



# BREAST; BREAST CARCINOMA

Done by Aseel Abdeen

Maram Abdaljaleel, MD  
Dermatopathologist and Neuropathologist  
University of Jordan, School of Medicine

# EPIDEMIOLOGY:

Breast carcinoma is

- ◉ **The most common non-skin malignancy of women** Worldwide. If we exclude the non melanoma skin cancer like basal cell carcinoma and squamous cell carcinoma
- ◉ **2<sup>nd</sup> most common cause of cancer deaths in women, following carcinoma of the lung.**
- ◉ The worldwide incidence and mortality are increasing at an alarming rate. This trend is due to social changes especially in the developing countries.
- ◉ **Those** social changes **Include** delayed childbearing, fewer pregnancies, and reduced breastfeeding and with lack of access to optimal health care.





Estimated New Cases\*

The most common malignancy in woen is breast carcinoma while in men it is prostatic carcinome

	Males			Females		
Prostate	241,740	29%		Breast	226,870	29%
Lung & bronchus	116,470	14%		Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%		Colon & rectum	70,040	9%
Urinary bladder	55,600	7%		Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%		Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%		Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%		Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%		Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%		Ovary	22,280	3%
Pancreas	22,090	3%		Pancreas	21,830	3%
<b>All Sites</b>	<b>848,170</b>	<b>100%</b>	<b>All Sites</b>	<b>790,740</b>	<b>100%</b>	

Estimated Deaths

Breast carcinoma is considered the second most common cause of death in women after lung carcinome

	Males			Females		
Lung & bronchus	87,750	29%		Lung & bronchus	72,590	26%
Prostate	28,170	9%		Breast	39,510	14%
Colon & rectum	26,470	9%		Colon & rectum	25,220	9%
Pancreas	18,850	6%		Pancreas	18,540	7%
Liver & intrahepatic bile duct	13,980	5%		Ovary	15,500	6%
Leukemia	13,500	4%		Leukemia	10,040	4%
Esophagus	12,040	4%		Non-Hodgkin lymphoma	8,620	3%
Urinary bladder	10,510	3%		Uterine Corpus	8,010	3%
Non-Hodgkin lymphoma	10,320	3%		Liver & intrahepatic bile duct	6,570	2%
Kidney & renal pelvis	8,650	3%		Brain & other nervous system	5,980	2%
<b>All Sites</b>	<b>301,820</b>	<b>100%</b>	<b>All Sites</b>	<b>275,370</b>	<b>100%</b>	



- ◉ Since 1980s the mortality rate has dropped from 30% to <20% → due to improvement in detecting cancers before they metastasize through screening (mammographic screening) and more effective systemic treatment.
- ◉ Almost all breast malignancies are adenocarcinomas (>95%).



# CLASSIFICATION SYSTEMS:

The most clinically used classification system for breast cancer depends on the expression of hormone receptors

- hormone receptors are:
  - Estrogen receptor (ER), progesterone receptor (PR)  
& human epidermal growth factor receptor 2 (HER2, or ERBB2)
- Can be classified according to expression of hormone receptors into three major groups:
  - ER positive (HER2 negative; 50%–65% of cancers)
  - HER2 positive (ER positive or negative; 10%–20% of cancers)
  - Triple negative (ER, PR, and HER2 negative; 10%–20% of cancers)



- The three groups show striking differences in patient characteristics, pathologic features, treatment response, metastatic patterns, time to relapse, and outcome
- Within each group are additional histologic subtypes, some of which also have clinical importance.



- An alternative classification system relies on gene expression profiling.
  - used mainly in clinical research
  - divides breast cancers into four major types:
    - **Luminal A.** majority of cases are lower grade, ER-positive & HER2 negative cancers
    - **Luminal B.** majority of cases are higher grade ER-positive +/- HER2 positive cancers
    - **HER2-enriched.** overexpress HER2 and ER-negative.
    - **Basal-like.** gene expression profiling resemble basally located myoepithelial cells and are ER-negative, HER2-negative

# RISK FACTORS:

## ◉ Age:

It is considered rare in women younger than 25 and incidence increase after the age of 30. more than two thirds of women with breast cancer are older than the age of 50 and only 5% are younger than the age of 40

## ◉ Gender:

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

## ◉ Family History of Breast Cancer:

- The greatest risk is for individuals with multiple affected first-degree relatives with early onset breast cancer mostly related to various combinations of low penetrance or weak cancer genes. However, in about 5 to 10% of cases a highly penetrance germline mutations in the tumor suppressor genes is associated with lifetime risk greater than 90%



## ◎ ***Geographic Factors:***

- higher in the Americas and Europe than in Asia and Africa

The mortality rates of breast cancer in America is 5 times greater than Japan .

Immigration studies showed that migration from low incidence to high incidence areas tends to acquire the rates of their new home countries.

In this context, diet, reproductive patterns, and breast feeding practices are thought to be involved .

Breast cancer rates appear to be rising in parts of the world that are adopting the western habits.



## ○ ***Race/Ethnicity:***

- highest rate in women of European descent because of higher incidence of ER-positive cancers.
- Hispanic and African American → develop cancer at a younger age and develop aggressive tumors.

This is thought to result from combination of differences in genetic social factors and access to health care.



## ○ ***Reproductive History.***

- **Includng** Early age of menarche, nulliparity, absence of breastfeeding, **with** older age at first pregnancy are all associated with increased risk → due to increased the exposure **of the epithelial cells of the breast** to estrogenic stimulation.

## ○ ***Ionizing Radiation.***

- Chest Radiation **especially if the breast is developing**

## ○ ***Other Risk Factors.***

- Postmenopausal obesity
- postmenopausal hormone replacement **therapy**
- mammographic density
- alcohol consumption



# PATHOGENESIS:

- Factors that contribute directly to the development of breast cancer can be grouped into:
  - Genetic
  - Hormonal
  - Environmental



# GENETIC FACTORS:

- *BRCA1* and *BRCA2*: Are classic tumor suppressor genes and the cancer only occur if both alleles are defected
  - encode proteins that are required for repair of DNA damage.
  - most carriers develop breast cancer by the age of 70 years
  - For unclear reasons, *BRCA2* mutations are primarily associated with ER-positive tumors, whereas *BRCA1* mutations are associated with triple-negative cancers
- Other mutated genes: *TP53* and *PTEN* TP53 AKA guardian of the genom
- The pathways in which familial breast cancer genes function also are often disturbed in sporadic cancers



- **HER2 gene amplification :** It is a receptor tyrosine kinase that promotes the cell proliferation and suppress apoptosis
  - Cancers that overexpress HER2 are highly proliferative.
  - In the past they had a poor prognosis; **Nowadays** , the availability of therapeutic agents targeting HER2 has improved the prognosis.



# *HORMONAL FACTORS:*

- ⦿ **Estrogens** are considered an important hormonal factors since they stimulate the production of growth factors promoting the tumor development.
- ⦿ Estrogen receptors regulate other genes in an estrogen dependent fashion. Some of those genes are important for the tumor development or growth.
- ⦿ Estrogens also drives the proliferation from precursor regions to a fully malignant and metastatic carcinoma.
- ⦿ **Estrogen antagonists:** reduce the development of ER-positive cancers in women at high risk and are mainstays in the treatment of established ER-positive tumors.



# MORPHOLOGY:

- Location:
  - upper outer quadrant (50%)
  - central portion(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.



# BREAST CARCINOMA:

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

1. Ductal carcinoma in situ **Discussed in previous lectures**
2. Lobular carcinoma in situ **Discussed in previous lectures**

**B. Invasive (infiltrating):**

1. Invasive ductal carcinoma (includes all carcinomas that are not of a special type) → 70% to 80%
2. Invasive lobular carcinoma → 10% to 15%
3. Carcinoma with medullary features → 5%
4. Mucinous carcinoma (colloid carcinoma) → 5%
5. Tubular carcinoma → 5%
6. Other types



the cut surface felt gritty. irregular mass very firm center (scirrhous) and white because of the desmoplasia. tumor is infiltrating into the surrounding breast and adipose tissue.

Breast carcinoma, not well circumscribed



# INVASIVE DUCTAL CARCINOMA

usually associated with DCIS

- 70-80%
- Also called **Carcinomas "not otherwise specified"**
- **Precancerous lesion:** usually DCIS
- **Clinical presentation:**
  - a mammographic density; a hard, palpable irregular mass.
  - Nipple retraction, or fixation to the chest wall can be seen in advanced cancers
- **Receptor profile:**
  - ER (+ve in 50-60%)
  - HER2 (+ve in 20%)
  - 15% are negative for both

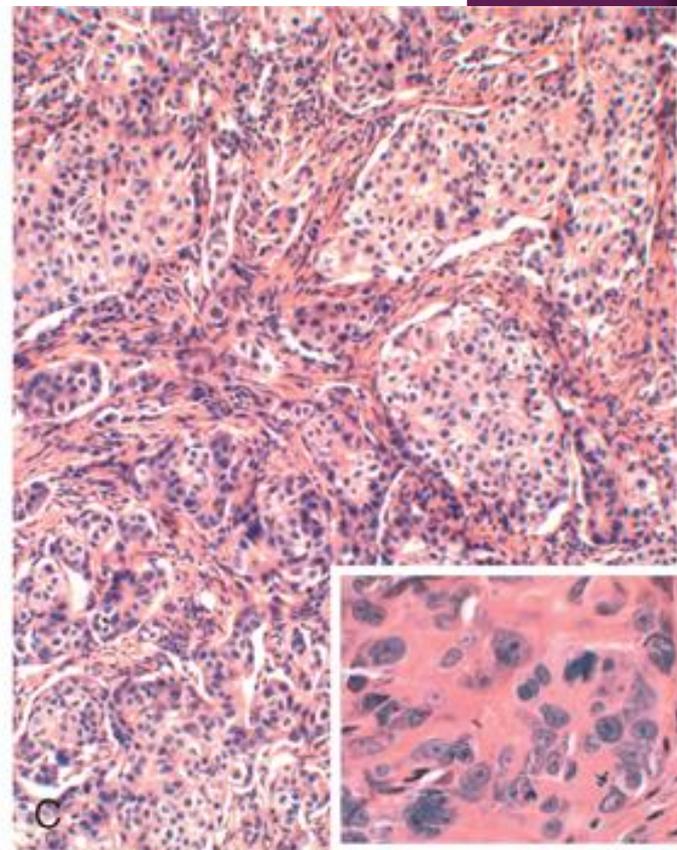
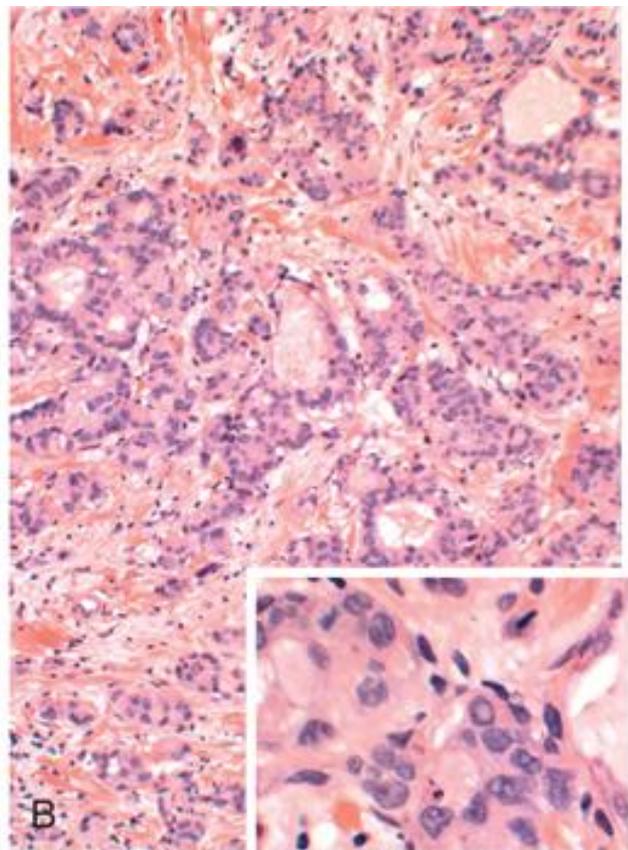
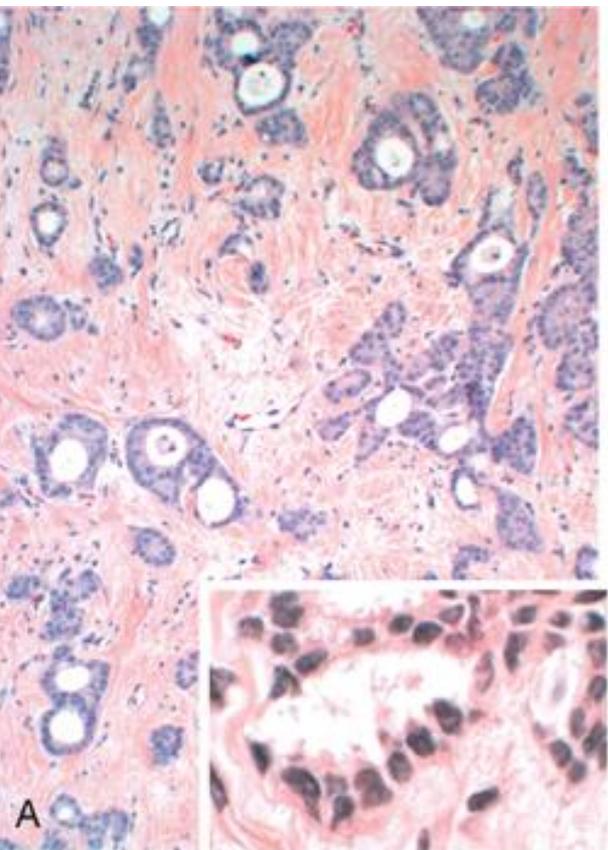
Cases with invasive ductal carcinoma produces desmoplastic response which replaces the normal fat and result in mammographic densities





This shows different grades of DC  
Grading of IDC depends on 3 criteria: 1- tubular formation 2- atypia 3- mitotic activity

# INVASIVE DUCTAL CARCINOMA



Well differentiated carcinoma consisting of tubules with small monomorphic nuclei

Kumar et al: Robbins Basic Pathology, 9e.  
Copyright © 2013 by Saunders, an imprint of Elsevier Inc

Moderate differentiation carcinoma with less tubular formation more solidness of cells and monomorphic nuclei

Poorly differentiated carcinoma with sheets of pleomorphic cells containing numerous mitotic figures and central areas of tumor necrosis



# INVASIVE LOBULAR CARCINOMA

- 10-15%
- **Precancerous lesion.** associated with LCIS.
- 10% to 20% are multicentric and bilateral
- **Clinical presentation.** Most present as palpable masses or mammographic densities
- cells invade stroma **individually** and often are aligned in “**single-file**”
- Almost all of these carcinomas express hormone receptors, but HER2 overexpression is very rare or absent.

Lobular carcinoma in situ

Metastasis of lobular carcinoma is unique since it frequently reaches the CSF, serosal surfaces, bone marrow, ovary, and uterus

# CARCINOMA WITH MEDULLARY FEATURES:

- 5%
- Triple negative
- **Microscopically:** large anaplastic cells with pushing, well-circumscribed borders with a pronounced lymphocytic infiltrate.
- **Precancerous lesions.** usually absent
- increased frequency in women with **BRCA1** mutations,.
- **Receptor profile.** lack hormone receptors and do not overexpress HER2/NEU.

Those carcinoma typically grow as rounded masses that can be difficult to distinguish from benign tumors on imaging

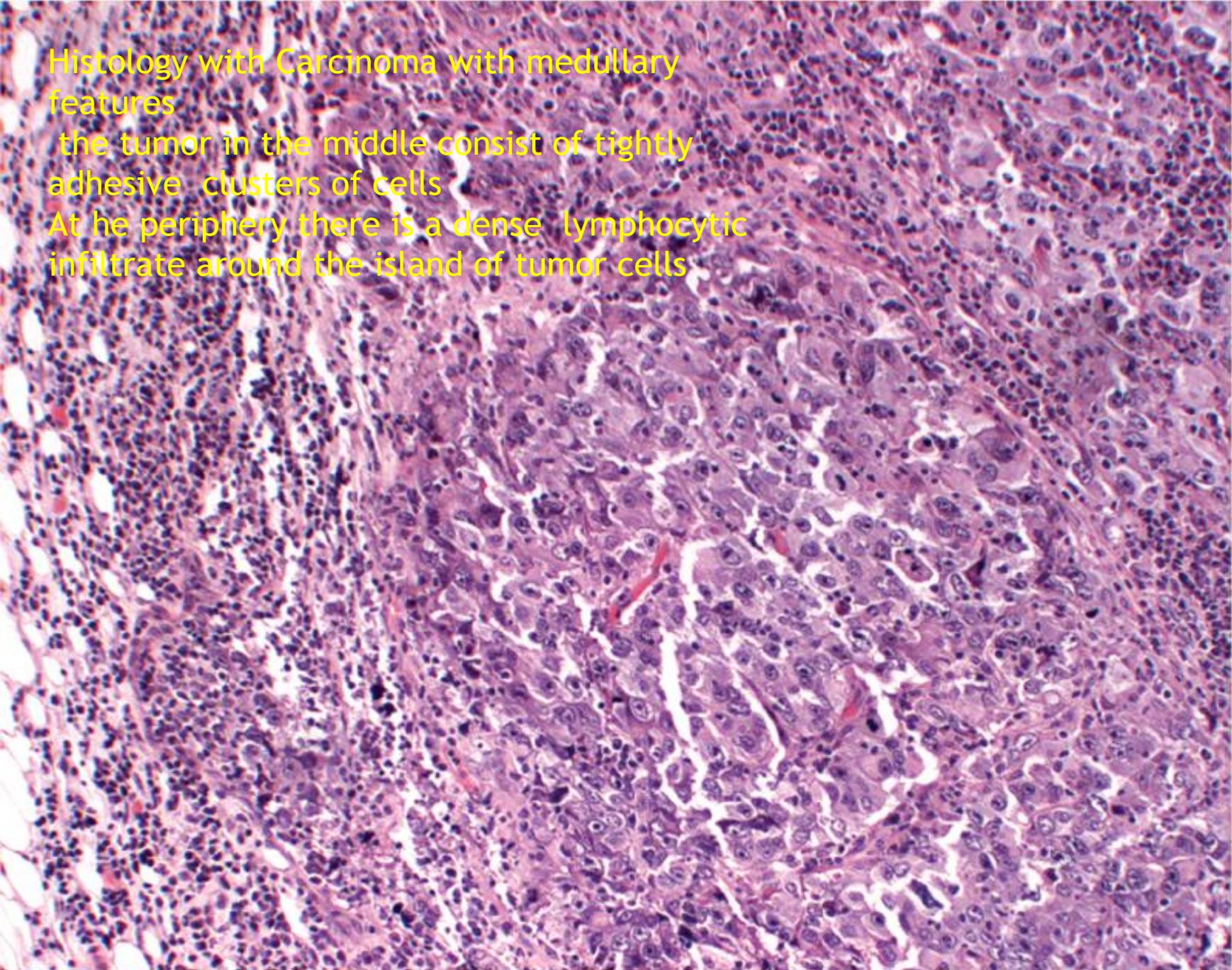




Histology with Carcinoma with medullary features

the tumor in the middle consist of tightly adhesive clusters of cells

At he periphery there is a dense lymphocytic infiltrate around the island of tumor cells



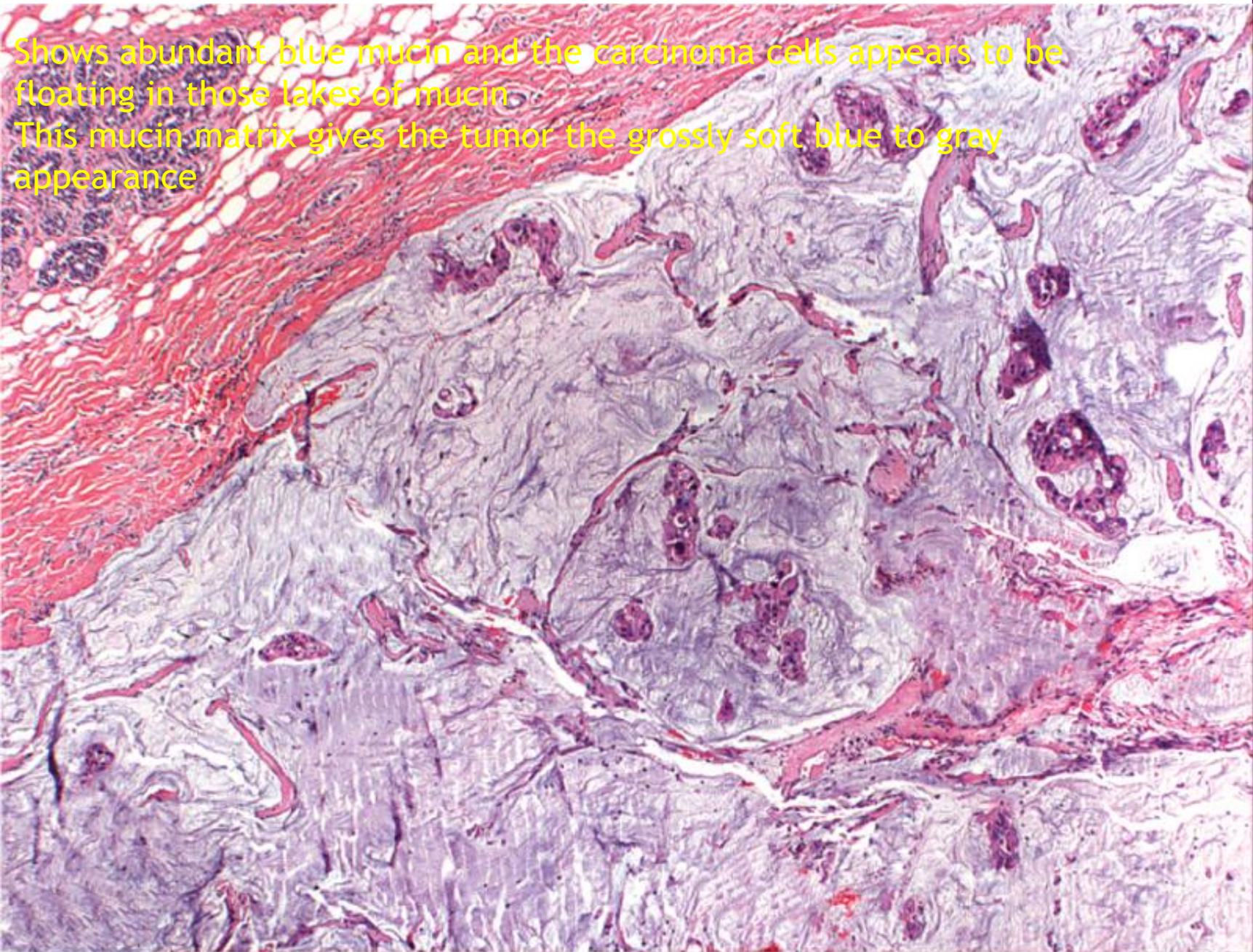


# COLLOID (MUCINOUS) CARCINOMA

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



Shows abundant blue mucin and the carcinoma cells appears to be floating in those lakes of mucin  
This mucin matrix gives the tumor the grossly soft blue to gray appearance

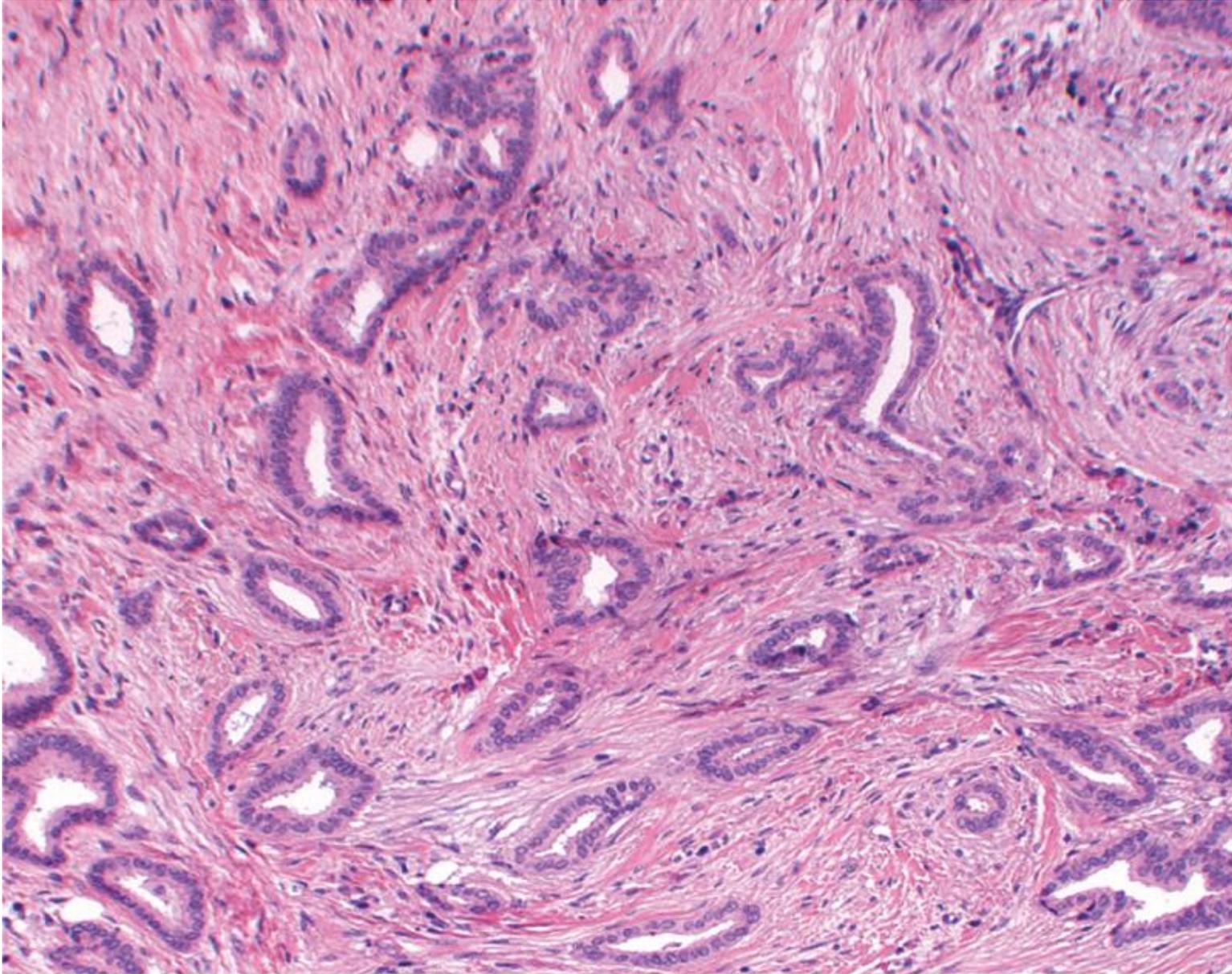




# TUBULAR CARCINOMAS

- ◉ **10%** of invasive carcinomas
- ◉ **Clinical presentation.** irregular mammographic densities.
- ◉ **Microscopically**, well-formed tubules with low-grade nuclei. **Sometimes mistaken for benign sclerosing lesions. Calcification may present in the tumor lumen**
- ◉ **Lymph node metastases are rare, and prognosis is excellent.**
- ◉ ER-positive/HER2- negative cancer

well-differentiated neoplastic cells form a single cuboidal layer in small, round to tear drop shaped ductules widely spaced in a fibrous stroma.





# SPREAD OF BREAST CANCER

- ⊙ through **lymphatic** and **hematogenous** channels.
- ⊙ Favored metastasis are the **bone, lungs, skeleton, liver, and adrenals** and (less commonly) the brain, spleen, and pituitary.
- ⊙ ***Metastases may appear many years after apparent therapeutic control of the primary lesion*** ***that's why we use screening program***
- ⊙ **SCREENING :**
  - mammographic screening
  - Magnetic resonance imaging, MRI



# BREAST CANCER PROGNOSIS:

- The outcome for women with breast cancer depends on the **biologic features of the carcinoma (molecular or histologic type)** and the extent to which the cancer has spread (**stage**) at the time of diagnosis.



# PROGNOSTIC FACTORS:

- ◉ **Tumor stage:**
  - *Invasive carcinoma versus carcinoma in situ*
  - *Distant metastases.*
  - *Lymph node metastases.*
  - *Tumor size. In cm*
  - *Locally advanced disease*
- ◉ ***Inflammatory carcinoma***
- ◉ ***Lymphovascular invasion***
- ◉ ***Molecular subtype.***
- ◉ ***Special histologic types.***
- ◉ ***Histologic grade***
- ◉ ***Estrogen and progesterone receptors and HER2 expression***



## TUMOR STAGE:

- ⦿ ***Invasive carcinoma versus carcinoma in situ.***
- ⦿ ***Distant metastases.*** Once distant metastases are present, cure is unlikely,
- ⦿ ***Lymph node metastases.***
  - Axillary lymph node status is the most important prognostic factor for invasive carcinoma in the absence of distant metastases.
  - biopsy is necessary for accurate assessment.

With no lymph involvement the ten years survival is 70-80%

1 -3 lymph involvement → 35-40%

If mor than 10 lymph nodes → 10-15%



# TUMOR STAGE:

- ⦿ ***Tumor size.*** The risk of axillary lymph node metastases increases with the size of the primary tumor, but both are independent prognostic factors.
- ⦿ ***Locally advanced disease.*** Carcinomas invading into skin or skeletal muscle are usually large and may be difficult to treat surgically.



# INFLAMMATORY CARCINOMA:

- Presents with breast erythema and skin thickening
- very poor prognosis
- mimics the surface of an orange peel, an appearance referred to as *peau d'orange*.
- caused by blockage of dermal lymphatics by metastatic carcinoma.
- The underlying carcinoma is usually diffusely infiltrative and does not form a discrete palpable mass.



## *LYMPHOVASCULAR INVASION:*

- ◉ strongly associated with the presence of lymph node metastases.
- ◉ poor prognostic factor



## *SPECIAL HISTOLOGIC TYPES:*

- The survival rate of women with **tubular, mucinous, lobular, papillary, and adenoid cystic** is greater than that of women with cancers of no special type.
- women with **metaplastic carcinoma or micropapillary carcinoma** have a poorer prognosis.



# HISTOLOGIC GRADE:

- **All invasive carcinomas are** graded using Histologic Score composed of Nuclear grade, tubule formation, and mitotic rate
  - *Proliferative rate:*
    - measured by mitotic counts.
    - **Highly proliferative tumors have** poorer prognosis but may respond better to chemotherapy



# ER, PR, HER2:

## ◎ **ER & PR:**

- Eighty percent of carcinomas that are both ER- and PR-positive respond to hormonal manipulation
- 40% of CA positive for only ER or PR respond.
- Strongly ER-positive cancers are less likely to respond to chemotherapy.
- cancers that fail to express either ER or PR have a less than 10% likelihood of responding to hormonal therapy but are more likely to respond to chemotherapy.

## ◎ **HER2:**

- HER2 overexpression is associated with poorer survival
- predictor of response to agents that target this receptor.



# QUESTIONS!

I am happy to answer your questions, Please use the following email:

[M.Abdaljaleel@ju.edu.jo](mailto:M.Abdaljaleel@ju.edu.jo)



THANK YOU