



# Lecture:breast cancer

## Objectives:

- Know the risk factors for the development of breast cancer
- Know the classification of breast cancer
- Understand the behavior and spread of breast cancer
- Know the prognostic indicators of breast carcinoma

Notes of this lecture are very important



MED437  
KING SAUD UNIVERSITY



Important  
Terminology  
Doctor's Notes  
Extra Information

# Introduction

- Carcinoma of the breast is one of the **most common** cancer in women.
- Women who live to age 90 years, have a one in eight chance of developing breast cancer
- **Mammographic** screening has dramatically **increased the detection** of small invasive cancers.
- DCIS by itself is almost exclusively detected by mammography, so the incidence of DCIS is increased with the use of mammography. Therefore number of women with invasive/advanced cancer is markedly decreased.
- The **mortality rate** have started to **decline**. Currently only 20% of women with breast cancer are expected to die of the disease.

## Classification “depending on the etiology”

Breast carcinomas can, therefore, be divided into **sporadic cases**, possibly related to hormonal exposure, and **hereditary cases**, associated with a family history or germ-line mutations.

- Hereditary Breast Cancer (family history or germ line mutation):
  - A family history of breast cancer in a first-degree relative.
  - About 25% of familial cancers (or around **3% of all breast cancers**) can be attributed to two autosomal-dominant genes: **BRCA1 and BRCA2**.
- Sporadic Breast Cancer:
  - The major risk factors for sporadic breast cancer are related to **hormone exposure**, gender, age at menarche and menopause, reproductive history, breast-feeding, and exogenous estrogens.
  - The majority of these cancers occur in postmenopausal women and in case of **overexpression of estrogen**.
- ❖ Etiology in most women is **unknown** but most likely is due to a combination of genetic, hormonal and environmental risk factors.
- ❖ The major risk factors being **hormonal and genetic** (family history).

# Risk factors

## Age

Increased incidence in older women Majority >50 years of age. Rare before 25 years except in familial forms.

## Estrogen Exposure

Factors associated with exposure to increased levels of estrogen have been shown to increase a woman's risk for breast cancer.

These factors include:

- Early age at menarche: the younger the age at menarche, the higher her risk of breast cancer..
- Late age at menopause
- Nulliparity (no break 9 months from estrogen)
- Late age at first child-birth: e.g. A woman who has her first birth after 30 years has an increased risk. The earlier a woman has her first birth, the lower her lifetime risk for breast cancer.
- Also postmenopausal hormone replacement slightly increases the risk.

## First Degree relative with Breast Cancer

Women with history of cancer in a first degree relative ,Example: Mother, sister, aunt or daughter.

- The risk increases with the number of affected first degree relatives as well.
- At least two genes that predispose to breast cancer → BRCA 1 & 2
- Majority of cancers occur in women without such history.

## Race & Geographic influence

- Low Incidence in African American women.
- Generally Caucasians have the highest rate of breast cancers
- Breast cancer is more common in Western industrialized countries than in developing countries.

# Risk factors

## Exercise

- some studies showed decreased risk with exercise.

## Breast feeding

- The longer the women breastfeed, the lower the risk.

## Radiation exposure:

- Higher rate of breast cancer.

## History of breast cancer:

- Women who have had a breast cancer or have cancer in one breast are at increased risk of developing a second primary breast cancer.

## History of other cancers:

- women who have a history of ovarian or endometrial cancer are at high risk.

## Certain breast diseases:

- As noted previously women with certain types of benign breast diseases are at risk.'

## Dietary factors and Obesity

- e.g. high fat intake and excessive alcohol consumption.

## Environmental toxins:

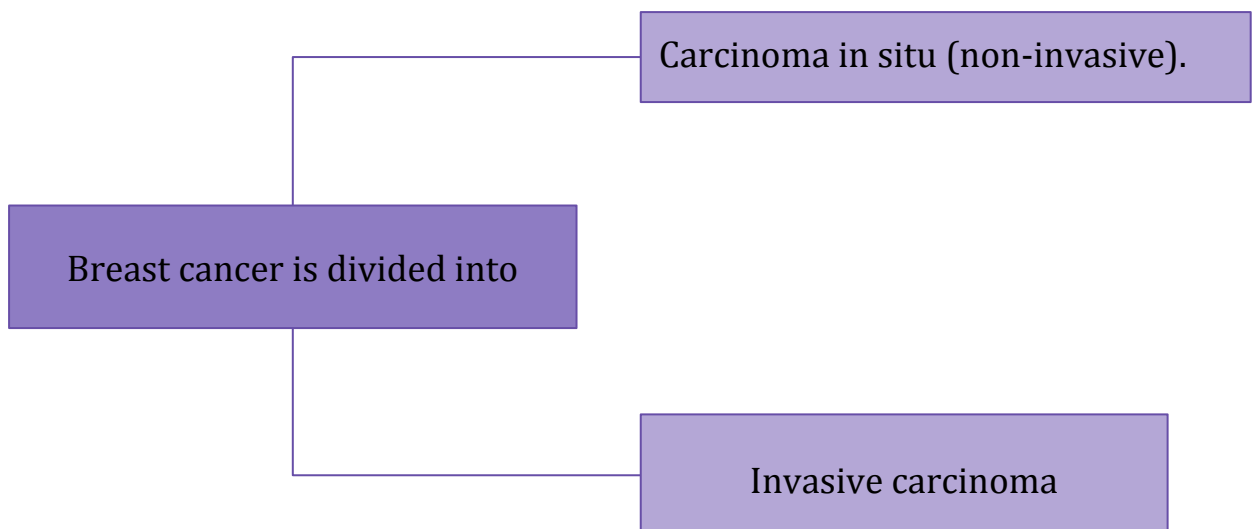
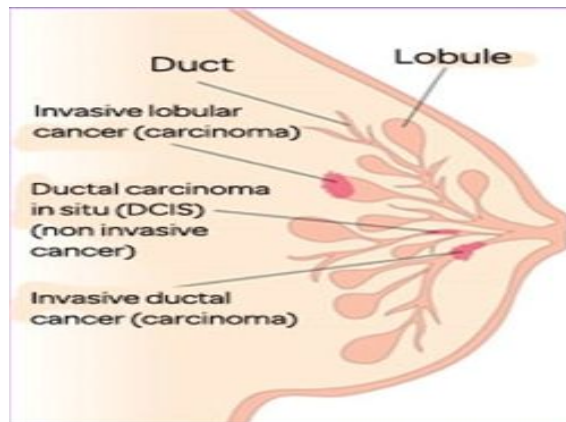
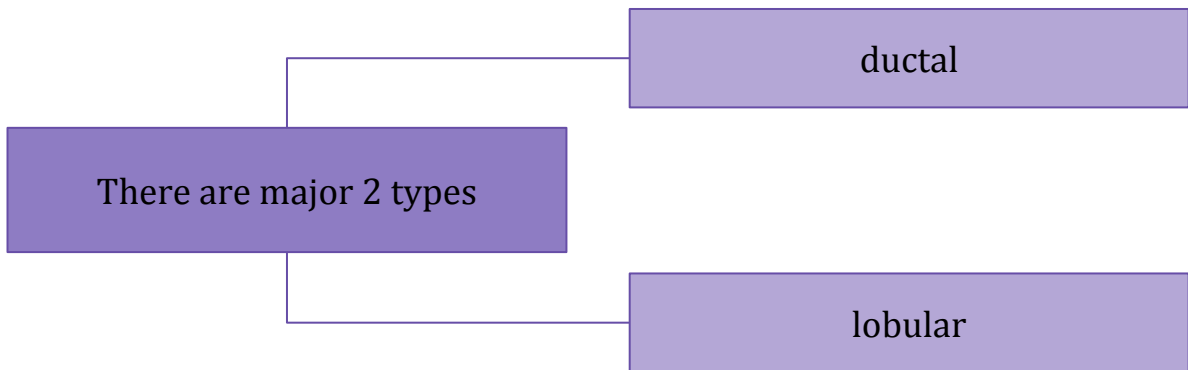
- pesticides.'

## Tobacco:

- Not associated with breast cancer, but associated with the development of periductal mastitis or sub-areolar abscesses.

# Classification of Breast Cancer

- Almost all (majority) are adenocarcinoma



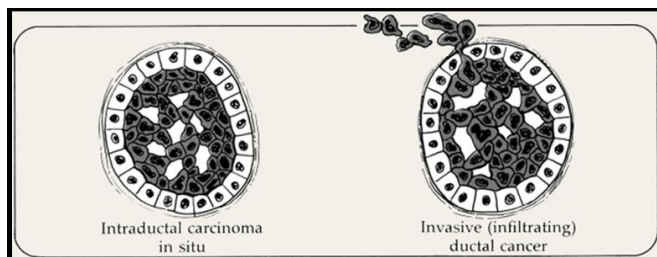
# Carcinoma In Situ

This is an epithelial proliferation that is still confined to the TDLU and **has not invaded beyond the basement membrane** and is therefore incapable of metastasis.

**There are two subtypes:**

Ductal carcinoma in situ (DCIS)  
or intraductal carcinoma (80%)

Lobular carcinoma in situ  
(20%)



## Ductal Carcinoma In Situ

Normally there are 2 cell types: epithelial and myoepithelial.

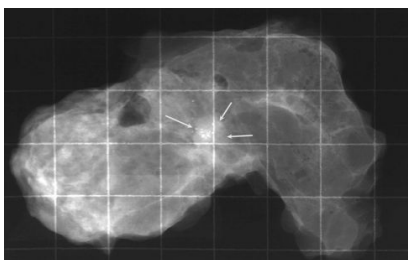
**DCIS** → monoclonal proliferation “one cell type” → malignant

Usual duct **hyperplasia** → 2 cell types → benign

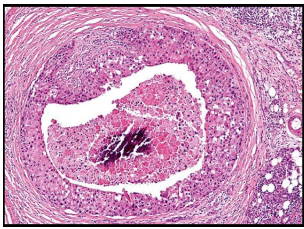
- DCIS is the **non-invasive** proliferation of malignant cells within the duct system without breaching the underlying basement membrane.
- They have a **very high risk** of developing a subsequent invasive carcinoma.
- The tumor distends and distorts the ducts.
- Age range: same age range of invasive breast carcinoma.
- Often **multifocal**: malignant cells can spread widely through the ductal system without breaching the basement membrane.
- Women with DCIS are at **risk of recurrent** DCIS following treatment.

## Mammography:

- DCIS frequently shows **micro-calcifications on mammography**. Mammography is a very sensitive diagnostic procedure for detecting DCIS since majority of DCIS are **not palpable**. Less frequently they can present as a mammographic density or a vaguely palpable mass or nipple discharge.
- Because of mammography there has been a marked increase in the detection and diagnosis of DCIS in the last two decades.



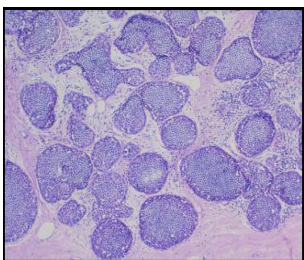
## Ductal Carcinoma In Situ



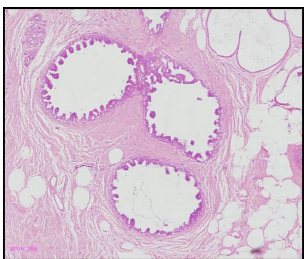
Comedo DCIS



Cribriform DCIS



Solid Pattern



Micropapillary Pattern

**Patterns/Subtypes:** Different patterns/subtypes of DCIS can be seen e.g.

- **Comedo (central necrosis)**
- Cribriform (cells arranged around “punched-out” spaces); papillary
- Micropapillary
- Solid (cells fill spaces)
- DCIS can be of different grades i.e. low, intermediate and high grade.
- **Comedo DCIS:** is characterized by large **central zones of necrosis with calcified debris**. This type of DCIS is most frequently detected as radiologic calcifications. Less commonly, the surrounding desmoplastic response results in an ill-defined palpable mass or a mammographic density.
- **Cribriform DCIS** comprises cells forming round, regular (**cookie cutter**) spaces. The lumens are often filled with calcifying secretory material.

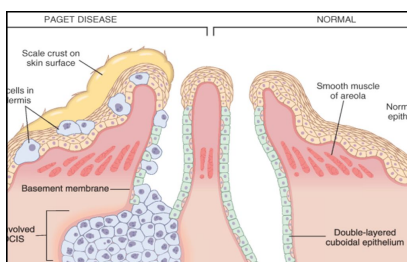
**Clinical Behavior:** may vary depending on the subtype and the grade

- **Comedocarcinoma** has essentially a **100%** chance of **becoming invasive if left untreated**.
- Pure cribriform/micropapillary carries only a 30% chance of becoming invasive carcinoma.

**Treatment:**

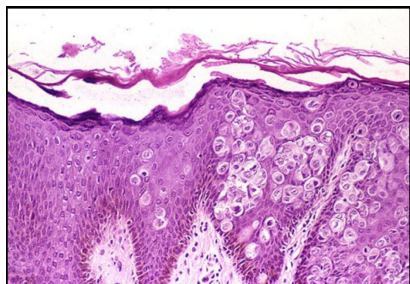
- Wide local excision
- Mastectomy

## Paget's Disease



- Paget's disease of the breast is a rare type of breast cancer that is characterized by a **red, scaly eczematous** lesion on the nipple and surrounding areola.
- Paget's disease may be subtle or appear as an eroded and weeping erythematous eruption. **Pruritus “itching”** is common and it might be mistaken for eczema.
- Malignant cells are called Paget cells and are **found scattered in the epidermis**.

## Paget's Disease



### Histology:

- The histologic hallmark of Paget's disease of the nipple is the **infiltration of the epidermis** by large neoplastic ductal cells with abundant cytoplasm, pleomorphic nuclei and prominent nucleoli. The cells usually stain positively for mucin.
- Paget cells extend from DCIS within the ductal system into nipple skin **without crossing** the basement membrane.
- Palpable mass can be seen in 50% of women with Paget disease indicating an underlying invasive carcinoma nearby.

How does it occur?

DCIS expand and extend into the large lactiferous duct and reach the opening & epidermis. It's **in situ** because the cells traveling along the basement membrane without invasion.

## Lobular Carcinoma In Situ

### LCIS:

No calcification → **can't** be detected on mammogram

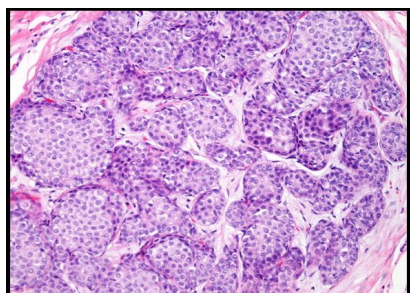
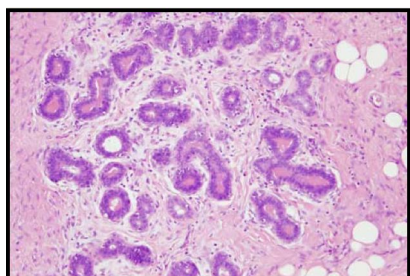
No masses

Bilateral

Multifocal: involve the same quadrant

Multicentric: involve more than quadrant

**Check the notes page**



- LCIS alone is always an incidental finding in breast biopsies performed for another reason. LCIS **does not form a palpable mass** and cannot be detected clinically on palpation or on gross pathological examination. "Remember that DCIS also not palpable"
- Microcalcifications in LCIS are infrequent and so mammography is not useful for detection. "DCIS shows microcalcification"
- LCIS is uncommon.
- LCIS tends to be **multicentric and bilateral** and therefore subsequent carcinomas can occur **both breasts**. "DCIS → same breast"

### Clinical Behavior:

- If LCIS is left untreated, about **30%** of women develop an **invasive** cancer within 20 years of diagnosis. The invasive cancer that develops is **usually lobular** (but can be **ductal** too).
- LCIS is a marker of increased cancer risk in both breasts.

### Histology:

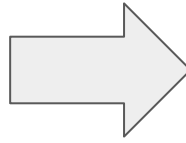
- Monomorphic population of small, rounded cells fills and **expands the acini** of lobules. The underlying lobular architecture can still be recognized.



# INVASIVE BREAST CARCINOMA

Monoclonal proliferation of epithelial cells invading the basement membrane

Invasive breast carcinoma is tumor that has **extended across the basement membrane**



This permits access to lymphatics and vessels and therefore the potential to **metastasize**

Invasive breast carcinoma is subdivided into

Ductal 80% (NOS= no otherwise specified)

Doesn't have specific features

Lobular 10%

Tubular 6%

Mucinous(Colloid) 2%

Medullary 2%

Papillary 1%

Metaplastic Carcinoma 1%

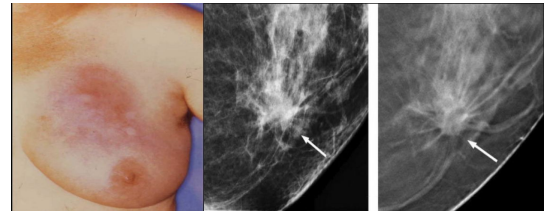
## Clinical Features

- **Palpable mass.**
- About half of the patients will have **axillary lymph node metastases.**
- Larger carcinomas may be fixed to the chest wall or cause **dimpling of the skin**. "Since it can invade the underlying chest wall it will be fixed and this feature could differentiate between fibroadenoma which is mobile (breast mouse)"
- Lymphatics may become involved and the lymphatic drainage of that area and the overlying skin gets blocked causing lymphedema and thickening of the skin, a change referred to as **peau d'orange**. the carcinoma will invade the dermis and the lymphatic within the breast → block lymphatic drainage accumulation of lymphatic fluid → edema → thickening of breast skin and inflammatory reaction "redness swelling". the breast has fibrous "suspensory" ligaments which can not expand like the skin of the breast due to edema so it will appear as peau d'orange "تشر البرتقال"

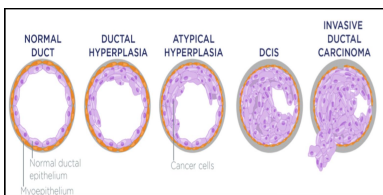


## Clinical Features cont.

- When the tumor involves the central portion of the breast, **retraction of the nipple** may develop.
- On mammography, invasive carcinomas commonly present as a **density**.
- Invasive carcinomas presenting as scattered mammographic calcifications without an associated density are usually very small in size.
- The term "**inflammatory carcinoma**" refers to the **clinical presentation** of a carcinoma extensively involving **dermal lymphatics**, resulting in an enlarged **erythematous** breast with a **peau d'orange** appearance. The diagnosis is made on clinical grounds and **does not** correlate with a specific histologic type of carcinoma



### Invasive Ductal Carcinoma, NOS

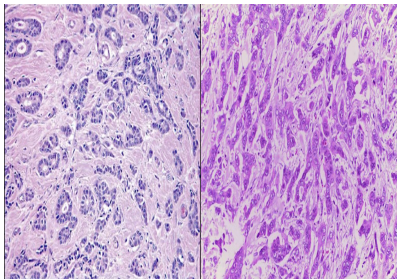


- Invasive ductal carcinoma, NOS, is the **most common type** of breast cancer, forming up to 80% of these cancers.
- Most of these tumors induce a marked fibroblastic (desmoplastic) stromal reaction to the invading tumor cells producing a **palpable mass** with a **hard** consistency (**scirrhous carcinoma**) Is an invasive ductal carcinoma with **extensive** desmoplastic reaction "it is not just firm its stony hard". And therefore a **palpable mass** is the most common presentation.
- The tumor shows an infiltrative attachment to the surrounding structures and may cause **dimpling of the skin** (due to traction on suspensory ligaments) or **nipple retraction**.

Firm and hard masses are due to the presence of desmoplastic reaction so in case of absence of desmoplastic reaction the tumor will be soft



The whitish area is the fibrous breast tissue and the yellow area is the fatty breast tissue



## Invasive Lobular Carcinoma

- **Grossly:** tumor is:

firm → hard → with an irregular borders

- **Cut surface:** gritty “رملی” and shows irregular margins with stellate infiltration (sometimes it can be soft and well demarcated) and in the center there are small foci of **chalky white** stroma and occasionally **calcifications** which have characteristic grating **sound when cut or scraped**.
- IDC *invasive ductal carcinoma* is usually accompanied by varying amounts of DCIS *ductal carcinoma in situ*.
- **Histology:**
  - the tumor cells are **large** and **pleomorphic** usually within a dense stroma.
  - They are adenocarcinomas and so they show **glandular formation** but can also be arranged in cords or sheets of cells.
- The tumors range from well differentiated to moderate or poorly differentiated.
- Carcinomas associated with a large amount of DCIS require large excisions with wide margins to reduce local recurrences

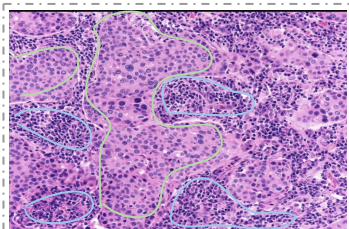
- It is the second most common type of invasive breast cancer forming up to 10% of breast cancers.
- The tumor may occur alone or in combination with ductal carcinoma.
- It tends to be **bilateral** and **multicentric**. “Same as LCIS”
- it doesn't usually cause desmoplastic reaction thus no mass so it will be silent and detected late.



The malignant cells line up as single cells in line

- The amount of stromal reaction to the tumor varies from marked fibroblastic (desmoplastic) response to little reaction and therefore the presentation varies from a discrete mass to a subtle, diffuse indurated area. Most are **firm to hard with irregular margins**.
- **Histology:**
  - **single infiltrating malignant cells**, forming a line often one cell width (called as **Indian file pattern**).
  - No tubules or papillary formation.

## Medullary Carcinoma

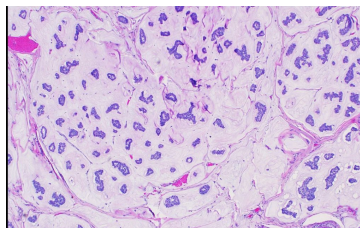


lymphoplasmacytic infiltrate

solid sheets of malignant cells

- This subtype of breast cancer presents as a **well circumscribed mass**.
- May be mistaken clinically and radiologically for a fibroadenoma.
- It **does not** produce any fibroblastic (desmoplastic) reaction and therefore it is **soft and fleshy**.
- **Histology:**
  - the tumor is composed of solid sheets of malignant cells surrounded by many **lymphocytes and plasma cells**.
  - There is scant fibrous stroma.

## Colloid (Mucinous) Carcinoma



- It tends to occur in older women.
- It is **sharply circumscribed**, **lacks fibrous** stroma and it is slow growing.
- It is **soft** “because it lacks fibrous” and **gelatinous** and has a glistening cut surface.
- It may be in pure mucinous or mixed with another type of invasive breast carcinoma.
- The tumor is composed of small islands of tumors cells and **single** tumor cells **floating in pools of extracellular mucin**

# INVASIVE BREAST CARCINOMA

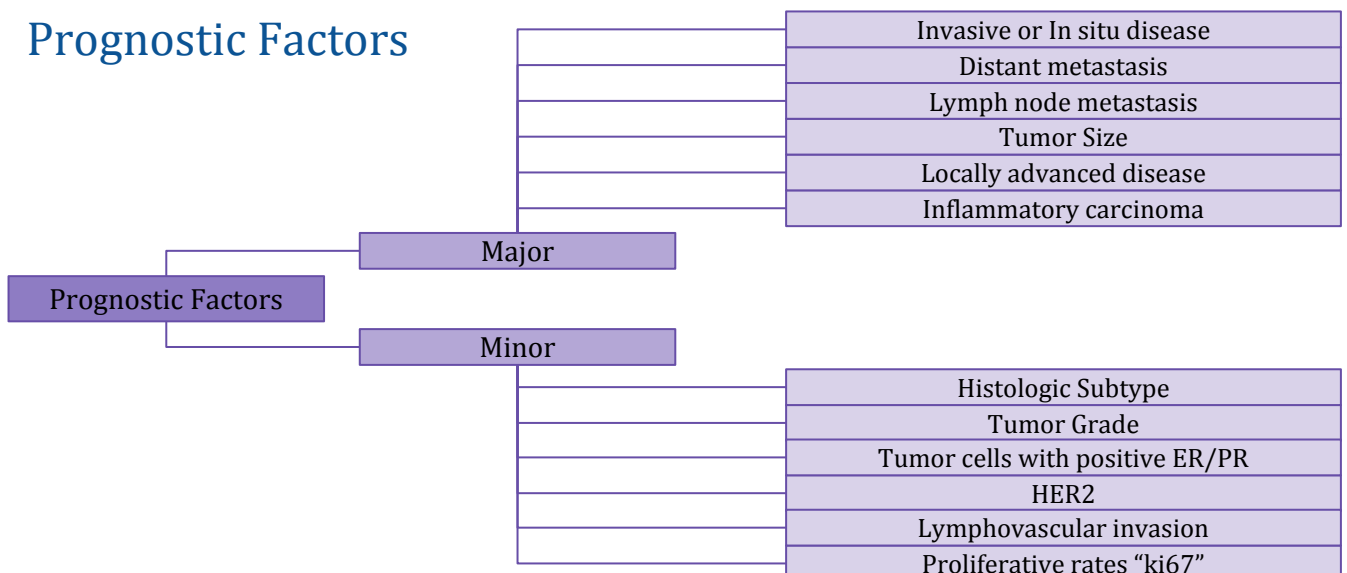
## Treatment

Wide local excision (lumpectomy)

Mastectomy

“ Simple - Modified radical - Radical”

## Prognostic Factors



# INVASIVE BREAST CARCINOMA

## Prognostic Factors

-There are major and minor prognostic factors it is **important** to know them  
-Major prognostic factors are related to TNM staging system

### Major:

- **Invasive or In situ disease:**

- **Invasive** carcinoma has **poorer** prognosis as it can **metastasize**.
- **In-situ** carcinoma is confined to the ductal/lobular system and **cannot metastasize**, so it has **better** prognosis.

- **Distant metastasis:**

- Once distant metastases is present, cure is unlikely, although long-term remissions and palliation can be achieved.
- Favored sites for dissemination are the **lungs, bones, liver, adrenals, brain, and meninges**.

- **Lymph node metastasis:**

- Axillary lymph node status is the **most important prognostic factor** for invasive carcinoma.
- The clinical assessment of nodal involvement is very inaccurate, therefore, biopsy is necessary for accurate assessment.

- **Tumor Size:**

- The size of the carcinoma is the **second** most important prognostic factor.
- The **risk of axillary lymph node metastases** increases with the size of the carcinoma.

- **Locally advanced disease:**

- Tumors invading into overlying skin or underlying skeletal muscle are frequently associated with concurrent or subsequent distant disease.
- With increased awareness of breast cancer detection, such cases have fortunately decreased in frequency and are now rare at initial presentation.

- **Inflammatory carcinoma:**

- Women presenting with the clinical appearance of breast **swelling** and skin **thickening** have a **poor** prognosis.

**Note:** all the above parameters are used to **stage** the tumor.

- Stage is a combination of: **TNM**



- Tumor size less than 2 cm is associated with a favorable prognosis.
- The single most important prognostic indicator is the lymph node status.
  - Negative lymph nodes have the best prognosis.
  - Involvement of 1 to 3 lymph nodes has an intermediate prognosis
  - 4 or more positive nodes have the worse prognosis

## Minor :

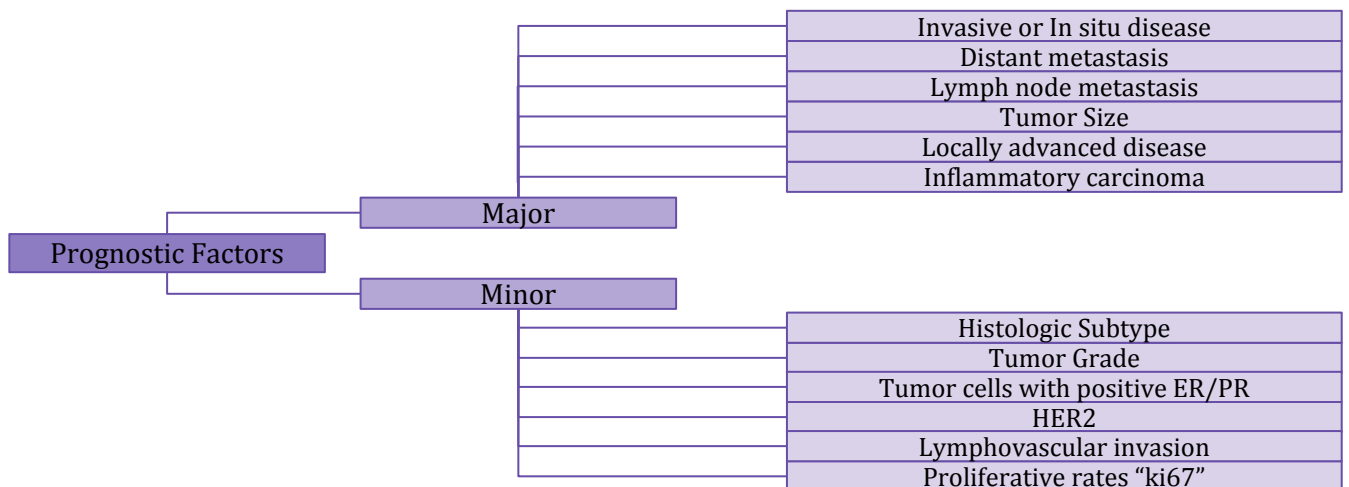
- **Histologic Subtype:**
  - **Infiltrating ductal** and **lobular carcinomas** have the **worst prognosis**.
  - Medullary and mucinous have intermediate prognosis.
  - **Tubular** and **cribriform** have the **most favorable prognosis**
- **Tumor Grade:**
  - It is calculated using a grading system called modified Scarff- Bloom-Richardson (SBR) grading system.
  - There are three grades: 1, 2 and 3. Grade 1 has better prognosis and grade 3 has poorer prognosis.
  - This SBR grading system is based on the estimation of the amount of well formed glands, the degree of nuclear pleomorphism, and the mitotic rate, on microscopic examination.
  - It is calculated by the pathologist.
- **Tumor cells with estrogen and progesterone positive receptors:**
  - majority of breast carcinoma cells express **estrogen** and **progesterone** receptors.
  - Such hormone **positive** cancers have **better prognosis**.
  - They respond well to specific drugs e.g. **Tamoxifen**.
  - Therefore it is mandatory to identify which tumors are ER/PR positive as they respond well to treatment and have better prognosis when compared to ER/PR negative tumors
- **HER2 (human epidermal growth factor receptor 2):**
  - is a glycoprotein overexpressed in about 30% of breast carcinomas.
  - Many studies have shown that overexpression of **HER2** is associated with a **poor prognosis**.
  - In addition, ongoing studies have shown that **HER2**-overexpressing tumors respond very well to a chemotherapy drug named **Trastuzumab** (Herceptin).
  - Therefore, it is mandatory to determine the HER2 status of the tumor when reporting breast cancer in order to help decide the chemotherapy plan.
- **Lymphovascular invasion:**
  - is strongly associated with the presence of lymph node metastases and is a poor prognostic factor.
- **Proliferative rates:**
  - ki67 index (the higher the ki67 proliferative index, the more aggressive the tumor is) Its indicate the proliferative cells so the more the worst.

### - What does it mean to have ER/PR positive?

- That's mean that the tumor has estrogen/ progesterone receptors thus the tumor can respond to anti-estrogen or anti-progesterone drugs and that's why having positive ER/PR have better prognosis
- The tumor could be positive to both ER and PR or to only one of them or could be negative for all of them

Staining for ER,PR and HER2 is helpful for determining the treatment plan so if i have a triple negative result "all are negative" that's associated with the worst prognosis

|           | Invasive Ductal Carcinoma, NOS   | Invasive Lobular Carcinoma   | Medullary Carcinoma  | Colloid (Mucinous) Carcinoma  |
|-----------|--|--|--|---|
| Clinical  | - <b>palpable mass</b> is the most common presentation<br>- may cause dimpling of the skin<br>nipple retraction.   | presentation varies from a discrete mass to a subtle, diffuse indurated area   | May be mistaken clinically and radiologically for a fibroadenoma   | -   |
| Grossly   | - Firm<br>- Hard<br>- irregular borders  | Most are firm to hard with irregular margins.  | soft and fleshy “since It <b>does not produce any fibroblastic (desmoplastic) reaction</b> ”   | - soft and gelatinous and has a glistening cut surface.   |
| Histology | the tumor cells are:<br>- large and pleomorphic usually within a dense stroma<br>- they show glandular formation but can also be arranged in cords or sheets of cells. | - <b>single infiltrating malignant cells</b> , forming a line often one cell width (called as <b>Indian file pattern</b> ).<br>- <b>No tubules or papillary formation.</b> | - the tumor is composed of <b>solid sheets of malignant cells</b> surrounded by many <b>lymphocytes and plasma cells.</b><br>- There is scant fibrous stroma | The tumor is composed of small islands of tumors cells and single tumor cells floating in pools of extracellular <b>mucin</b> |
| Other     | The tumors range from well differentiated to moderate or poorly differentiated   | tends to be <b>bilateral</b> and multicentric.   | well circumscribed mass  | - tends to occur in older women<br>- sharply circumscribed, lacks fibrous stroma.<br>- slow growing.                          |





# Doctor notes

- The **second** most common cancer after lung cancer.
- The majority of sporadic breast cancers occur in postmenopausal women and in cases of overexpression to **estrogen**.
- About 25% of familial cancers (or around 3% of all breast cancers) can be attributed to two autosomal-dominant genes: **BRCA1** and **BRCA2**.
- **DCIS** is the non-invasive proliferation of malignant cells within the duct system **without breaching** the underlying **basement** membrane, frequently shows **micro-calcifications** on mammography.
- Paget's disease characterized by a **red, scaly** eczematous lesion on the nipple and surrounding areola.
- **LCIS** is **not** associated with **calcification**, they don't form masses! tends to be multicentric multifocal and **bilateral**.
- **Very IMP**: The different between ALH [Atypical lobular hyperplasia] and LCIS : **ALH**> 1- partial involvement of the lobule (few acini) 2- do not expand the acini. **LCIS**> 1-complete involvement of the lobule 2- expands the acini. benign لمحاضرة ALH اللي ببسأل وشو ارجعوا
- The different between **fibroadenoma** and **invasive carcinoma** clinically: invasive> the mass is **fixed**, fibroadenoma> the mass is **movable**.
- **peau d'orang** and **retraction of nipple** are seen in invasive carcinoma.
- **Invasive ductal carcinoma** is the most common type of breast cancer, induce a marked **fibroblastic (desmoplastic)** stromal reaction, producing a palpable mass with a **hard** consistency (**scirrhous carcinoma**).
- **Invasive lobular carcinoma** is usually silent.
- **Medullary carcinoma** is a **well circumscribed** mass, does **not** produce any fibroblastic reactions so its **soft**, on histology: composed of **solid sheets** of malignant cells surrounded by **lymphocytes** and plasma cells.
- Notice that any **combination** of these types can occur!
- Its very **imp** to differentiate between minor and major prognostic factors!
- The **major prognostic** factors involve the **stage** which is **TNM**:

1-T: The **size** of the tumor which is the 2nd most imp. Prognostic factor

2-N: **Lymph node** involvement is the 1st most imp prognostic factor .

3-M: **Metastasis** Third most imp. Prognostic factor

- The **minor prognostic** factors involve:

1-Histologic Subtype: ductal and lobular > **worst** prognosis, Medullary and mucinous> **intermediate** prognosis, tubular and cribriform> the **best** prognosis.

2- **tumor grade**> using **SBR**.

3-**estrogen** and **progesterone** positive receptors> good prognosis.

4-**HER2** > poor prognosis

5-**Lymphovascular invasion**> poor prognosis. !لسى ماوصل فرقو بينها وبين حقت الميجر

6-**Proliferative rates: ki67** index> poor prognosis.

# Pathoma summary

## BREAST CANCER

### I. BASIC PRINCIPLES

- A. Most common carcinoma in women by incidence (excluding skin cancer)
- B. 2nd most common cause of cancer mortality in women
- C. Risk factors are mostly related to estrogen exposure.
  - 1. Female gender
  - 2. Age-Cancer usually arises in postmenopausal women, with the notable exception of hereditary breast cancer.
  - 3. Early menarche/late menopause
  - 4. Obesity
  - 5. Atypical hyperplasia
  - 6. First -degree relative (mother, sister, or daughter) with breast cancer

### II. LOBULAR CARCINOMA IN SITU (LCIS)

- A. Malignant proliferation of cells in lobules with no invasion of the basement membrane
- B. LCIS does not produce a mass or calcifications and is usually discovered incidentally on biopsy.
- C. Characterized by dyscohesive cells lacking E-cadherin adhesion protein
- D. Often multifocal and bilateral
- E. Treatment is tamoxifen (to reduce the risk of subsequent carcinoma) and close follow-up; low risk of progression to invasive carcinoma

### III. INVASIVE LOBULAR CARCINOMA

- A. Invasive carcinoma that characteristically grows in a single-file pattern (Fig. 16.9); cells may exhibit signet-ring morphology.
  - 1. No duct formation due to lack of E-cadherin.

# Pathoma summary

## IV. DUCTAL CARCINOMA IN SITU (DCIS)

- A. Malignant proliferation of cells in ducts with no invasion of the basement membrane
- B. Often detected as calcification on mammography; DCIS does not usually produce a mass
  - 1. Mammographic calcifications can also be associated with benign conditions such as fibrocystic changes (especially sclerosing adenosis) and fat necrosis.
  - 2. Biopsy of calcifications is often necessary to distinguish between benign and malignant conditions.
- C. Histologic subtypes are based on architecture; comedo type is characterized by high-grade cells with necrosis and dystrophic calcification in the center of ducts.
  - Paget disease of the breast is DCIS that extends up the ducts to involve the skin of the nipple
    - 1. Presents as nipple ulceration and erythema
    - 2. Paget disease of the breast is almost always associated with an underlying Carcinoma

## V. INVASIVE DUCTAL CARCINOMA

- A. Invasive carcinoma that classically forms duct-like structures
- B. Most common type of invasive carcinoma in the breast, accounting for > 80% of cases
- C. Presents as a mass detected by physical exam or by mammography
  - 1. Clinically detected masses are usually 2 cm or greater.
  - 2. Mammographically detected masses are usually 1 cm or greater.
  - 3. Advanced tumors may result in dimpling of the skin or retraction of the nipple.
- D. Biopsy usually shows duct-like structures in a desmoplastic stroma; special subtypes of invasive ductal carcinoma include:
  - 1. Tubular carcinoma-characterized by well-differentiated tubules that lack myoepithelial cells; relatively good prognosis
  - 2. Mucinous carcinoma-characterized by carcinoma with abundant extracellular mucin ('tumor cells floating in a mucus pool',
    - i. Tends to occur in older women (average age is 70 years)
    - ii. Relatively good prognosis
  - 3. Medullary carcinoma-characterized by large, high-grade cells growing in sheets with associated lymphocytes and plasma cells
    - i. Grows as a well-circumscribed mass that can mimic fibroadenoma on mammography
    - ii. Relatively good prognosis
    - iii. Increased incidence in BRCA1 carriers
  - 4. Inflammatory carcinoma-characterized by carcinoma in dermal lymphatics
    - i. Presents classically as an inflamed, swollen breast (tumor cells block drainage of lymphatics) with no discrete mass; can be mistaken for acute mastitis
    - ii. Poor prognosis

# Pathoma summary

## VI. PROGNOSTIC AND PREDICTIVE FACTORS

A. Prognosis in breast cancer is based on TNM staging.

1. Metastasis is the most important factor, but most patients present before metastasis occurs.
2. Spread to axillary lymph nodes is the most useful prognostic factor (given that metastasis is not common at presentation); sentinel lymph node biopsy is used to assess axillary lymph nodes.

B. Predictive factors predict response to treatment.

1. Most important factors are estrogen receptor (ER), progesterone receptor (PR), and HER2/neu gene amplification (overexpression) status.
2. Presence of ER and PR is associated with response to antiestrogenic agents (e.g., tamoxifen); both receptors are located in the nucleus
3. HER2/neu amplification is associated with response to trastuzumab (Herceptin), a designer antibody directed against the HER2 receptor; HER2/neu is a growth factor receptor present on the cell surface
4. 'Triple-negative' tumors are negative for ER, PR, and HER2/neu and have a poor prognosis; African American women have an increased propensity to develop triple-negative carcinoma.

## VII. HEREDITARY BREAST CANCER

A. Represents 10% of breast cancer cases

B. Clinical features that suggest hereditary breast cancer include multiple first-degree relatives with breast cancer, tumor at an early age (premenopausal), and multiple tumors in a single patient.

C. BRCA1 and BRCA2 mutations are the most important single gene mutations associated with hereditary breast cancer.

1. BRCA1 mutation is associated with breast and ovarian carcinoma.
2. BRCA2 mutation is associated with breast carcinoma in males.

D. Women with a genetic propensity to develop breast cancer may choose to undergo removal of both breasts (bilateral mastectomy) to decrease the risk of developing carcinoma.

1. A small risk for cancer remains because breast tissue sometimes extends into the axilla or subcutaneous tissue of the chest wall.

## VIII. MALE BREAST CANCER

A. Breast cancer is rare in males (represents 1% of all breast cancers).

B. Usually presents as a subareolar mass in older males

1. Highest density of breast tissue in males is underneath the nipple.
2. May produce nipple discharge

C. Most common histological subtype is invasive ductal carcinoma.

1. Lobular carcinoma is rare (the male breast develops very few lobules).

D. Associated with BRCA2 mutations and Klinefelter syndrome

# Questions

1- A 30-year-old woman suffers traumatic injury to her breast while playing soccer. Physical examination reveals a 3-cm area of ecchymosis on the left breast. Two weeks later, the patient palpates a firm lump beneath the area where the bruise had been located. Which of the following is the most likely pathologic diagnosis?

- (A) Duct Ectasia
- (B) Fat necrosis
- (C) Fibrocystic Change
- (D) Granulomatous Mastitis

2- A 53-year-old woman discovers a lump in her breast and physical examination confirms a mass in the lower, outer quadrant of the left breast. Mammography demonstrates an ill-defined, stellate density measuring 1 cm. Needle aspiration reveals malignant ductal epithelial cells. A modified radical mastectomy is performed. The surgical specimen reveals a firm irregular mass (arrows). Which of the following cellular markers would be the most useful to evaluate before considering therapeutic options for this patient?

- (A) Collagenase
- (B) Estrogen receptors
- (C) Galactosyltransferase
- (D) Lysosomal acid hydrolases

3- A 35-year-old nulliparous woman complains that her breasts are swollen and nodular upon palpation. A mammogram discloses foci of calcification in both breasts. A breast biopsy reveals cystic duct dilation and ductal epithelial hyperplasia without atypia (shown in the image). What is the appropriate diagnosis?

- (A) Ductal carcinoma in situ
- (B) Fibroadenoma
- (C) Fibrocystic Change
- (D) Granulomatous Mastitis

1- B  
2- B  
3- C

4- A 24-year-old woman delivers a 3.5-kg baby and begins breastfeeding her infant. The patient presents 2 weeks later with a fever of 38°C (101°F). Physical examination shows no abnormal vaginal discharge or evidence of pelvic pain but does reveal redness on the lower side of the left breast. The patient stops nursing the infant temporarily, but the symptoms persist, and the entire breast becomes swollen and painful. What is the most likely diagnosis?

- (A) Acute Mastitis
- (B) Chronic mastitis
- (C) Duct Ectasia
- (D) Granulomatous Mastitis

5- A 35-year-old woman consults her family physician because of painful swelling of her breasts, particularly as she approaches the end of her menstrual cycle. On self-examination she recently felt a tender nodule in the right breast. Physical examination reveals an irregular nodularity of both breasts with diffuse tenderness. Examination of the axilla is negative. A mammogram demonstrates irregular areas of density in the lower, outer quadrants of both breasts. Which of the following histopathologic features is considered to be a risk factor for the development of carcinoma in this patient?

- (A) Apocrine metaplasia
- (B) Cystic change
- (C) Duct ectasia
- (D) Papillomatosis

6- A 20-year-old woman asks for your advice regarding her risk of developing breast cancer. Her mother, maternal aunt, and maternal grandmother all developed breast cancer. She would like to know if she has a genetic predisposition. Laboratory tests for mutations in which of the following genes would be most likely to answer your patient's question?

- (A) BRCA1
- (B) C-myc
- (C) Estrogen Receptor
- (D) HER2/neu

7- Sporadic cases of breast cancers are more than inheritance:

- (A) true
- (B) False

4- A  
5- D  
6- A  
7- A

8- 7- A 26-year-old woman presents with a breast mass that was detected on self-examination 1 week earlier. Mammography reveals a round, sharply demarcated 1-cm nodule in the right breast (shown in the image). Biopsy of the breast mass shows neoplastic epithelial ductal structures situated within a fibro-myxoid stroma. The patient refuses further treatment and informs you that she wishes to become pregnant. Which of the following is the most likely effect of pregnancy on this breast lesion?

- (A) Development of invasive ductal carcinoma within the lesion
- (B) Fibrocystic change with sclerosing adenosis
- (C) Formation of intraductal papilloma
- (D) Rapid growth

9- A 52-year-old woman presents with a 3-month history of a palpable breast mass. Physical examination confirms a 1-cm nodule in the upper outer quadrant of the right breast. A biopsy reveals small cuboidal cells, with round nuclei and prominent nucleoli. The cells are arranged in single cell columns, between strands of connective tissue (shown in the image). Which of the following is the appropriate diagnosis?

- (A) Ductal carcinoma in situ
- (B) Invasive ductal carcinoma, tubular type
- (C) Invasive lobular carcinoma
- (D) Lobular carcinoma in situ

10- A 45-year-old woman presents with an oozing, reddish patch on her left nipple (patient shown in the image). The patient has a history of skin rashes and food allergies and believes this condition is due to an allergic reaction to her bra. Cytologic examination of fluid oozing from the skin lesion reveals neoplastic cells. Excisional biopsy shows large clear malignant cells in the epidermis of the areola. Which of the following is the most likely diagnosis?

- (A) Chronic Dermatitis
- (B) Colloid carcinoma
- (C) Intraductal Papilloma
- (D) Paget Disease

8- D

9- C

10- D



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