# BREAST CANCER

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Epidemiology:

The most common and deadly malignancy of women

> 2 million women are newly diagnosed, 1/3 of whom will die of disease

The incidence is 4-7 times > in US and Europe than elsewhere

Worldwide the incidence and mortality is increasing rapidly especially in lower income countries due to social changes

# Epidemiology:

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

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

Since the mid 1980 the toll mortality rate has dropped from 30 to <20% Due to screening and more effective treatments.

Almost all breast malignancies are adenocarcinomas

**Table 17.8** Risk Factors for Developing Breast Cancer

| Risk Factors | Relative Risk[a] |
|---|---|
| Female sex<br>Increasing age<br>Germline mutations of high penetrance<br>Strong family history (>1 first-degree relative, young age, multiple cancers)<br>Personal history of breast cancer<br>High breast density | >4.0 |
| Germline mutations of moderate penetrance<br>High-dose radiation to chest at young age<br>Family history (1 first-degree relative) | 2.1–4.0 |
| Early menarche (age <12 years)<br>Late menopause (age >55 years)<br>Late first pregnancy (age >35 years)<br>Nulliparity<br>Absence of breastfeeding<br>Exogenous hormone therapy<br>Postmenopausal obesity<br>Physical inactivity<br>High alcohol consumption | 1.1–2.0 |

[a]Relative risk is the likelihood of developing invasive carcinoma compared to women without any risk factors.

# Risk factors:

## *Age:*

- Breast cancer is rare in women younger than age 25
- incidence increases rapidly after age 30
- 75% of women with breast cancer are >50
- only 5% are younger than 40

## *Gender*

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

## *Family History and genetics*

- Germline mutation of moderate to high penetrance
- family history (affected first-degree relatives, multiple cancers, young age)
- Personal hx of breast CA

# 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*

*Alcohol consumption*

*physical inactivity*

# 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 in carriers is 45-75% by the age of 70 (compared to 12/5 in general pop)
  - BRCA1 mutations are associated with triple negative tumors
  - BRCA2 mutations are associated with ER positive tumors

- ***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.

**Table 17.9** Most Common Single Gene Mutations Associated With Hereditary Susceptibility to Breast Cancer

| Gene (Syndrome) | % of Single Gene Cancers[a] | Risk of Breast Cancer to Age 70[b] | Other Cancers | Comments |
|---|---|---|---|---|
| **High Penetrance Germline Mutations** | | | | |
| *BRCA1* (familial breast and ovarian cancer) | ~55% | ~40%–90%, females; 1%, males | Ovarian (~20%–40%), fallopian tube, pancreas, prostate, others | Majority of cancers are TNBC |
| *BRCA2* (familial breast and ovarian cancer) | ~35% | ~30%–60%, females; 6%, males | Ovarian (~10%–20%), pancreas, prostate, others | Majority of cancers are ER positive. Biallelic mutations cause a form of Fanconi anemia. |
| *TP53* (Li-Fraumeni) | <1% | ~50%–60%, females; <1%, males | Sarcoma, leukemia, brain tumors, others | Majority of cancers are ER and HER2 positive |
| *PTEN* (Cowden) | <1% | ~20%–80%, females; <1%, males | Thyroid, endometrium, others | Also associated with benign tumors |
| *STK11* (Peutz-Jeghers) | <1% | ~40%–60%, females | Ovarian, colon, pancreas, others | Also associated with benign colon polyps |
| *CDH1* (hereditary diffuse gastric cancer) | <1% | ~50%, females | Gastric signet ring cell carcinoma, colon | Majority of cancers are lobular in type |
| *PALPB2* (hereditary breast cancer) | <1% | ~30%–60%, females; <1%, males | Pancreas, prostate | Biallelic mutations cause a form of Fanconi anemia |
| **Moderate Penetrance Germline Mutations** | | | | |
| *ATM* (ataxia-telangiectasia) | ~5% | ~15%–30%, females | | Biallelic mutations cause ataxia-telangiectasia |
| *CHEK2* (hereditary breast cancer) | ~5% | ~10%–30%, females | Prostate, thyroid, colon, kidney | Majority of cancers are ER positive |

High penetrance germline mutations confer a >4-fold increased risk and represent 3%–7% of all breast cancers. Moderate penetrance germline mutations have a 2- to 4-fold increased risk and represent 5%–10% of breast cancers.

*ER*, Estrogen receptor; *TNBC*, triple-negative breast cancer.

[a]The percentage of all breast cancers that are associated with a germline mutation conferring an increased risk of breast cancer.

[b]Risk for specific patients can vary with the specific mutation and the presence of other gene mutations.

# 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

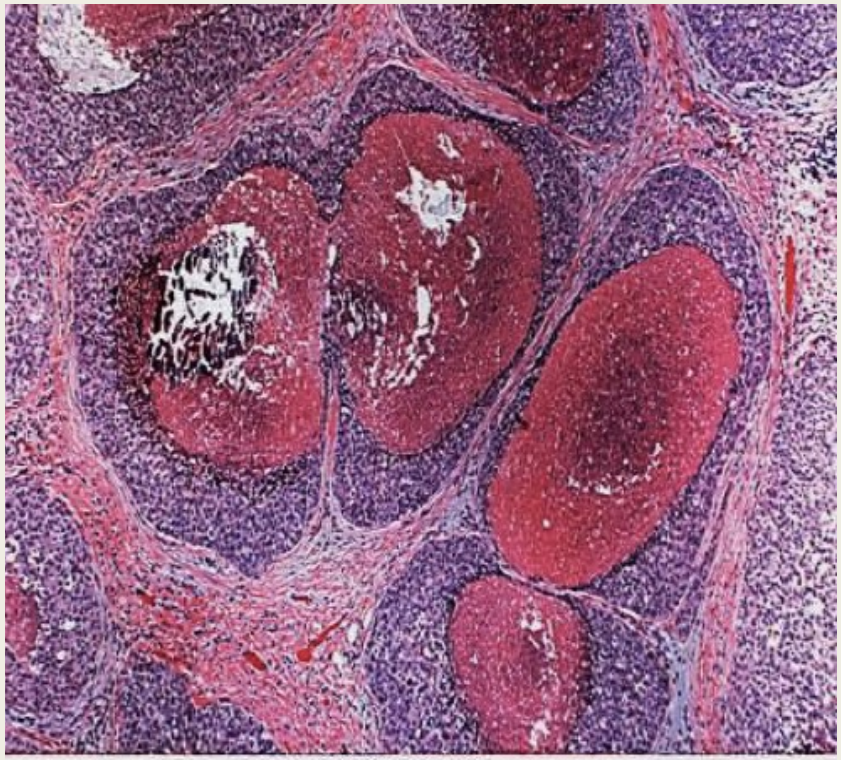
- **By definition both confined by a basement membrane and do not invade into stroma or lymphovascular channels**

# LOBULAR carcinoma in-situ (LCIS)

- Malignant clonal proliferation of cells
- Cells grow in a discohesive fashion →an **acquired loss of the tumor suppressive adhesion protein E-cadherin**.
- The term "lobular" was used to describe this lesion because the proliferation expands the involved lobules so the **appearance resembling lobules**

# Ductal carcinoma in-situ (DCIS)

- malignant clonal proliferation of epithelial cells
- DCIS **distort the lobules into duct like spaces**
- has a wide variety of histologic appearances

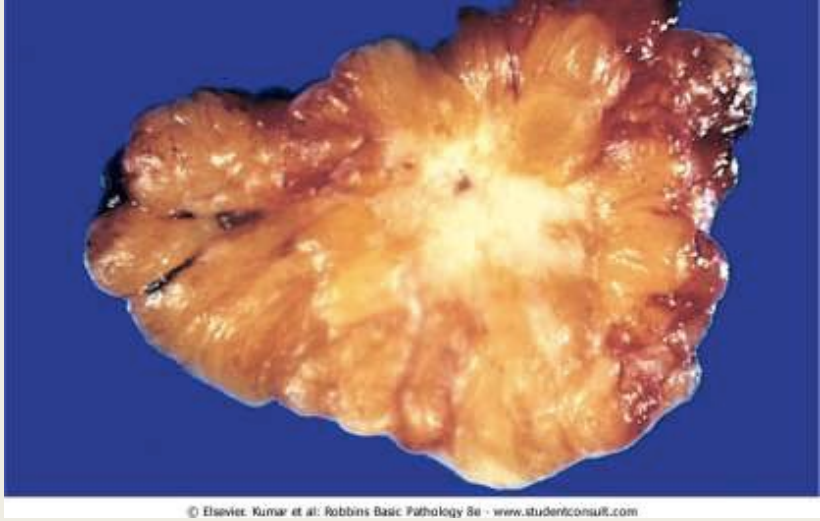


# Paget disease of the nipple

- 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:



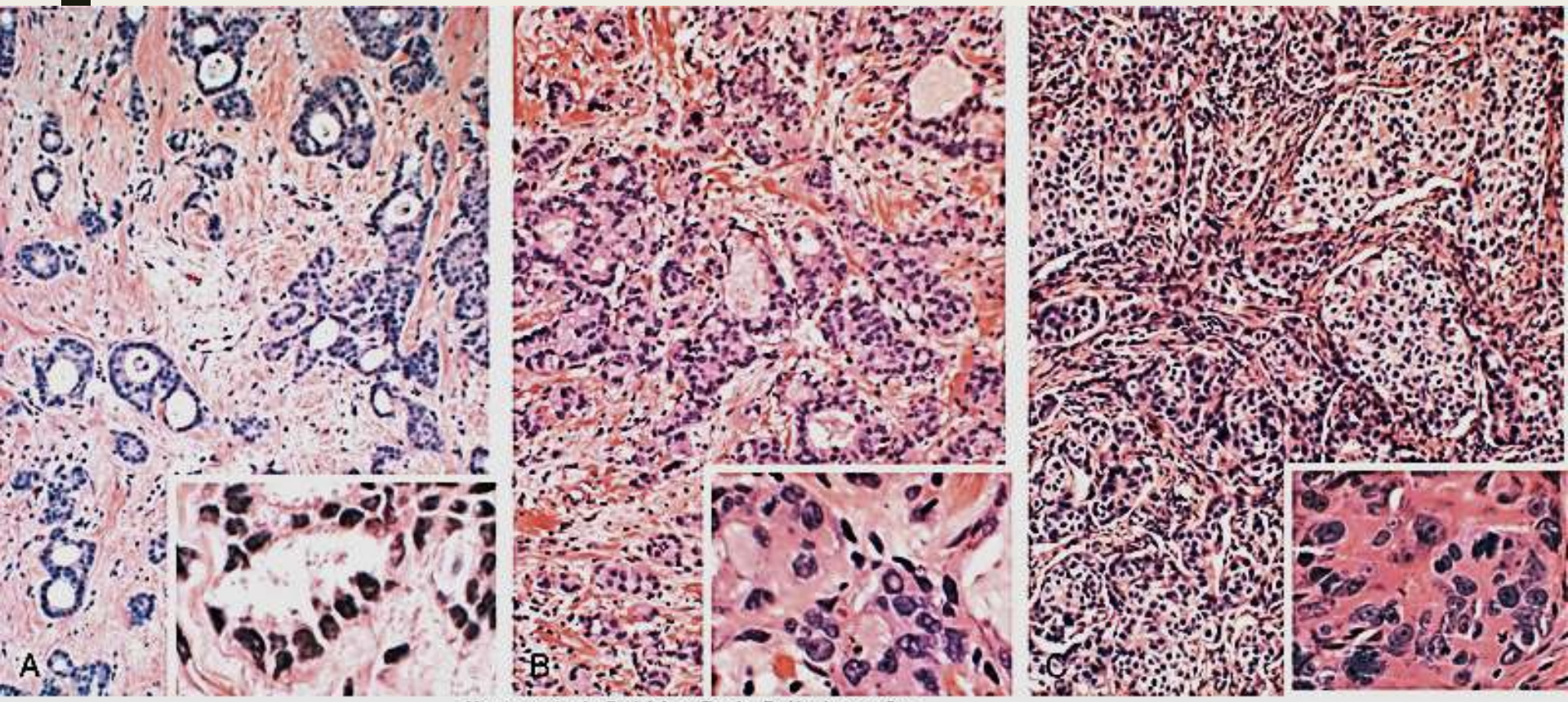

- Location:
  - *upper outer quadrant (50%)*
  - *central portion- subareolar (20%).*
  - *Lower outer quadrant 10%*
  - *Upper inner quadrant 10%*
  - *Lower inner quadrant 10%*

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

# Invasive ductal carcinoma

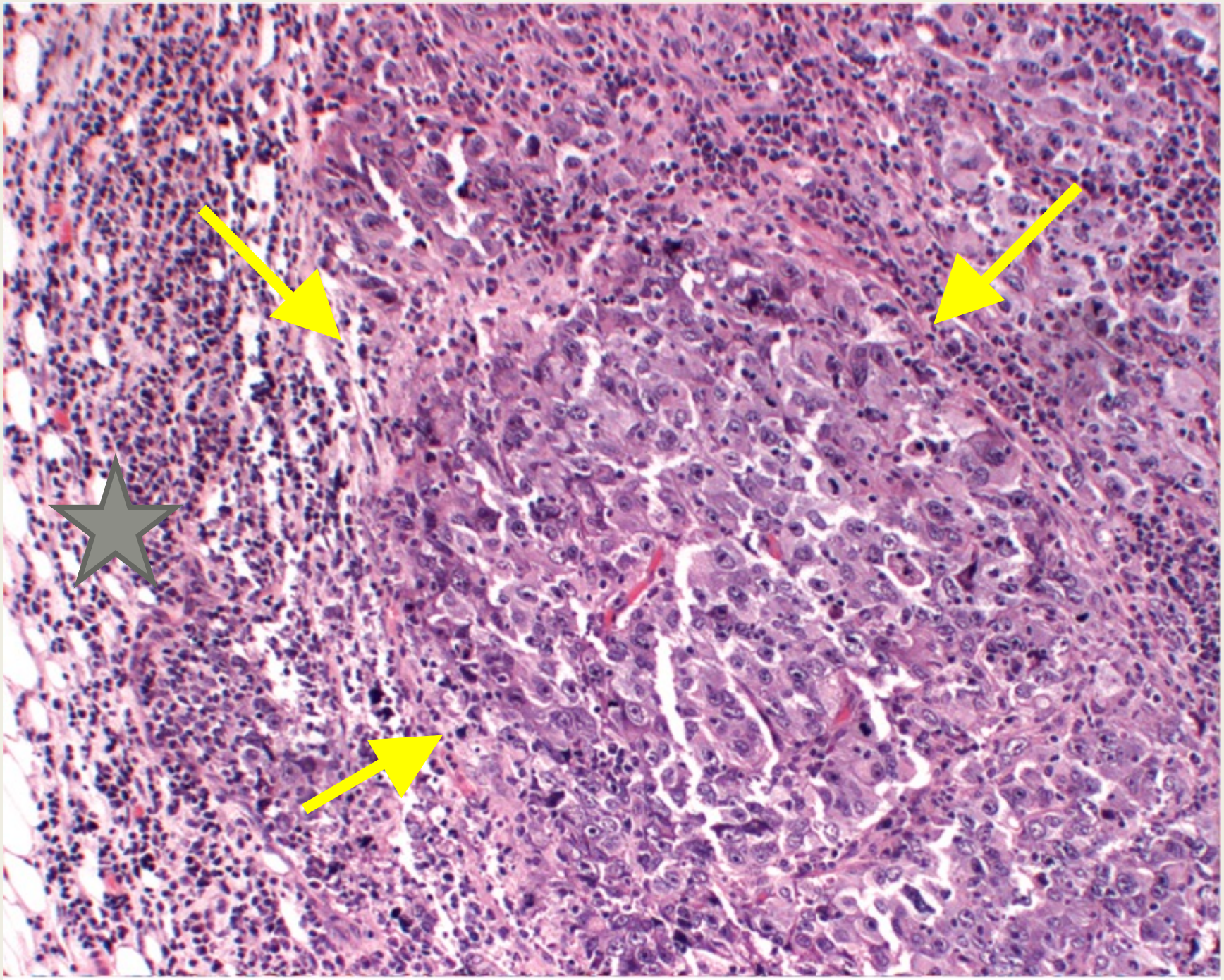
- 70% to 80%
- Also called Carcinomas "not otherwise specified”
- **Precancerous lesion**: usually DCIS
- **Clinical presentation:** mammographic density or hard, palpable irregular mass.
- Receptor profile:

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



# carcinoma with Medullary pattern:

- 5%
- **Microscopically: sheets of** large anaplastic cells with pushing, well-circumscribed borders. With a pronounced lymphocytic infiltrate composed of T lymphocytes.
- **Precancerous lesions**. usually absent
- increased frequency in women with ***BRCA1*** **mutations**.
- receptor profile: almost always Triple negative (ER, PR, and HER2 all negative).



# 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

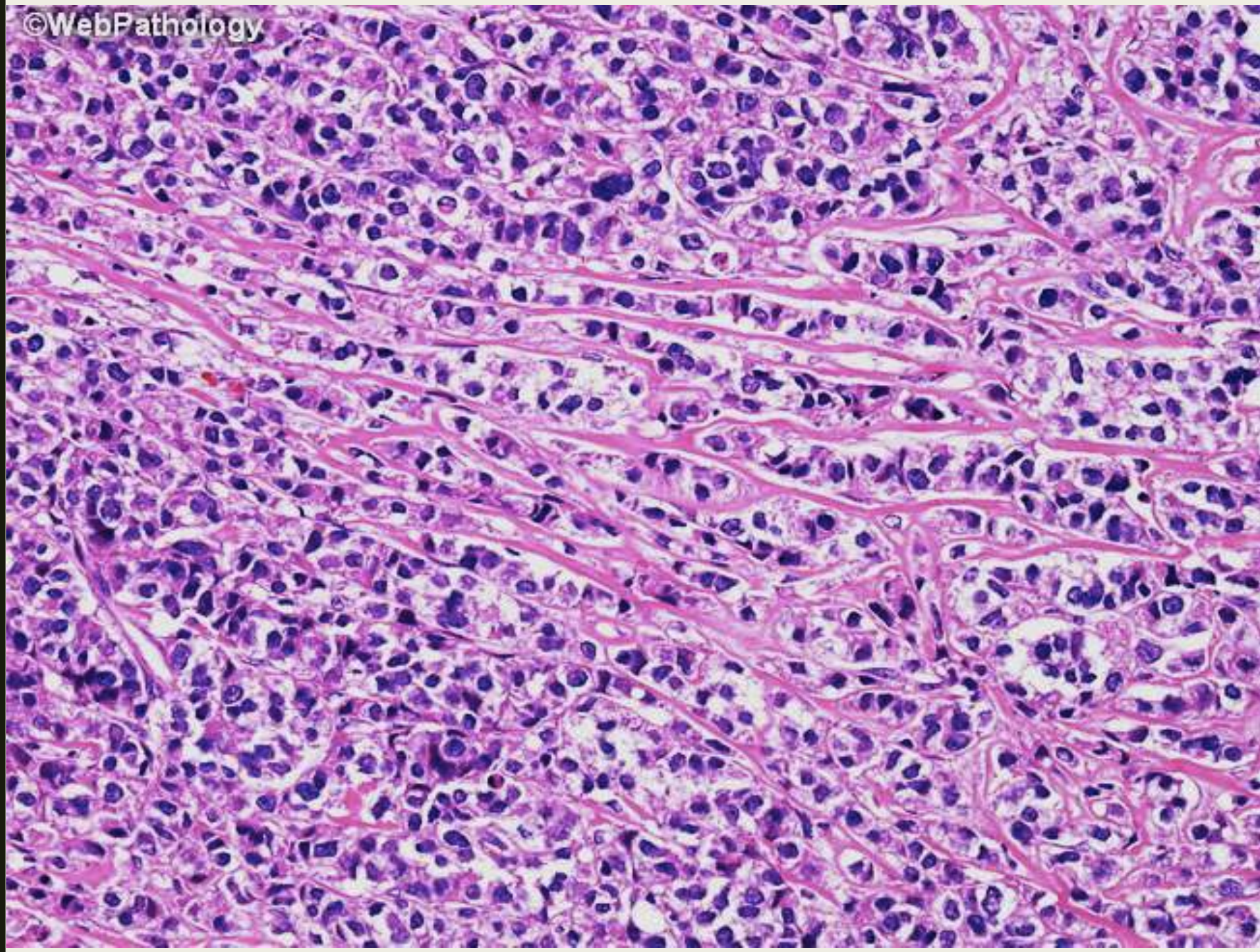
# Invasive lobular carcinoma

- 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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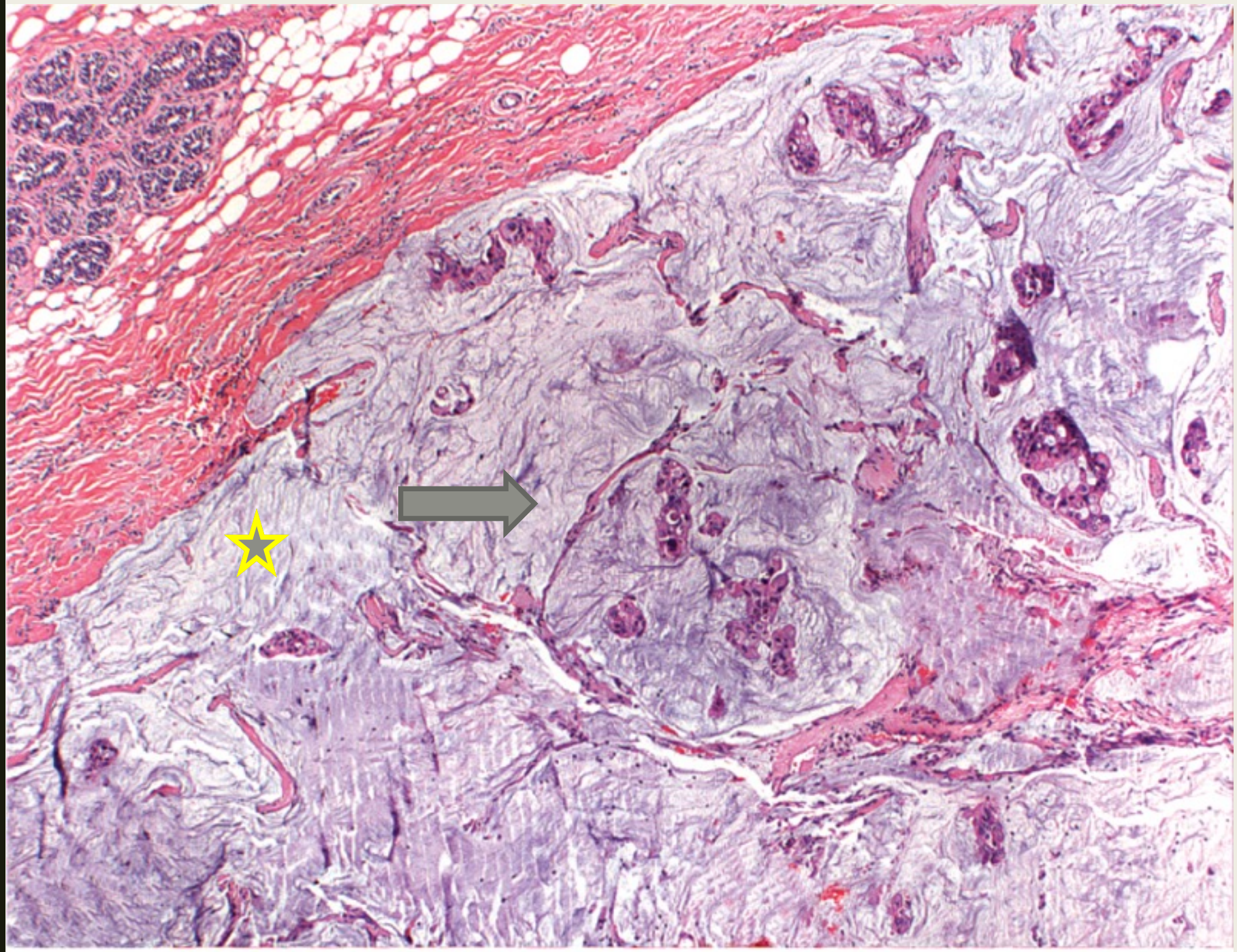
# Inflammatory carcinoma:

- Defined by it's clinical presentation
- The pt presents with swollen erythematous breast without a palpable mass (mimicing inflammatory conditions of the breast)
- Caused by poorly differentiated carcinoma that infiltrates the dermal lymphatic spaces causing obstruction → edema and skin thickening (peau d'orange)
- No true inflammation in this cancer
- Usually caused by high grade cancer

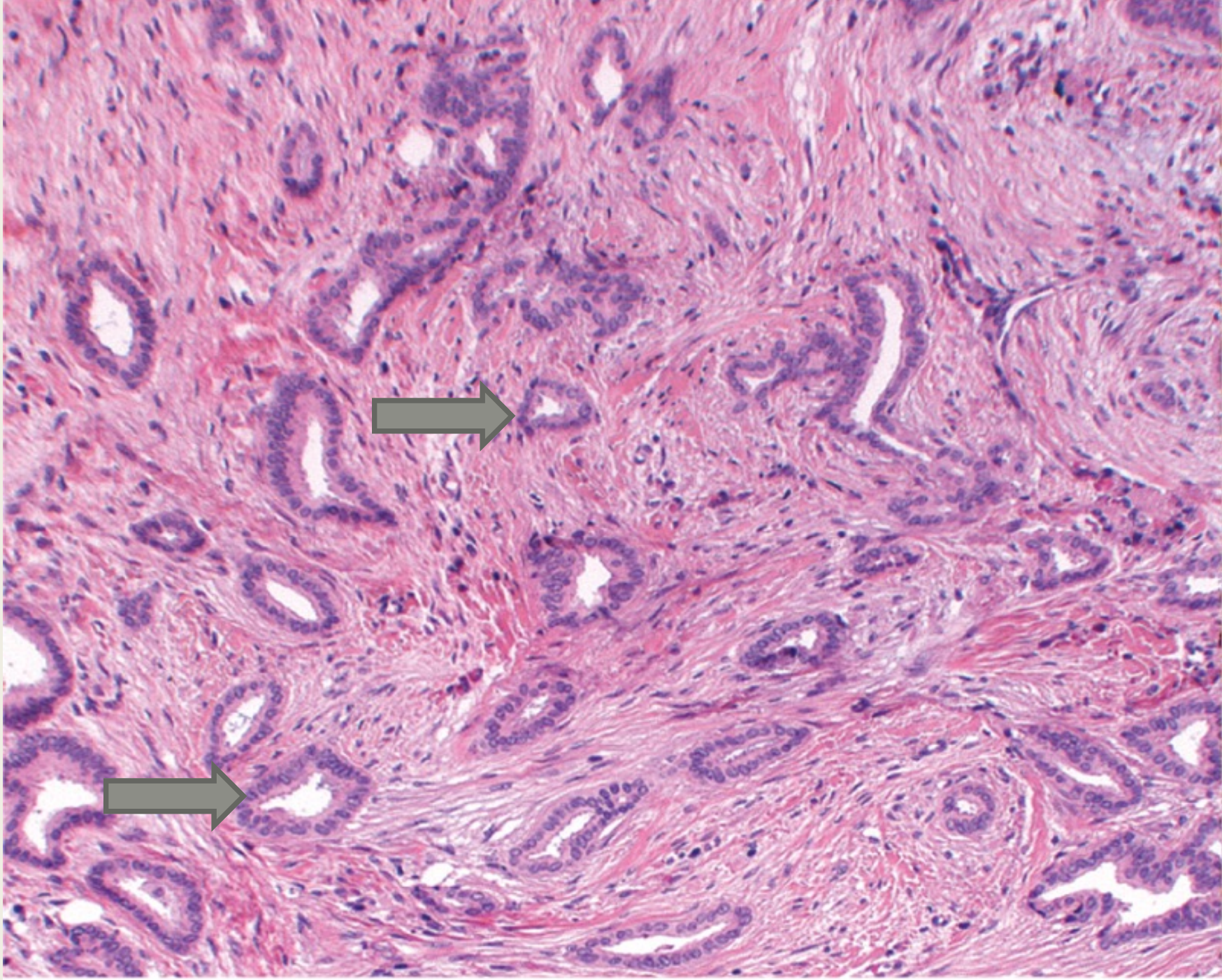
# Colloid (mucinous) carcinoma

- a rare subtype.
- **Grossly** the tumors are usually soft and gelatinous.
- **Microscopic picture**. The tumor cells produce abundant quantities of extracellular **mucin** that dissects into the surrounding stroma.
- **receptor profile:** ER-positive, HER2- negative



# Tubular carcinomas

- <5%
- **Clinical presentation**. Almost always detected as irregular mammographic densities.
- **Microscopically**, well-formed tubules with low-grade nuclei.
- **Lymph node metastases:** rare
- **Prognosis:** excellent**.**
- **Receptor profile:** luminal group --> ER-positive, HER2-negative



# 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.

# References:


- Diagnostic pathology book, normal histology, 2nd edition, LINDBERG LAMPS
- Robbins basic pathology,11th edition
- Robbins and Cortan Atlas of Pathology,3rd edition
- https://www.webpathology.com


QUESTIONS!

# THANK YOU