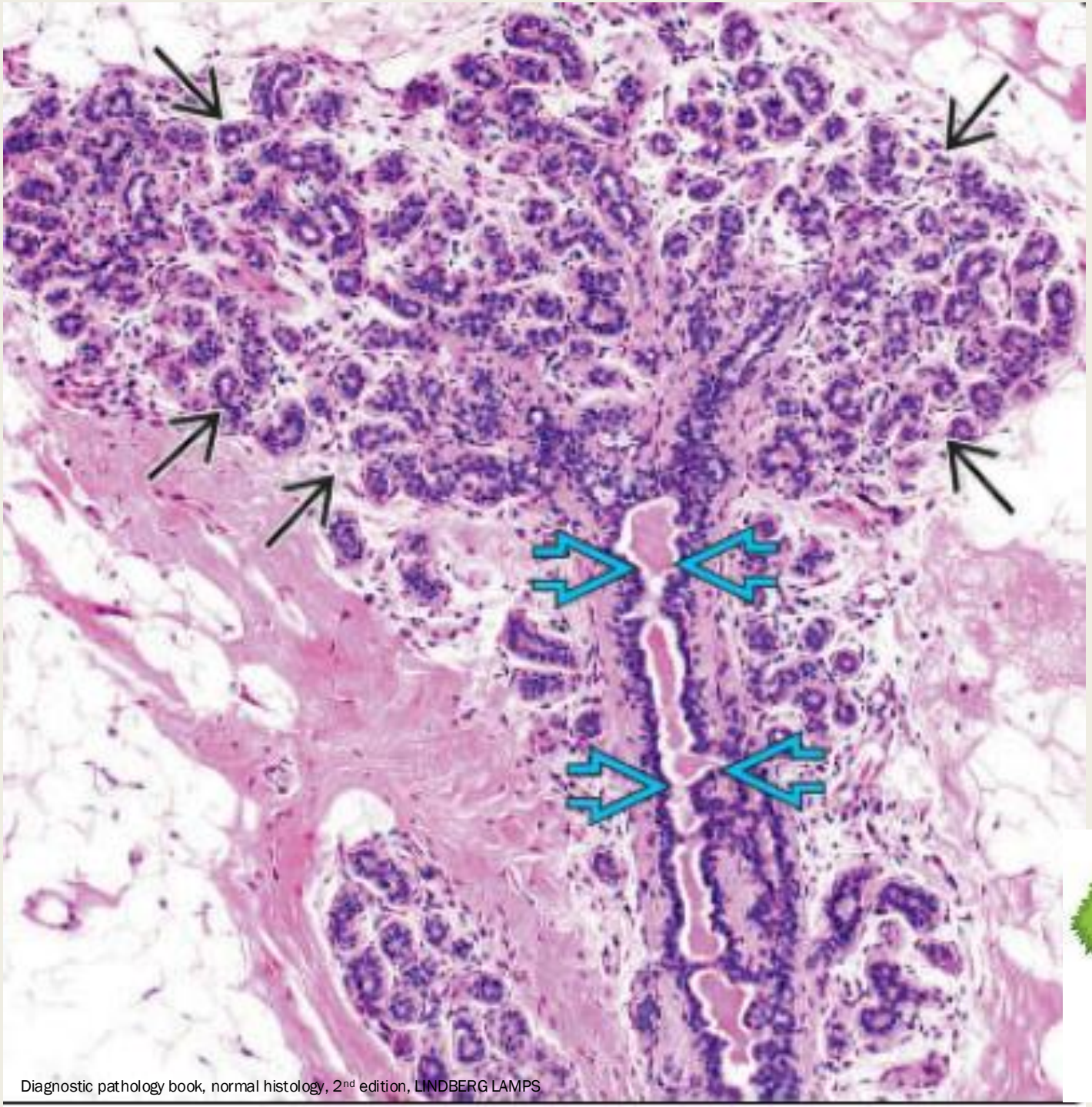

Luminal cells (blue)
Myoepithelial cells (black)
Intralobular stroma (green)
Interlobular stroma (red)
Nipple
Papilloma
DCIS
Epithelial hyperplasia
Normal lobule
Fibroadenoma
Invasive carcinoma
Phyllodes tumor
Hemangioma
Angiosarcoma
NORMAL
BENIGN
MALIGNANT



Diagnostic pathology book, normal histology, 2nd edition, LINDBERG LAMPS

Regardless of the symptom:

- The underlying cause is **benign** in >90% of cases.

- The likelihood of malignancy increases with **age**:
  - *the risk of nipple discharge being due to cancer increases from 7% in women <60 years vs. 30% in women >60.*

  - *only 10% of palpable masses in women <40 years are carcinomas vs. 60% in women >50.*

- Of women with cancer:
  - *about 45% have symptoms*
    - Palpable mass>>>>> pain> nipple discharge > inflammatory changes
  - *the remainder come to attention through screening tests*

Women with breast cancer!

Mammographic screening:

- detects early, nonpalpable asymptomatic breast carcinomas before metastasis.

- the average size of invasive carcinomas detected by mammography is ≈ 1 cm, at this stage only 15% will have metastasized to regional lymph nodes

- The sensitivity and specificity of mammography increase with age→ due to replacement of the fibrous, radiodense tissue of young women with the fatty, radiolucent tissue of older women

CLINICAL PRESENTATIONS OF BREAST DISEASE:

- **Pain** (mastalgia or mastodynia):

- common
- Related to menses (cyclic edema and swelling).
- Localized due to ruptured cyst, or physical trauma.

Almost all painful masses are **benign** except for 10% of cases that relates to cancers

- **Inflammation**:

- Rare, causes edema and erythema.
- Mostly caused by infections (during lactation and breastfeeding).
- An important mimic of inflammatory breast cancer

❑ Nipple discharge:

- **Normal:** when small in quantity and bilateral.
- **Milky discharges (galactorrhea):**
  - *are associated with elevated prolactin levels (pituitary adenoma), hypothyroidism, or endocrine anovulatory syndromes, patients taking OCPs, tricyclic antidepressants, methyldopa, or phenothiazines.*
- **Bloody or serous discharges**:
  - *commonly due to large duct papillomas.*
  - *During pregnancy, result from the rapid growth and remodeling of the breast.*
- **BUT spontaneous, unilateral, and bloody discharge increases concern for malignancy.**

- **Palpable masses:**

- 95% are benign
- all palpable masses require evaluation.
- **The most common palpable lesions are cysts, fibroadenomas, and invasive carcinomas**
- generally detected when they are 2 to 3 cm in size.

- **Gynecomastia:**

- The only common breast symptom in **males**.
- There is an increase in both stroma and epithelial cells resulting from an imbalance between **estrogens**, which stimulate breast tissue, and **androgens**, which counteract these effects.

STROMAL NEOPLASMS

Stromal neoplasms:

- The two types of stroma: intralobular and interlobular

- Tumors of the **Intralobular** stroma:
  - ***Include fibroadenoma and phyllodes tumor***

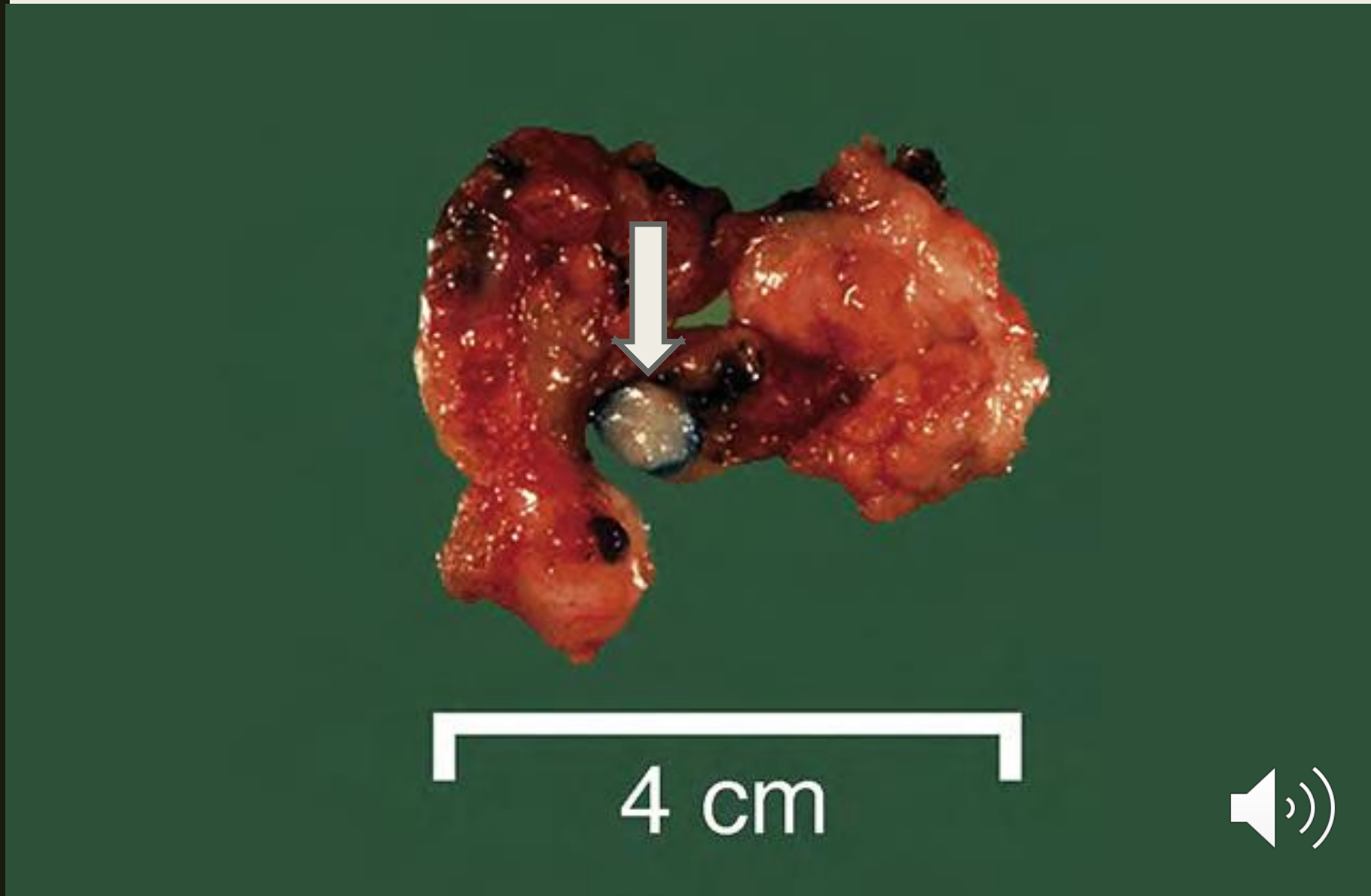
  - ***biphasic tumors****: composed of both stromal cells and epithelial cells*

Fibroadenoma

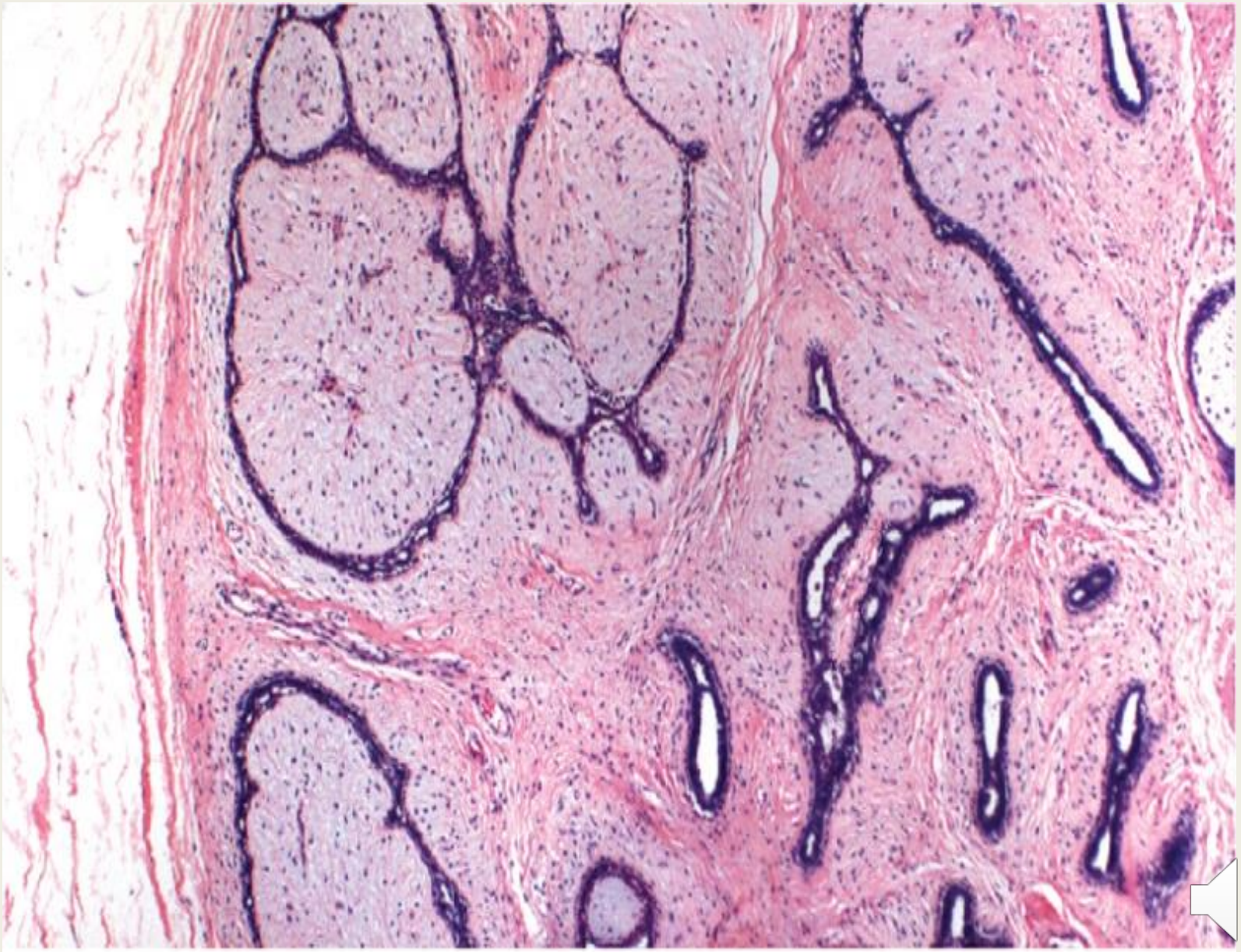
- The **most common benign neoplasm** of the female breast.
- Related to **estrogen activity**:
  - *may enlarge late in the menstrual cycle and during pregnancy.*
  - *After menopause usually regress and calcify.*

- Peak 20s and 30s
- discrete, solitary, freely movable nodule, (1-10 cm).

Fibroadenoma, gross



FIBROADENOMA



Phyllodes Tumor

- Much less common than fibroadenomas
- Arise from the intralobular stroma and not from preexisting fibroadenomas.
- mostly in the sixth decade
- Leaf-like clefts and slits➔
  - *due to the presence of nodules of proliferating stroma covered by epithelium*

Epithelial lesions of breast

Benign

- Non proliferative changes:
  - *cyst, fibrosis, adenosis*
- Proliferative diseases without atypia:
  - *epithelial hyperplasia, papilloma, sclerosing adenosis, complex sclerosing lesion*
- Proliferative disease with atypia:
  - *ADH, ALH*

Malignant

- Noninvasive carcinoma:
  - *DCIS, LCIS*
- Invasive carcinoma

benign epithelial lesions:

- The majority are incidental findings detected by mammography.

- **Benign changes are divided into three groups:**
  - ***Nonproliferative changes****: not associated with an increased risk of breast cancer.*
  - ***Proliferative disease without atypia****: polyclonal hyperplasia & associated with 1.5-2 folds increased risk of breast cancer.*
  - ***Proliferative disease with atypia****: monoclonal "**precancers**" & associated with 4-5 folds increased risk of breast cancer in **both** breast*

Nonproliferative Breast Changes (Fibrocystic Changes)

- Common

- three principal morphologic changes:

  (1) Cysts (most common): lined by layer of luminal cells often show apocrine metaplasia

  (2) Fibrosis

  (3) Adenosis: Increased number of acini per lobule

Proliferative disease without atypia

- are predictors of risk but unlikely to be true precursors of carcinoma.

- Includes:
  - ✓ *epithelial hyperplasia*
  - ✓ *sclerosing adenosis*
  - ✓ *complex sclerosing lesion*
  - ✓ *Papilloma*

- Each is associated with varying degrees of epithelial cell proliferation.

Proliferative disease with atypia

1. atypical lobular hyperplasia (ALH) : resembles lobular carcinoma in situ (LCIS)

2. atypical ductal hyperplasia (ADH): resembles ductal carcinoma in situ (DCIS)

- Associated with a moderately increased risk of carcinoma

- are monoclonal proliferations having some, but not all, histologic features that are required for the diagnosis of carcinoma in situ.

BREAST CANCER

Epidemiology:

The most common and deadly malignancy of women

Worldwide the incidence and mortality are increasing rapidly especially in lower income countries due to social changes that increases the risk of breast cancer

Social changes: delayed childbearing, fewer pregnancies and reduced breastfeeding combined with longer life span and lack of access to optimal health care

The lifetime risk of beast cancer is 1 in 8 for women living to age 90 in US

Almost all breast malignancies are adenocarcinomas

Risk factors:

Age:

- incidence increases rapidly after age 30
- 75% of women with breast cancer are >50

Gender

- The incidence in men is only 1% of that in women.

Family History and genetics

- family history (affected first-degree relatives, multiple cancers, young age)
- Personal hx of breast CA

physical inactivity

Alcohol consumption

Risk factors:

Reproductive History & lifetime exposure to estrogen)

- Early age of menarche<12
- Late menopause >55
- nulliparity (never pregnant)
- absence of breastfeeding
- older age at first pregnancy>35
- Exogenous hormone therapy: postmenopausal hormone replacement
- Postmenopausal obesity

Risk factors:

Race/Ethnicity and socioeconomic status

- Higher rates in high income countries and lowest in lower income countries.
- in the US the rate of new breast cancer is similar across socially defined races but age at diagnosis is higher in Europian americans and lowest in Hispanic americans

Radiation to chest at young age

high breast density

Pathogenesis:

- The major germline mutations associated with increased risk of breast cancer are:
- **BRCA1 and BRCA2:**
  - Tumor supressor genes: cancer arises only when both alleles are inactivated or defective .
  - encode proteins that are required for repair of certain kinds of DNA damage.
  - Breast cancer risk in carriers is 45-75% by the age of 70 (compared to 12% in general pop)
- **HER2 amplification:**
  - HER2 is a receptor tyrosine kinase, that promote cell proliferation and suppress apoptosis
  - Cancers with Overexpression of HER2 are pathogenically distinct and highly proliferative

Breast carcinoma:

A. ***Noninvasive:****(confined by a basement membrane and do not invade into stroma or lymphovascular channels), include:*

1. Ductal carcinoma in situ (DCIS)
2. Lobular carcinoma in situ (LCIS)

B. ***Invasive (infiltrating):***

1. Invasive ductal carcinoma-NOS → 70% to 80%
2. Invasive lobular carcinoma →10% to 15%
3. Carcinoma with medullary pattern→5%
4. Mucinous carcinoma (colloid carcinoma) →5%
5. Tubular carcinoma→5%
6. Other types

Classification Systems

- In all cases of breast cancer, we examine the following Receptors:
  - Estrogen receptor (ER); progesterone receptor (PR); human epidermal growth factor receptor 2 (HER2/neu)

- Cancer can be classified according to expression of mentioned proteins into three major biologic groups:

 luminal (50-65% of cancer): ER positive & HER2 negative

 HER2(10-20% of cancers): HER2 positive, ER positive or negative

Triple negative (10% of cancers): ER, PR, and HER2 negative

Table 17.7 Summary of the Major Biologic Types of Breast Cancer

Feature	ER Positive/HER2 Negative: "Luminal"	HER2 Positive (ER Positive or Negative): "HER2"	Triple Negative (ER, PR, and HER2 Negative): "TNBC"
Overall frequency	50%–65%	20%	15%
Typical patient groups	Older women; men; cancers detected by screening; germline *BRCA2* mutation	Younger women; germline *TP53* mutation	Young women; germline *BRCA1* mutation carriers; African American women
Grade	Mainly grade 1 and 2	Mainly grade 2 and 3	Mainly grade 3
Complete response to chemotherapy	~10%	ER positive (15%), ER negative (~30%–60%)	~30%
Timing of relapse	Low rate over many years; late recurrence possible (>10 years after diagnosis); long survival possible with bone metastases	Bimodal with early and late (10 years) peaks	Early peak at <8 years, late recurrence rare, survival with metastases rare
Metastatic sites	Bone (70%–80%), viscera (25%–30%), brain (~10%)	Bone (70%), viscera (45%), brain (30%)	Bone (40%), viscera (35%), brain (25%)
Common somatic mutations	*PIK3CA* (29%–45%), *TP53* (12%–29%)	*TP53* (70%–80%), *PIK3CA* (~40%)	*TP53* (70%–80%), *PIK3CA* (9%)

PIK3CA encodes phosphoinositide 3-kinase (PI3K); *TNBC*, triple-negative breast cancer.

NONINVASIVE (IN SITU) CARCINOMA

- **include:**
  1. Ductal carcinoma in situ, DCIS

  2. Lobular carcinoma in situ, LCIS

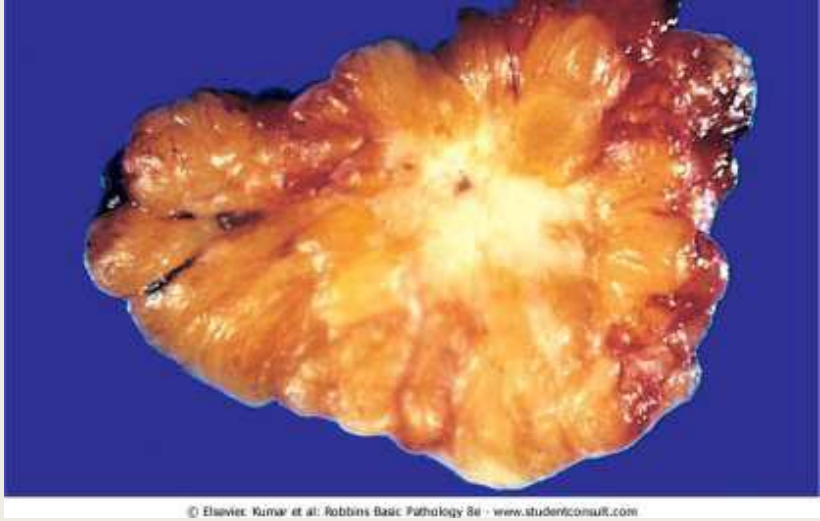
- Both are Malignant clonal proliferation of cells
- **But confined by a basement membrane and do not invade into stroma or lymphovascular channels**

Paget disease of the nipple

- Caused by extension of DCIS into the lactiferous ducts and then into the contiguous skin of the nipple
- the presence of paget disease of the nipple is often associated with invasive carcinoma

INVASIVE (INFILTRATING) BREAST CARCINOMA

Morphology:



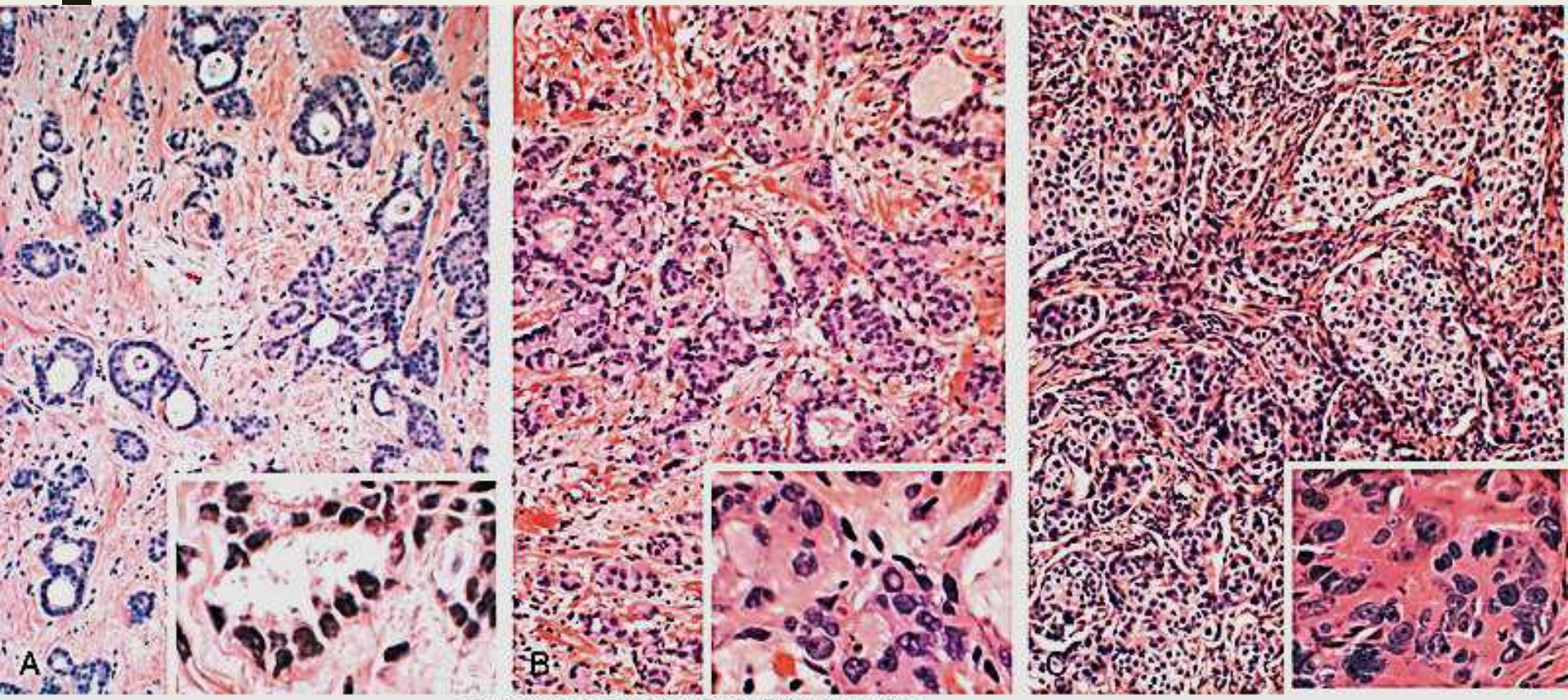
- Location:
  - *upper outer quadrant (50%)*
  - *central portion- subareolar (20%).*
  - *Lower outer quadrant 10%*
  - *Upper inner quadrant 10%*
  - *Lower inner quadrant 10%*

- 4% have bilateral primary tumors or sequential lesions in the same breast.

Invasive ductal carcinoma

- 70% to 80%
- Also called Carcinomas "not otherwise specified”
- **Precancerous lesion**: usually DCIS
- **Clinical presentation:** mammographic density or hard, palpable irregular mass.
- Receptor profile:

Usually: ER, PR (+), HER2 (-)



Kumar et al: Robbins Basic Pathology, 9e.

Invasive lobular carcinoma

- 10-15% of all breast carcinomas.
- **Precancerous lesion**. 2/3 associated with LCIS.
- multicentric and bilateral (10% to 20%).
- **Clinical presentation**. Most present as palpable masses or mammographic densities

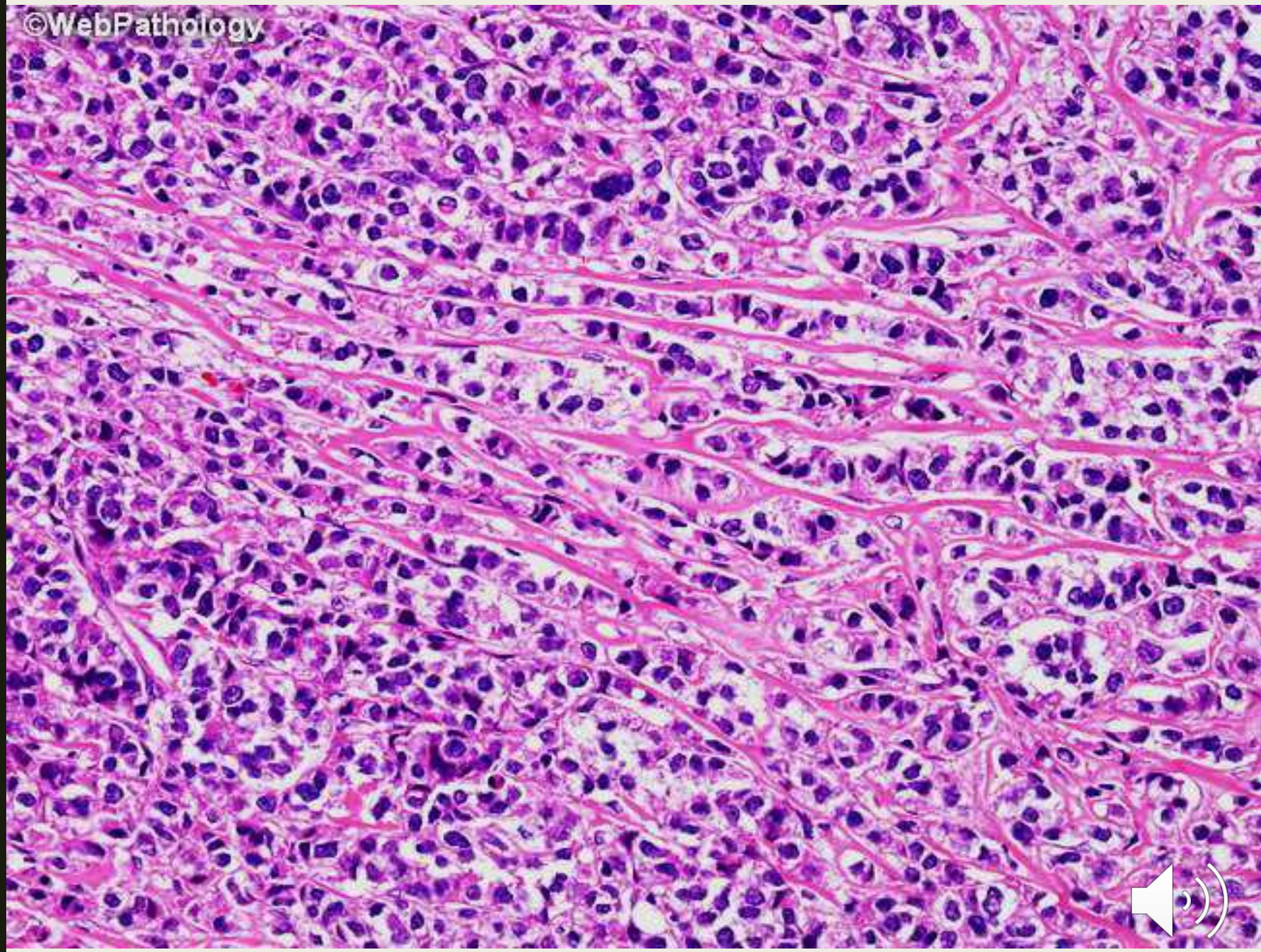
Invasive lobular carcinoma

- Histologically, cells invade stroma i**ndividually** and often are aligned in **“single-file”**

- This loss of adhesion in ALH, LCIS and lobular Ca is usually due to dysfunction of E-cadherin

- E-cadherin is a transmembrane protein contribute to the cohesion of normal epithelial cells in the breast and other glandular tissues

- receptor profile: Usually express ER & PR while HER2 overexpression is rare or absent.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Spread of Breast Cancer

- through **lymphatic** and **hematogenous** channels.
- The majority first metastasize to regional L.Ns
  - Lymphatic drainage goes to one or two sentinel LNs in axilla
  - If these LNs are negative, then the remaining axillary LNs are usually negative
  - Sentinel Node bx: standard to access for regional LN involvement

- Favored sites of mets are the **bone**, **lungs**, **skeleton**, **liver**, and **adrenals** and (less commonly) the brain, spleen, and pituitary.

PROGNOSIS

1. **Tumor stage:**
   1. ***Invasive carcinoma versus carcinoma in situ***
   2. ***tumor size***.
   3. ***Lymph node involvement and the number of lymph nodes involved by metastases***.
   4. *local invasion of skin or skeletal muscles*
   5. ***Distant metastases***.
2. **Histologic grade** (based on tubular formation, atypia and mitosis)

   - The higher the tumor proliferation rates the more response to cytotoxic chemotherapy

PROGNOSIS

3- histologic type of carcinoma:

- Better px: Mucinous and tubular
- Poor px: Inflammatory ca

4- Tumor biology: ER, PR, HER2 expression

- Expression of ER and PR predicts the response to antiestrogen therapy
- So you can inhibit the growth of cancers that responds to hormones for many years.

■ the importance of evaluating HER2 s to predict response to a monoclonal antibody ("Herceptin") against the gene product.

THANK YOU