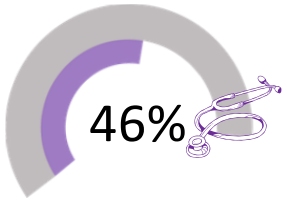

بسم الله الرحمن الرحيم

Breast Pathology

FINAL | Lecture #5

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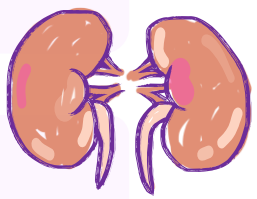
﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾



BREAST DISEASES

- Maram Abdaljaleel, MD
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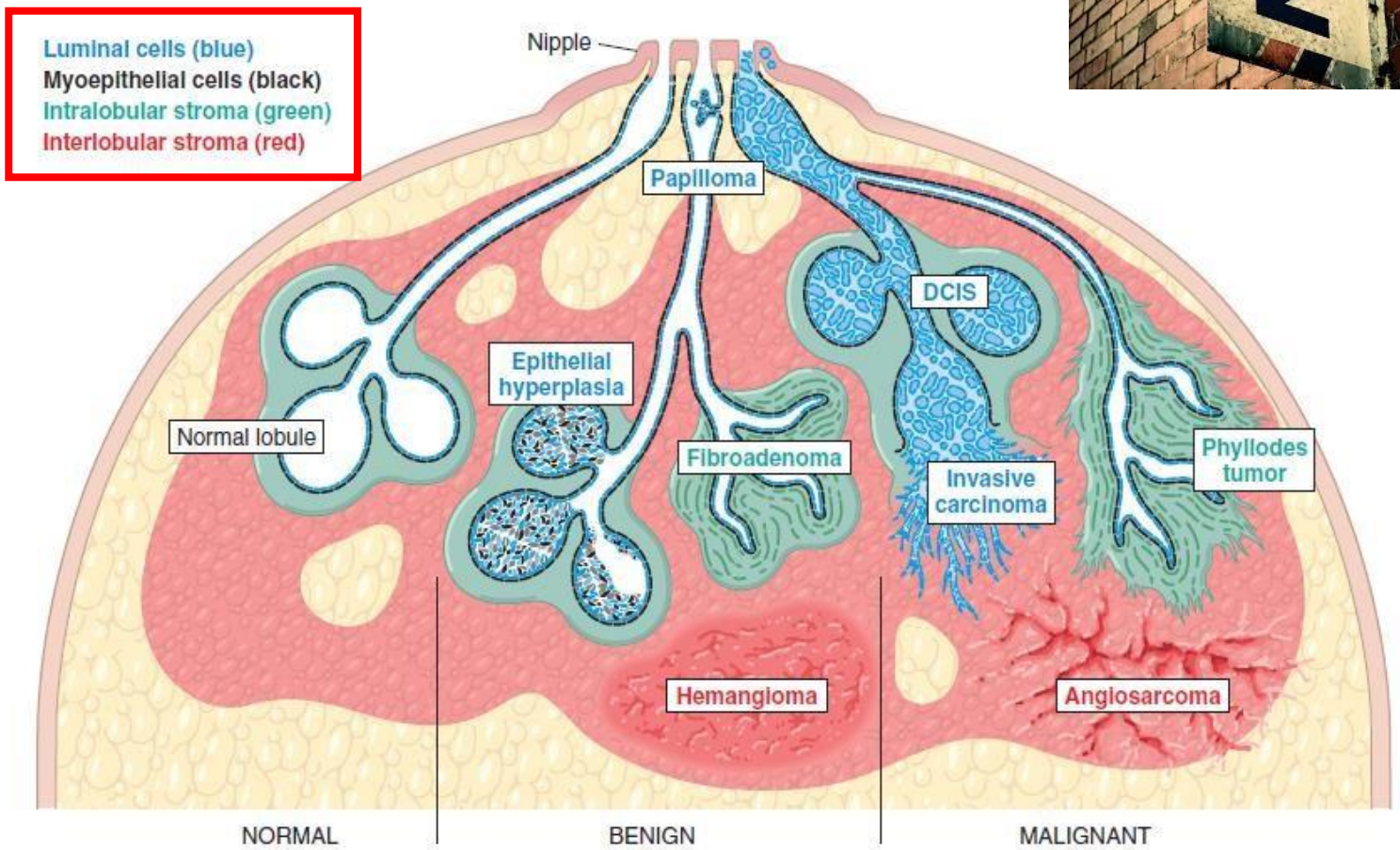

Luminal cells (blue)
Myoepithelial cells (black)
Intralobular stroma (green)
Interlobular stroma (red)
Nipple
Papilloma
DCIS
Epithelial hyperplasia
Normal lobule
Fibroadenoma
Invasive carcinoma
Phyllodes tumor
Hemangioma
Angiosarcoma
NORMAL
BENIGN
MALIGNANT

Next slide

Breast Structure and Histology

The breast is composed of **two main anatomical structures**, **two types of epithelial cells**, and **two types of stromal tissue**.

1. Large Duct System

The ductal system forms a complex **three-dimensional arborizing (branching) network**.

It begins with the **large ducts**, which divide into **segmental ducts**, then into **subsegmental ducts**, and finally terminate as **terminal ducts**.

2. Terminal Duct Lobular Unit (TDLU)

The **terminal duct lobular unit (TDLU)** is considered the **functional unit of the breast**.

It consists of clusters of **acini (lobules)** arranged around a terminal duct, into which they drain their secretions.

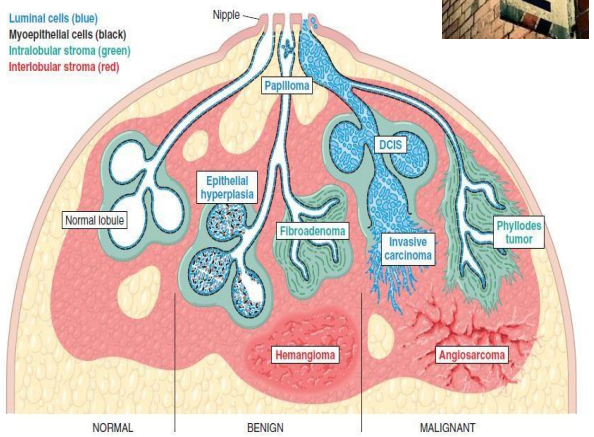
Epithelial Cells Lining Both the Ductules and the Lobules in the Terminal Duct Lobular Units

1. Luminal Cells (Blue)

Luminal cells form the **inner layer** of the **bilayered ductal epithelium** and line the ducts.

2. Myoepithelial Cells (Black)

Myoepithelial cells form the **outer cell layer** and lie directly on the **basement membrane**.



Stromal Components

1. Interlobar Stroma (Red)

The interlobar stroma surrounds the **large ducts** and **terminal duct lobular units**.

It is composed of:

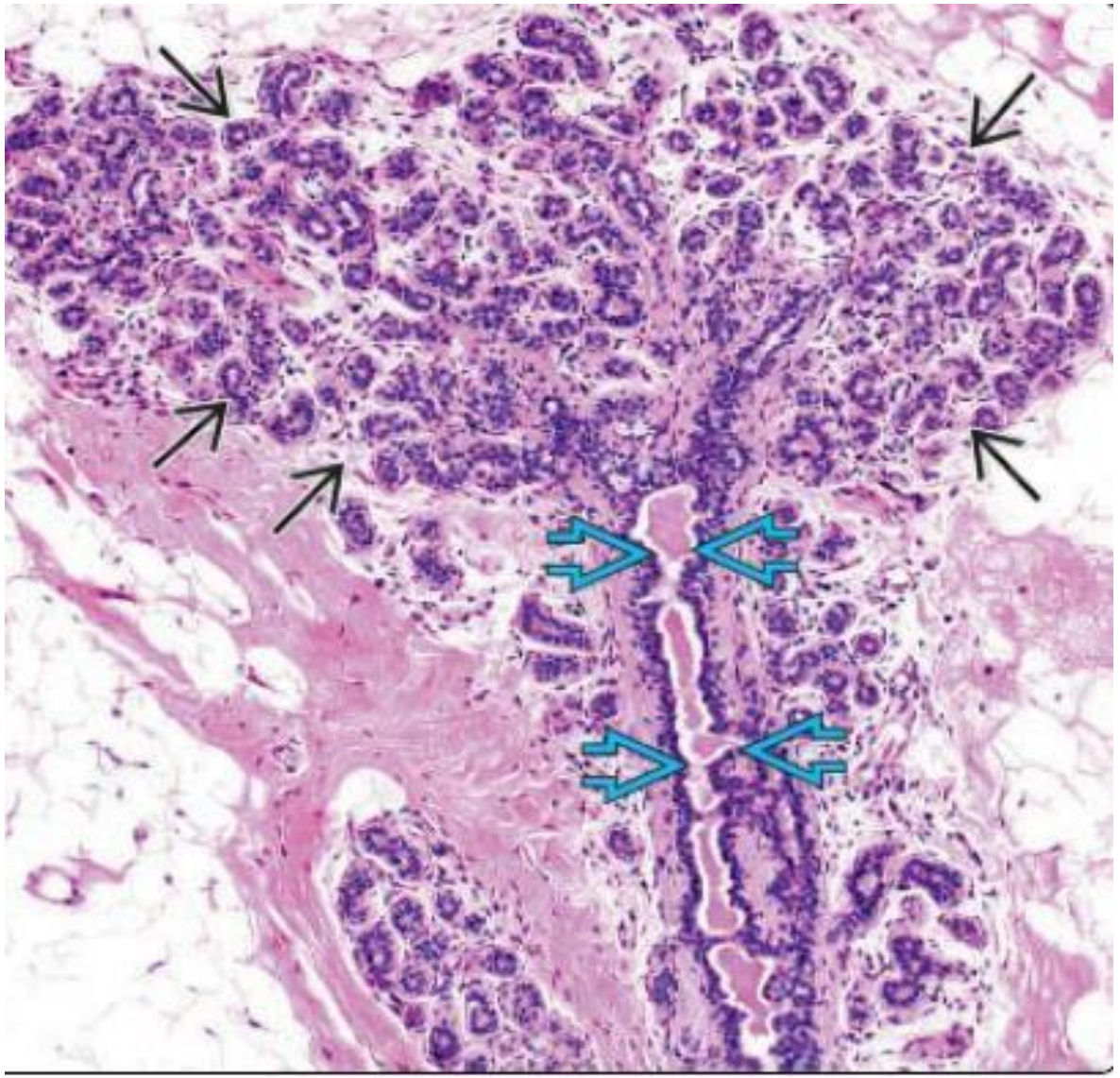
- **Mature adipose tissue** (which constitutes most of the breast volume),
- **Fibroconnective tissue**, including fibroblasts, myofibroblasts, blood vessels, lymphatics, and nerves.

2. Intralobular Stroma (Green)

The intralobular stroma surrounds the **terminal duct lobular unit (TDLU)**.

Figure showing the histology of the terminal duct lobular unit. It has architectural organization of a **tree**, where the **terminal duct forms the trunk** which opens into the smaller **acini (lobules)** resembling branches of a tree.

Terminal Duct Lobular Unit



Acini (lobules)

Terminal duct

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.* It is the same symptom, but the age of the patient is the main factor that determines the chances of a symptom or sign being related to malignancy.

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

- Of women with cancer:
  - *about 45% have symptoms* so not all patients with breast cancer will have symptoms.
    - Most common symptoms, in order: Palpable mass >>>> pain > nipple discharge > inflammatory changes
  - *the remainder (55%) come to attention through screening tests.* This highlights the importance of screening.

Women with breast cancer!

Mammographic screening:

- It is a screening test that uses X-ray pictures of breast (called mammograms) to detect early, nonpalpable asymptomatic breast carcinomas before metastasis (detection at an early stage = early management and better prognosis).

- the average size of invasive carcinomas detected by mammography is ≈ 1 cm, which is usually too small to be palpable or symptomatic, at this stage only 15% will have metastasized to regional lymph nodes (relatively early stage).

- 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:

These refer to breast diseases in general, not just cancers.

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

- common
- Related to menses (cyclic edema and swelling).
- Localized due to a localized lesion such as ruptured cyst, or physical trauma to adipose tissue that is associated with fat necrosis.

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

- **Inflammation**:

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

CLINICAL PRESENTATIONS OF BREAST DISEASE:

- **Nipple discharge can be :**

- **Normal:** when small in quantity and bilateral. However, it can also be a clinical presentation of breast disease as described below.

- **Milky discharges (galactorrhea):**
  - *are associated with elevated prolactin levels (pituitary adenoma), hypothyroidism, or endocrine anovulatory syndromes, patients taking OCPs* (oral contraceptive pill), *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 and further investigation is required .**

CLINICAL PRESENTATIONS OF BREAST DISEASE:

❑ Palpable masses:

- They are masses that can be detected by physical examination.
- 95% are benign
- All palpable masses require evaluation (evaluation and further workup are mandatory, even if the majority of masses are benign).
- **The most common palpable lesions are cysts, fibroadenomas, and invasive carcinomas**
- generally detected when they are 2 to 3 cm in size, because any mass less than 2 cm in size cannot be detected by physical examination .

❑ 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. This happens when estrogens become elevated and androgen levels drop.


STROMAL
NEOPLASMS

Stromal neoplasms:

- The two types of stroma: intralobular and interlobular

- Tumors of the **Intralobular** stroma (specialized stroma):
  - ***Include fibroadenoma (most common) and phyllodes tumor***
  - both are ***biphasic tumors***: *composed of both stromal cells and epithelial cells*

❑ Fibroadenomas and phyllodes tumors contain neoplastic and non-neoplastic proliferations. The neoplastic component of these tumors is the itralobular (specialized) stroma, while the non-neoplastic part is the epithelium. How does the epithelium proliferate if it is a non-neoplastic component? Answer: neoplastic proliferation of specialized fibroblasts within the intralobular stroma stimulates a reactive, non-neoplastic proliferation of intralobular epithelial cells through the secretion of growth factors.

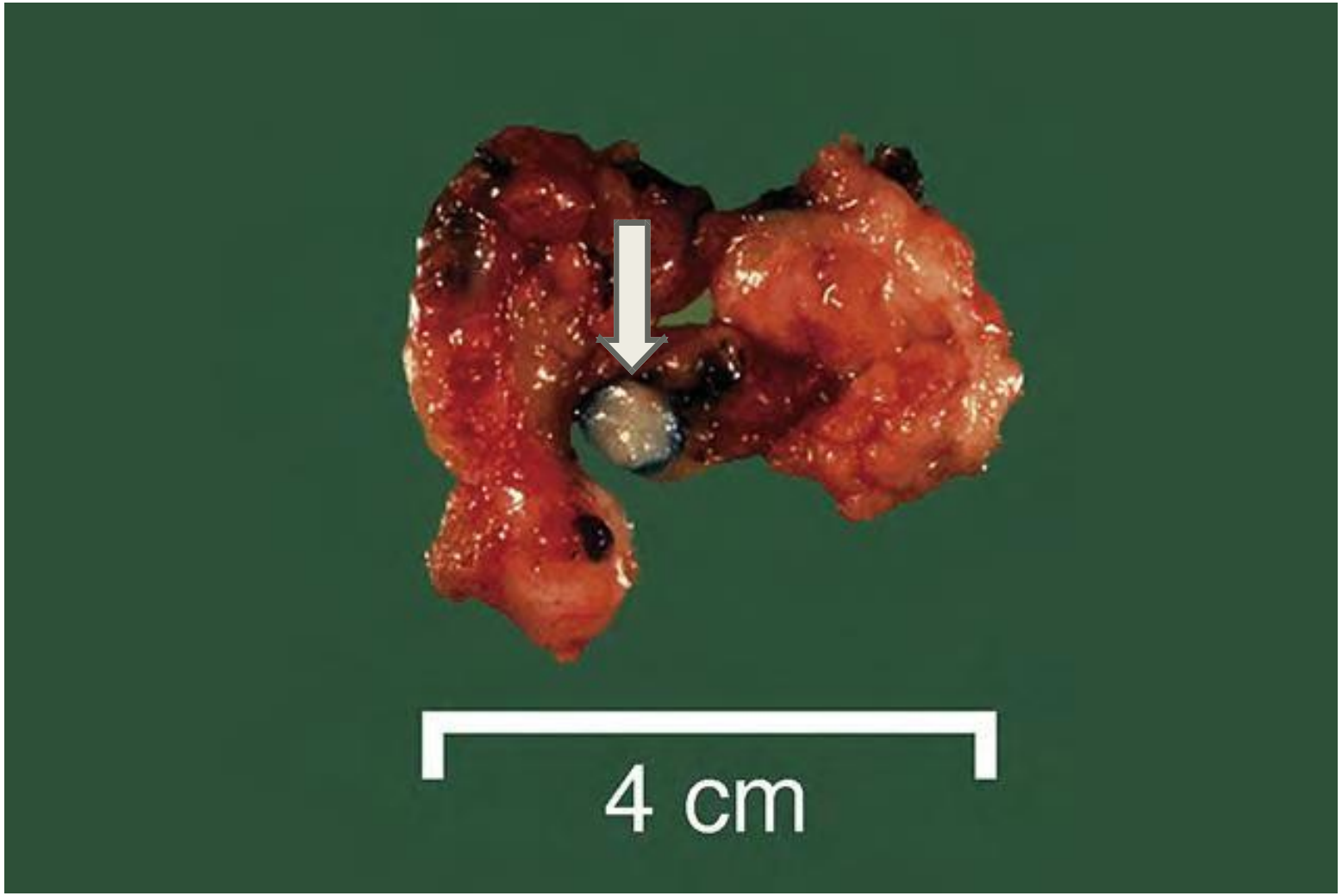
❑ The proliferating fibroblasts compress and distort the proliferating epithelial cells, resulting in elongated slit-like acini rather than the normal rounded acinar structures.

Fibroadenoma

- The **most common benign neoplasm** of the female breast.
- Related to **estrogen activity,** as it is composed of specialized stroma which responds very well to the elevated estrogen:
  - *may enlarge late in the menstrual cycle and during pregnancy.*
  - *After menopause* (low estrogen) *usually regress and calcify.*

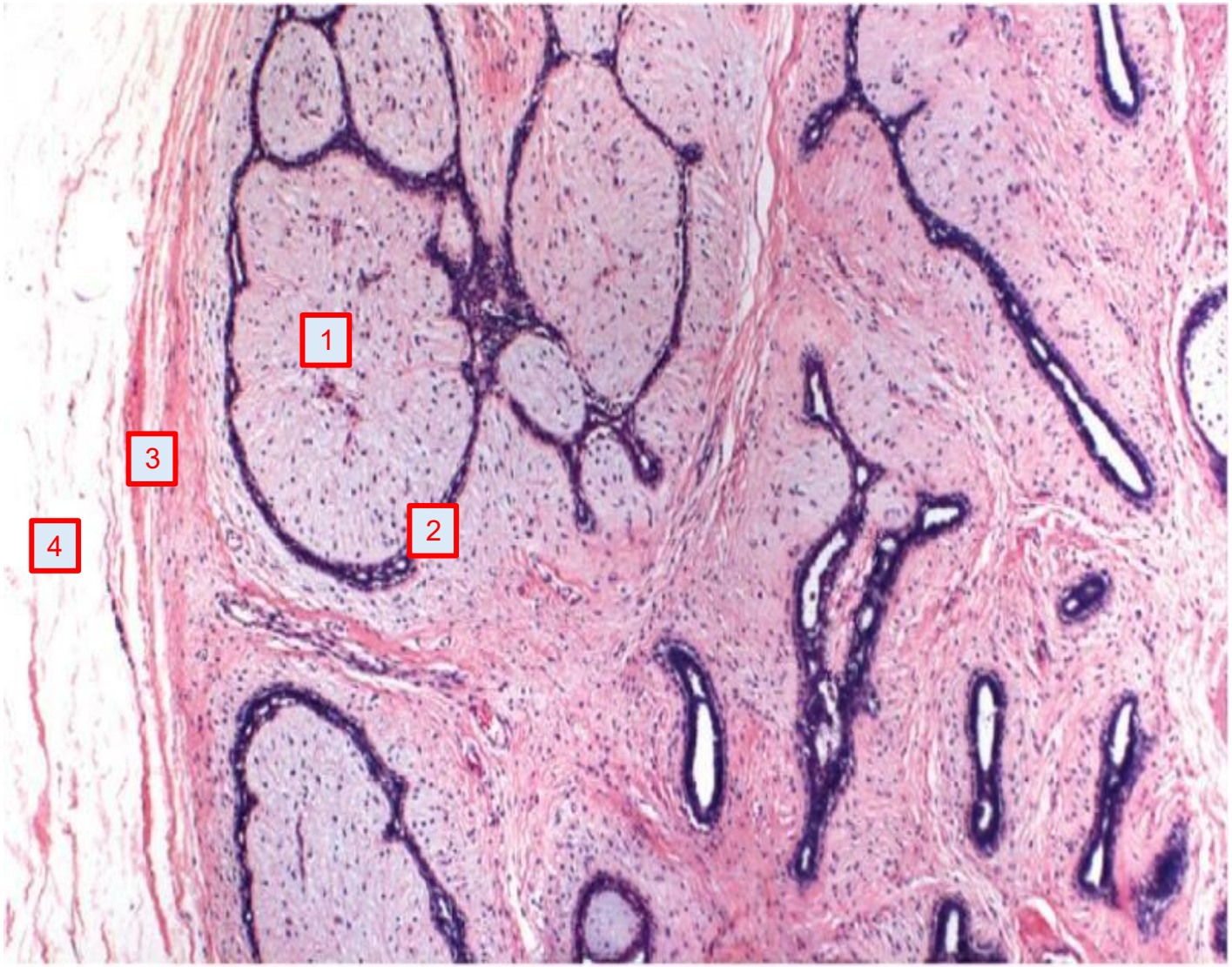
- Peak 20s and 30s (reproductive age)
- discrete, wellcircumscribed, well-defined, solitary, freely movable nodule, (1-10 cm), easy surgical excision as it is a discrete mass.

Fibroadenoma, gross (macroscopic)



- The white nodule is a fibroadenoma. Note how it is discrete, well-circumscribed, well-defined, and easily detected due to the clear contrast with background breast tissue.
- The surrounding blue color is the dye to stain the margins of the tumor in radiology, allowing the surgeon to identify masses in breast tissue more easily.

Fibroadenoma (microscopic)



- Notice the proliferation of the intralobular stroma, the characteristic feature of fibroadenomas.
- This causes the intralobular stroma[1] to increase in size and cellularity, pushing the adjacent epithelium.
- As a result, the epithelium[2] (dark purple) becomes compressed and forms slit-like spaces.
- In other words, fibroadeonmas involve the overproliferation of intralobular stroma resulting in the distortion of the architecture of the ducts and lobules.
- The boundary[3] between the fibroadenoma and the adjacent breast tissue[4] is sharply defined. This is an important characteristic of fibroadenomas, especially when comapred to other tumors discussed shortly.

Phyllodes Tumor

- Another intralobular stromal tumor
- Much less common than fibroadenomas
- Arise from the intralobular stroma and not from preexisting fibroadenomas.
- mostly an older lady 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*

ADH: Atypical ductal hyperplasia
ALH: Atypical lobular hyperplasia

Malignant

- Noninvasive carcinoma:
  - *DCIS, LCIS*

DCIS: ductal carcinoma in situ
LCIS: lobular carcinoma in situ

- Invasive carcinoma

benign epithelial lesions:

- The majority are incidental findings detected by mammography.

- **Benign changes are divided into three groups:**
  - ***Nonproliferative changes*** (cyst formation, fibrosis and adenosis)*: 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*** (including ADH and ALH)*: monoclonal "**precancers**" & associated with 4-5 folds increased risk of breast cancer in **both** breast*

Nonproliferative Breast Changes (Fibrocystic Changes)

Lesions are lined only by a single layer of luminal and a single layer of myoepithelial cells, with no epithelial proliferation (hence the name).

- Common
- three principal morphologic changes:

(1) *Cysts (most common):* dilated spaces *lined by a layer of luminal cells, often show apocrine metaplasia.* Cells have abundant granular cytoplasm, apical snouts, enlarged nuclei and prominent nucleoli. Theses cysts are at risk of rupture which induces chronic inflammation and fibrosis in response to the spillage of debris from the cystic contents, hence the name *fibrocystic changes*.

(2) *Fibrosis*

(3) *Adenosis: Increased number of acini per lobule*

Proliferative disease without atypia

- Commonly detected as a mammographic densities or calcifications, sometimes even incidentally when looking for other lesions.
- Polyclonal and not associated with genetic changes.
- Are predictors of risk (1.5-2 fold increase in risk of malignancy) = *stroma shows fibrosis, adenosis= number of glands is increased* but unlikely to be true precursors of carcinoma.
- Includes:
  - ✓ *epithelial hyperplasia: the lumen of the duct or lobule is filled with mixed populations of luminal and myoepithelial cells without atypia.*
  - ✓ *sclerosing adenosis: sclerosing= stroma shows fibrosis/sclerosis that compresses and distorts the glands, adenosis= number of glands is increased.*
  - ✓ *complex sclerosing lesion: central area of sclerosis, composed of fibrosis and elastosis, with the ducts and lobules radiating outwards.*
  - ✓ *Papilloma: finger like projections (papillae) with fibrovascular cores, that are lined by luminal and myoepithelial cells without atypia*
- Each is associated with varying degrees of epithelial cell proliferation including luminal and myoepithelial cells, but they do not show cellular atypia.

Proliferative disease with atypia

Proliferation of the luminal and myoepithelial cells 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 (remember that these lesions are monoclonal/precancerous and are associated with 4-5 folds increased risk of breast cancer in both breasts)

- 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, even exceeding non-melanocytic breast cancer.

Worldwide the incidence and mortality are increasing rapidly especially in lower income (developing) 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 (The incidence is increasing: more than two million women are newly diagnosed with a breast cancer every year,one third of whom will die of this disease).

Almost all breast malignancies are adenocarcinomas

Risk factors:

Age:

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

Breast cancer is considered rare in women younger than the age of 25.
· Only 5% are younger than the age of 40.

Gender

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

So being a female is a risk factor

Family History and genetics

- family history (the greatest risk is for individuals with affected first-degree relatives, multiple cancers, young age)
- Personal hx (history) of breast CA

physical inactivity

Alcohol consumption

Risk factors:

All of these factors increase the risk of breast cancer probably because they increase exposure to estrogen.

Reproductive History & lifetime exposure to estrogen)

- Early age of menarche<12 (menarche = first menstruation)
- Late menopause >55
- nulliparity (the lady has never been 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 European americans and lowest in Hispanic and African americans. This is due to social facors related to parity and breastfeeding.

· Moreover, breast cancer in Hispanic and African american women tends to develop in an aggressive manner due to differences in genetics, social factors and access to the health care.

Radiation to chest at young age

· Radiation to the chest increases the risk of breast cancer, especially if exposure happens while the breast is still developing. For example, breast cancer develops in about 25 to 30% of women who undergo irradiation for hodgkin lymphoma in their teens and 20s, but the risk for women treated later in life is not elevated, so the risk for irradiation to develop breast cancer is related to the time of exposure.

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. They are normally expressed in many different cells and tissues.
  - Breast cancer risk increases in carriers is 45-75% by the age of 70 (compared to 12% in the general population)
- **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

Based on histological features, breast cancer can be classified into:

A. Noninvasive: *(neoplastic cells are 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): tumor cells have invaded the basement membrane and infiltrate the underlying stroma. Within this group are many histological patterns, including:

1. Invasive ductal carcinoma-NOS → 70% to 80% (NOS = Not otherwise specified)
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

Apart from the histological classification mentioned in the previous slide, another way to classify breast cancer is based on the expression of three proteins: ER, PR, and HER2. This classification is important as it dictates the type of treatment to be used.

- 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

The three groups show striking differences in overall frequency, in patients characteristics, in pathological grade, and in response to chemotherapy, metastatic sites and the timing of relapse. This classification is very important for treatment purposes and to predict the prognosis for your patient.

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

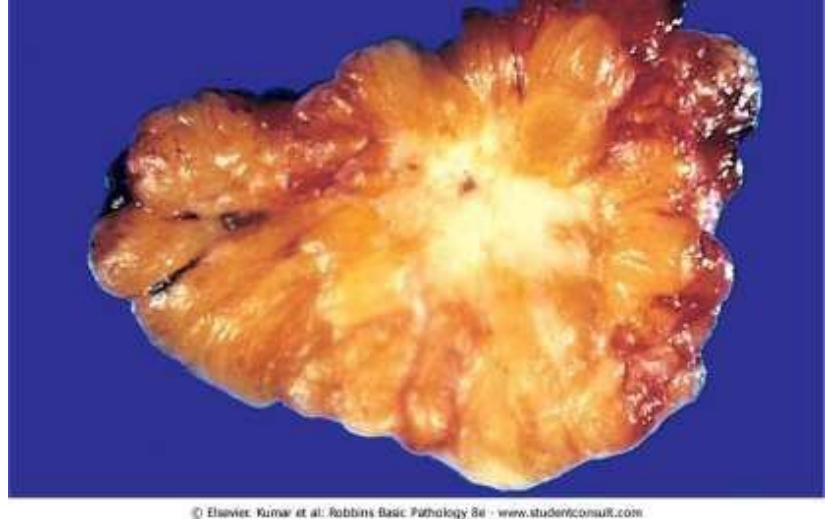
- Both are Malignant clonal proliferation of cells
- **But confined by a basement membrane and do not invade into stroma or lymphovascular channels**

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 of breast cancer:
  - *upper outer quadrant (50%)* – most common
  - *central portion- subareolar (20%).*
  - *Lower outer quadrant 10%*
  - *Upper inner quadrant 10%*
  - *Lower inner quadrant 10%*

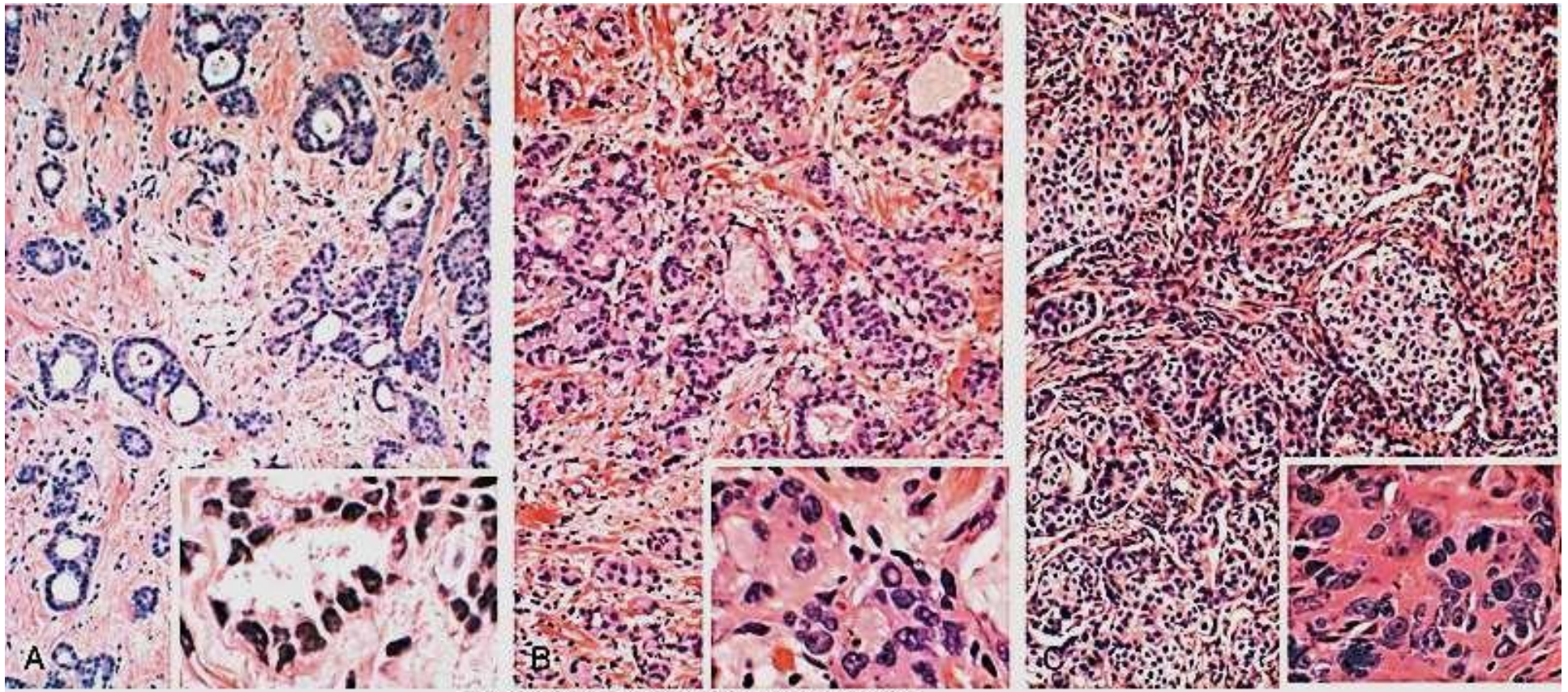
- 4% of women with breast cancer have bilateral primary tumors or sequential lesions in the same breast.

Invasive ductal carcinoma

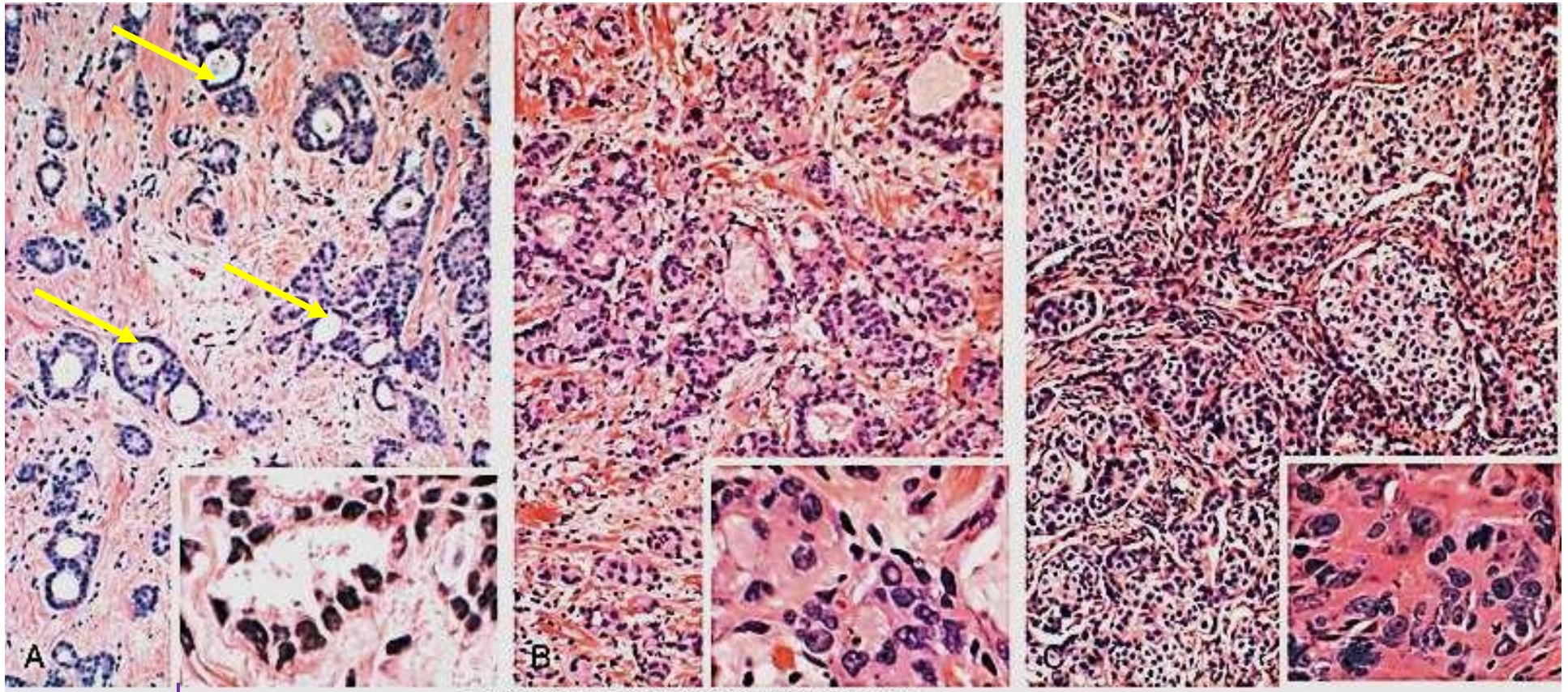
- 70% to 80% (most common histologic subtype of invasive breast cancer)
- Also called Carcinomas "not otherwise specified”
- Usually preceded by a **precancerous lesion**: usually DCIS
- **Clinical presentation:** mammographic density during regular screening or hard, palpable irregular mass.
- Receptor profile:

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

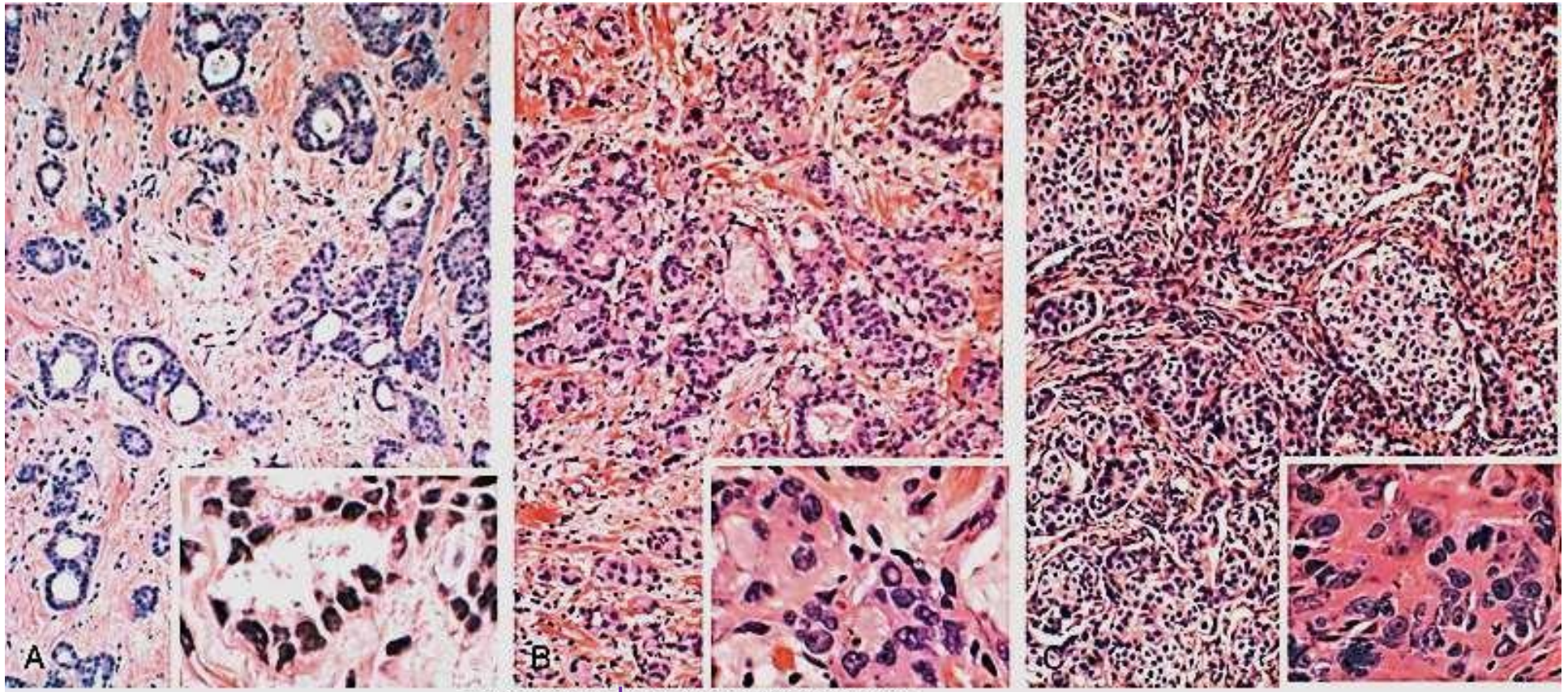
- Invasive ductal carcinoma is a graded into three main groups according to certain histologic features.
- The three histologic features that are used to classify invasive ductal carcinoma into three main grade are tubular formation, nuclear pleomorphism, and number of mitosis.
- The figure below shows the three histologic grades, discussed individually in the next slides.



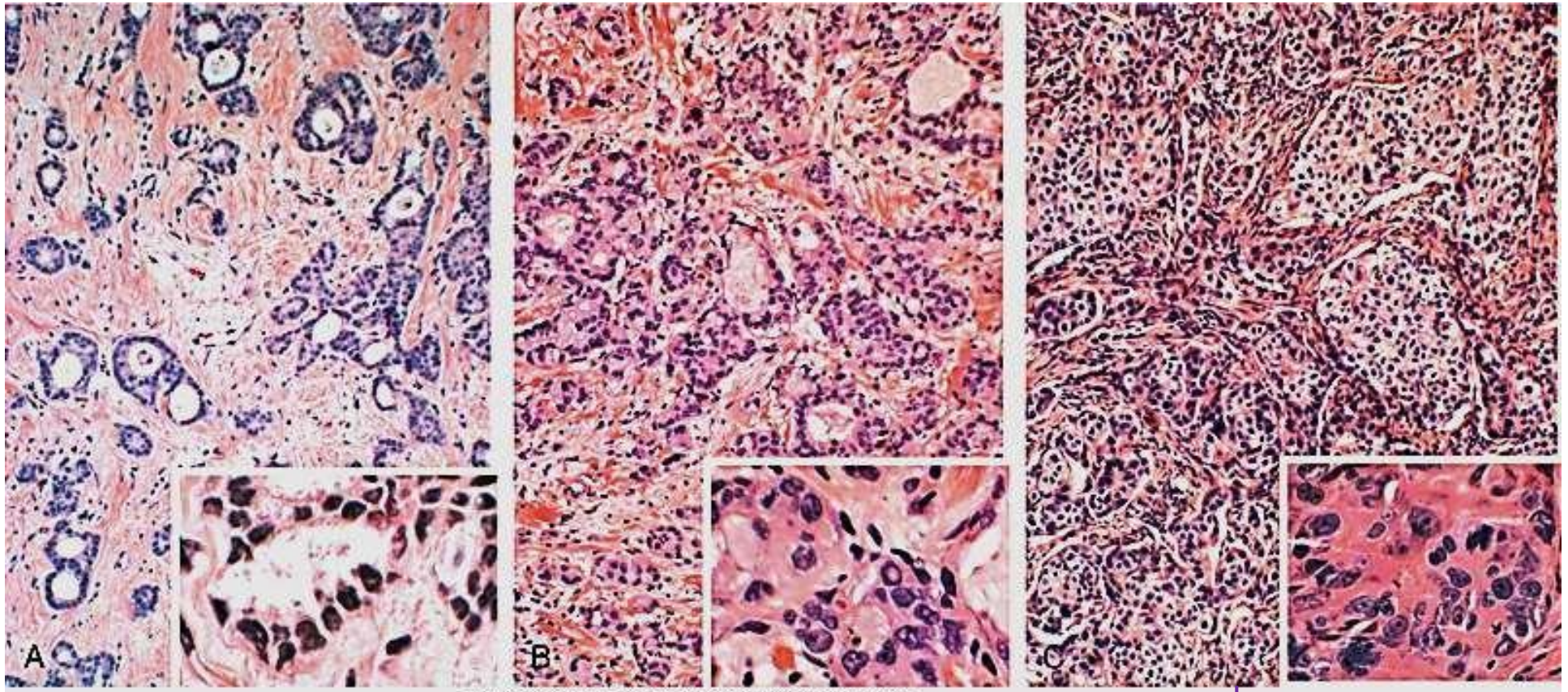
Kumar et al: Robbins Basic Pathology, 9e.



Grade 1, well-differentiated carcinoma because it shows frequent tubules (the first feature we rely on, indicated by arrows) and mild atypia (the cells are somewhat monomorphic and there are no frequent mytotic figures) in so this is classified as a grade 1 well-differentiated breast cancer.



Grade 2 tumor (moderately differentiated breast cancer). There is less tubular formation than the first tumor, more 'solidity' of tumor cells, and more atypia.



Grade 3 tumor (poorly differentiated carcinoma) because the tumor cells are mostly infiltrating as sheets and there is less tubular formation, if any (none is present in this figure). The high-power view on the bottom right corner shows atypia and frequent mitosis

Invasive lobular carcinoma

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

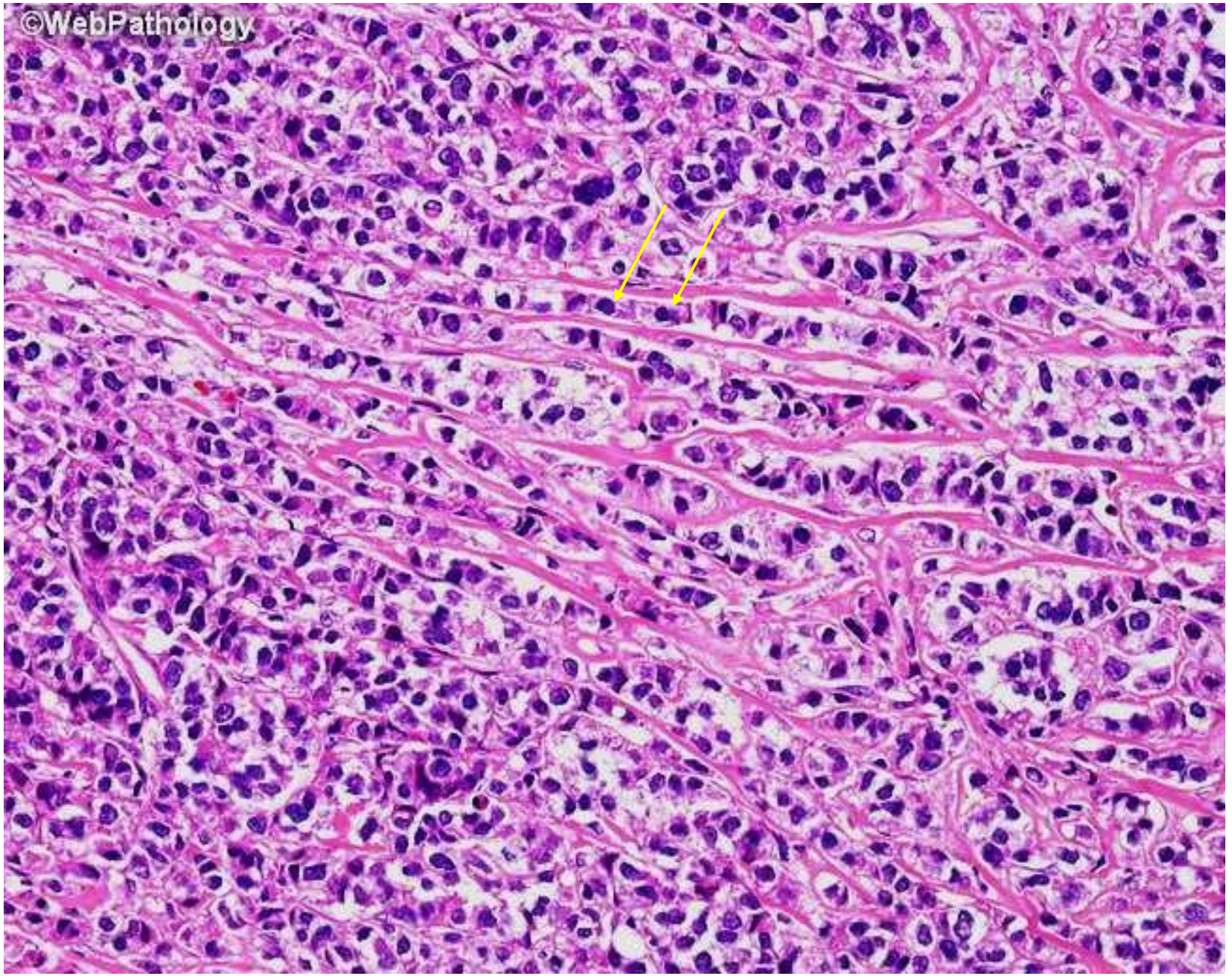
Invasive lobular carcinoma

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

- This loss of adhesion in ALH (atypical lobular hyperplasia), LCIS and lobular Ca (invasive lobular carcinoma) is usually due to dysfunction of E-cadherin

- E-cadherin is a transmembrane protein that contributes to the cohesion of normal epithelial cells in the breast and other glandular tissues (the loss of e-cadherin will result in loss of junctions between cells, so cells look like they are infiltrating individually).

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



This figure shows the histologic findings in invasive lobular carinoma

The tubular formations that we saw in invasive ductal carcinoma as not present here, rather cells infiltrate individually as a single file (see yellow arrows) and this happens due to the loss of E-cadherin.

Spread of Breast Cancer

- through **lymphatic** and **hematogenous** channels.
- The majority first metastasize to regional lymph nodes:
  - 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 (biopsy): standard procedure to access for regional LN involvement.

  So after the diagnosis of a patient with breast cancer, the surgeon takes a biopsy of the sentinel lymph nodes to be sent to histopathology. These are the first one or two nodes that receive the lymphatic drainage from the breast. If negative, then the axillary lymph nodes are by default considered negative as well. If positive, the remaining lymph nodes are excised.

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

PROGNOSIS

The clinical outcomes of breast cancer can be predicted based on molecular and morphological features, stage and time of diagnosis.

1. Tumor stage (remember TNM: tumor size, (lymph) node involvement and metastasis):

    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 (prognosis): 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 receptors is to predict response to a monoclonal antibody ("Herceptin") against the gene product. Herceptin targets the HER2 receptors to fight tumor cell growth in two ways: directly by blocking HER2 signalling, which decreases the growth of the tumor cells, and indirectly by stimulating an immune response that destroy tumor cells.

THANK YOU

PATHOLOGY QUIZ LECTURE #5

External Resources

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

اللهم إن هذا العمل عن روح جدي، فاجعل أجره نورًا يؤنس وحشته، ورحمةً تبلغه في قبره،
.ومغفرةً ترفع درجته في جناتك

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			