

# Lecture 9: Pathology of Breast Cancer

wiseGEEK

▣ Important

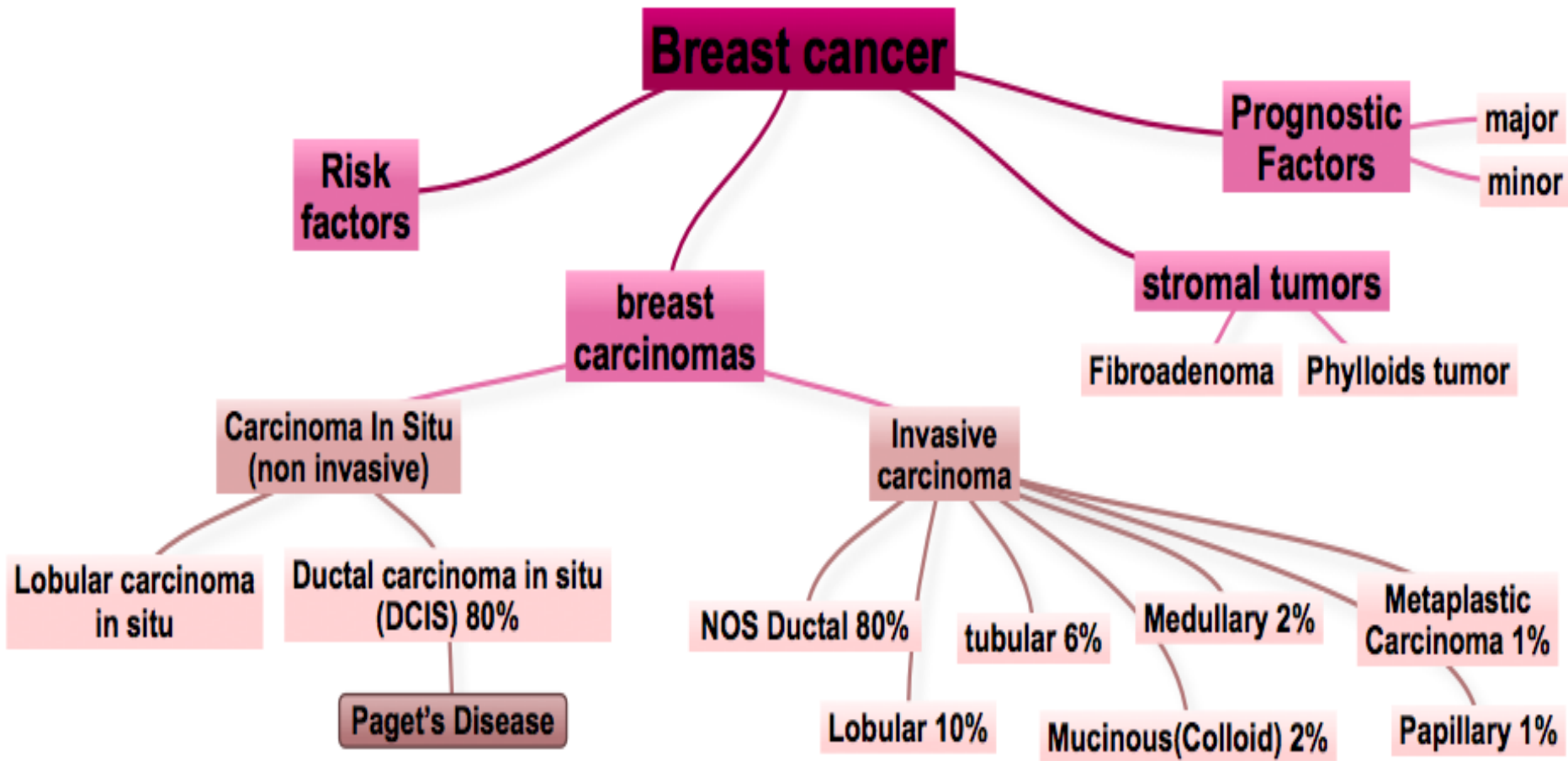
▣ Notes

▣ Explanation

# Objectives

The student should know :

- A. Know the risk factors for the development of breast cancer.
- B. Know the classification of breast cancer.
- C. Understand the behavior and spread of breast cancer.
- D. Know the prognostic indicators of breast carcinoma.
- E. Know the common benign breast tumours with special emphasis on fibroadenoma and phyllodes tumour.



# Breast Carcinoma

- The **most common malignancy** of breast is **carcinoma**.
- **Carcinoma of the breast** is the **most common cancer in women**.
- Women who lives to age 90 has a one in eight chance to have breast cancer.
- **Mammographic** screening increased dramatically 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.
- The number of women with an advanced cancer is markedly decreased.
- **The mortality rate started to decline**. Currently only 20% of the women with breast cancer are expected to die of the disease.

## Risk Factors :

- The **etiology of breast cancer in most women** is **unknown** but most likely is due to a **combination of the risk factors** i.e. **genetic, hormonal and environmental factors**
- The major risk factors being **hormonal** and **genetic (family history)**.
- Breast carcinomas can, therefore, be divided into **sporadic cases** and **hereditary cases**.

### Hereditary Breast Cancer

- **A family history :**  
**first-degree relative**. (in 13% of women with the disease).
- **germ-line mutations:**  
*About 25% of familial cancers (or around 3% of all breast cancers) can be attributed to two highly penetrant **autosomal-dominant genes: BRCA1 and BRCA2***

### Sporadic Breast Cancer

**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 overexpression of estrogen**

## Cont. Risk Factors of Breast Cancer :

- 1) **Age:** increase incidence of breast cancer **older women**. Breast cancer is rare **before 25 yrs**, **except** familial forms . Majority (77%) of cases occur in **women >50 yrs of age**.
- 2) **Age at Menarche:** The **younger a woman's age at menarche**, the **higher** her risk of breast cancer.
- 3) **First Live birth:** The **earlier** a woman has her first birth, the **lower** her lifetime risk for breast cancer. A woman who has her **first birth after 30 years** has an **increased** risk.
- 4) **First Degree relative with Breast Cancer .**
  - Women with history of cancer **in first degree relative** (mother, sister, aunt or daughter) are at **higher** risk of breast cancer. **The risk increases** with the **number of affected first degree relatives**.
  - NOTE: **majority of cancers occur in women without such history**.
  - At least two genes that predispose to breast cancer have been identified—**BRCA 1 and 2**
- 5) **Breast Biopsy:** **Atypical hyperplasia** increases the risk for breast cancer
- 6) **Race:** Overall incidence of breast cancer is lower in African American women . Generally **caucasian** have the highest rate of breast cancers
- 7) **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, late age at menopause, nulliparity and late age at first child-birth. Also postmenopausal hormone replacement slightly increases the risk
- 8) **Radiation exposure:** Higher rate of breast cancer
- 9) **History of breast cancer:** Women who have had a breast cancer **have a 10-fold increased** risk of developing a **second primary breast cancer**

## Cont. Risk Factors of Breast Cancer :

- 10) **History of Other Cancer:** A history of cancer in the other breast or a **history of ovarian or endometrial cancer**
- 11) **Geographic influence:** Breast cancer is more common in **Western** industrialized countries than in developing countries. Four to seven times in USA and Europe higher than those in other countries.
- 12) **Benign Breast Disease:** As noted previously women with certain types of benign breast disease are at risk
- 13) **Dietary factors** e.g. **high fat intake** and **excessive alcohol consumption**, and **exposure to ionizing radiation** have also been proposed as risk factors
- 14) **Obesity:** may play a role
- 15) **Exercise:** some studies showed **decreased** risk with exercise
- 16) **Breast feeding:** the **longer** the women breast feed, the **lower** the risk
- 17) **Environmental toxins:** pesticides .
- 18) **Tobacco:** Not associated with breast cancer, but associated with the development of peri-ductal mastitis, or sub-areolar abscess.

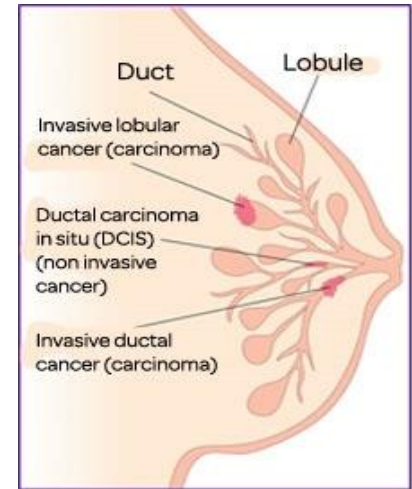
# Classification of Breast Carcinoma

Almost all (majority) are Adenocarcinoma\*

Divided into:

Carcinoma in situ( non-invasive)

Invasive carcinoma

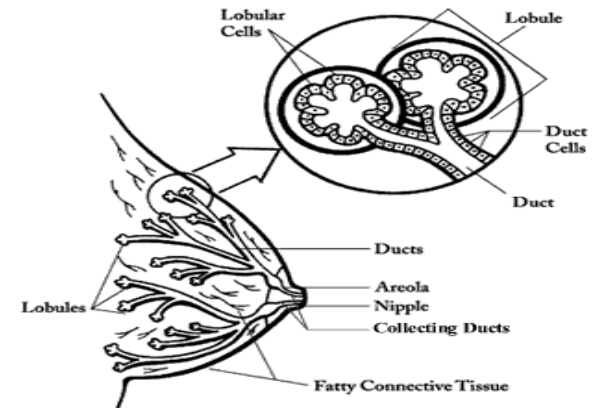


## Carcinoma in situ( non-invasive):

- ❖ This is **epithelial proliferation** that is still confined to the TDLU\*\*.
- ❖ has **not invaded** beyond the basement membrane.
- ❖ **incapable of metastasis.**
- ❖ There are **two** subtypes:

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

Lobular carcinoma in situ 20%.



\* (neoplasia of epithelial tissue that has glandular origin)

\*\* (terminal ductal-lobular unit)

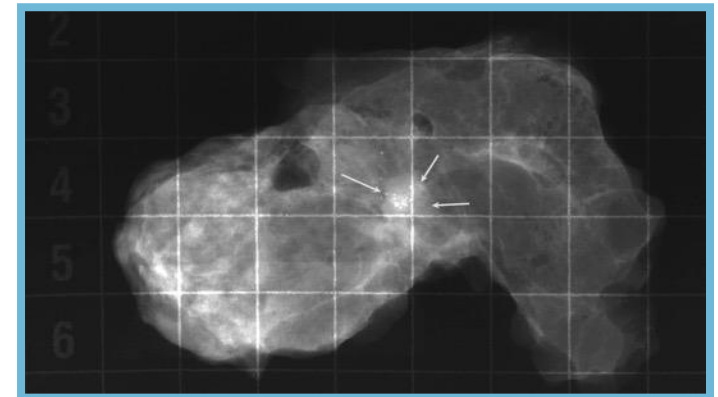
## DCIS (Ductal Carcinoma In Situ) :

is a group of neoplastic lesions have **proliferating malignant** cells within the duct system but **do not** breach the underlying **basement membrane** (**non-invasive**).

- Occurs between **50 and 59 years**, similar to the mean age of women with **invasive ductal carcinoma**.
- They have a **very high risk** of development of subsequent **invasive carcinoma**.
- Women with DCIS are at risk of **recurrent DCIS following treatment**.
- Often **multifocal**—malignant population can spread widely through the duct system without breaching the basement membrane.
- The tumor distends and **distorts the ducts**.
- Mammography is a **very sensitive diagnostic procedure for detecting microcalcifications** that found in **72 to 98% of DCIS**, as a substantial proportion is **not palpable**.
- Most frequently as a calcifications.
- Less frequently as a density or a vaguely palpable mass or nipple discharge.

### DCIS, microcalcifications

This type of calcification represents about a 20% chance of malignancy and should be biopsied. Mammography helps pathologists to sample the areas of greatest concern more heavily.





# DCIS (Ductal Carcinoma In Situ) :

Different patterns/subtypes of DCIS can be seen e.g.

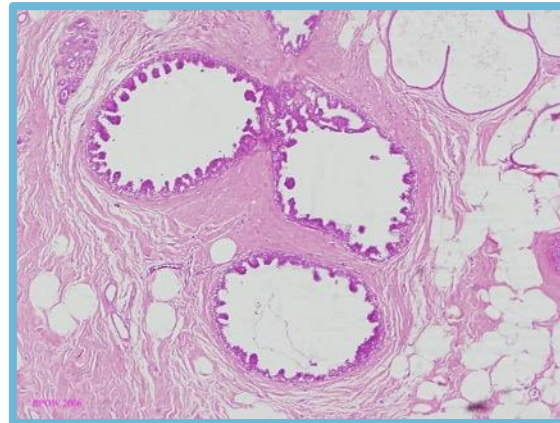
- ❖ **comedo** (central necrosis) has essentially a **100% chance of becoming invasive** if left untreated
- ❖ **Cribriform\*** (cells arranged around “punched-out” spaces);
- ❖ **papillary, Micropapillary\***
- ❖ **solid** (cells fill spaces)

\* Pure cribriform/micropapillary carries only a **30% chance of becoming invasive carcinoma.**

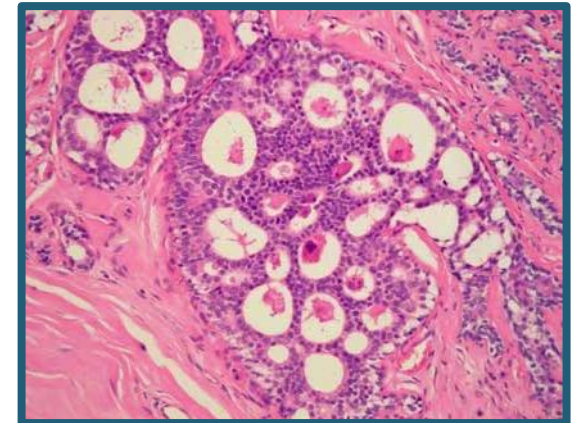
DCIS can be of **different grades** i.e. low, intermediate and high grade (e.g. comedo=high)



Comedo DCIS fills several adjacent ducts (or completely replaced lobules) and is characterized by large central zones of necrosis with calcified debris.



Micropapillary DCIS.



Cribriform DCIS comprises cells forming round, regular (“**cookie cutter**”) spaces. The lumens are often filled with calcifying secretory material.

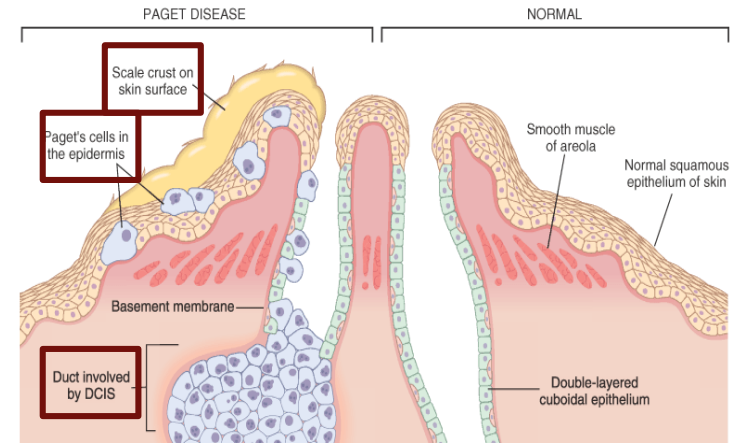
## • Treatment :

- ✓ **Wide local excision**
- ✓ **mastectomy**

# Paget's Disease (rare type of breast cancer)

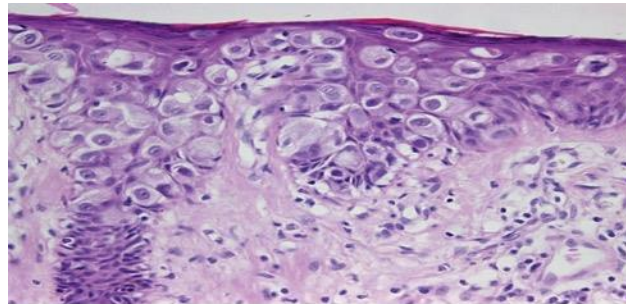
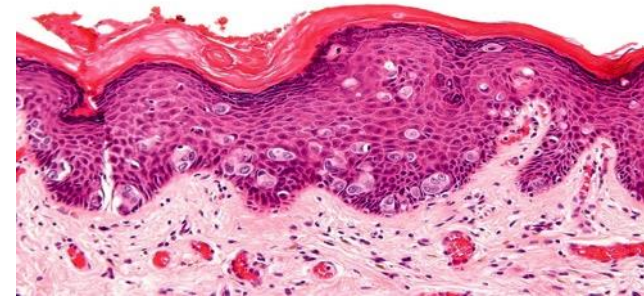
## Characteristics:

- **red, scaly** lesion on the **nipple** and surrounding areola (1 to 2 %).
- **eczematous** area of the **nipple**, which may be subtle or form an obviously **eroded, weeping lesion**
- **Pruritus** is common, might be mistaken for **Eczema**
- **unilateral erythematous eruption with a scale crust.**
- **Malignant cells**, referred to as Paget cells and are found **scattered in the epidermis.**
- Palpable mass is present in 50 to 60% of women with Paget disease indicating an underlying invasive carcinoma.



## The histologic hallmark of Paget's disease of the nipple:

- **infiltration of the epidermis** by large **ductal neoplastic cells** with **abundant clear or pale cytoplasm**
- **nuclei with 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**



## LCIS - Lobular Carcinoma in Situ :

- Always an **incidental finding in a biopsy performed for another reason**
- Infrequent (1% to 6% )of all carcinomas
- Lobular carcinoma in situ (LCIS) **does not form a palpable mass** and cannot be detected **clinically, felt at operation or seen grossly on pathological examination.**
- Although LCIS may have **microcalcifications**, these are infrequent and so mammography has not been useful for detecting it.

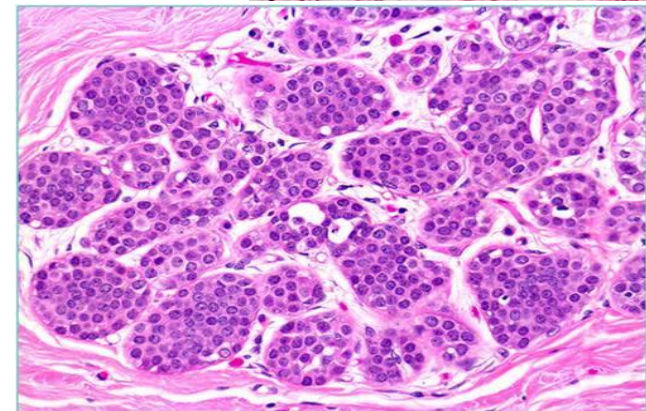
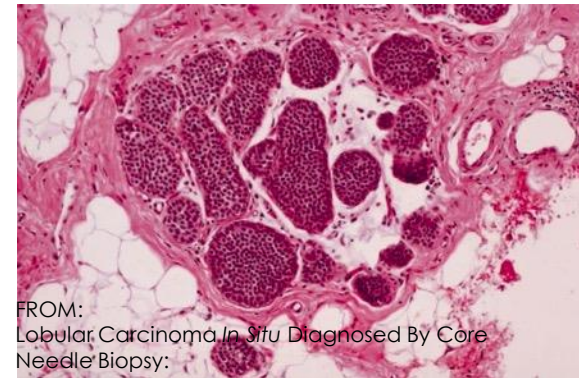
The disease tends to be **bilateral** (in 20% to 40% of the cases) and **multicentric**.

### Histology:

- **monomorphic population of small, rounded, loosely cohesive cells fills and expands the acini of a lobule.**
- The underlying lobular architecture can still **be recognized.**

### Clinical behavior

- If LCIS is left untreated, about 30% of women develop an **invasive cancer** within 20 years of diagnosis. The invasive cancer may be ductal or lobular. LCIS is a marker of increased cancer in both breasts



# Invasive Breast Carcinoma

Extends across the basement membrane thus access to lymphatics and blood vessels >Distant metastases. LETHAL outcome

## Classification:

- No otherwise specified Ductal (NOS Ductal) – 80%
- Lobular – 10%
- Tubular – 6%
- Mucinous (Colloid) – 2%
- Medullary – 2%
- Papillary – 1%
- Metaplastic – 1%

## Clinical Features:

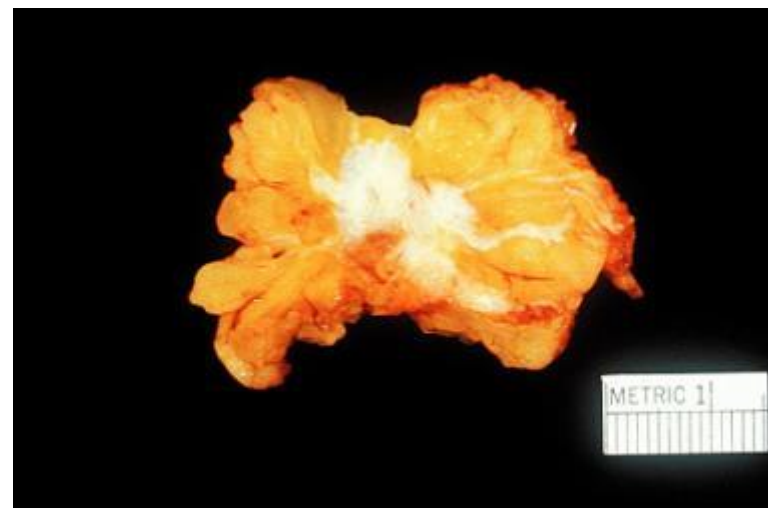
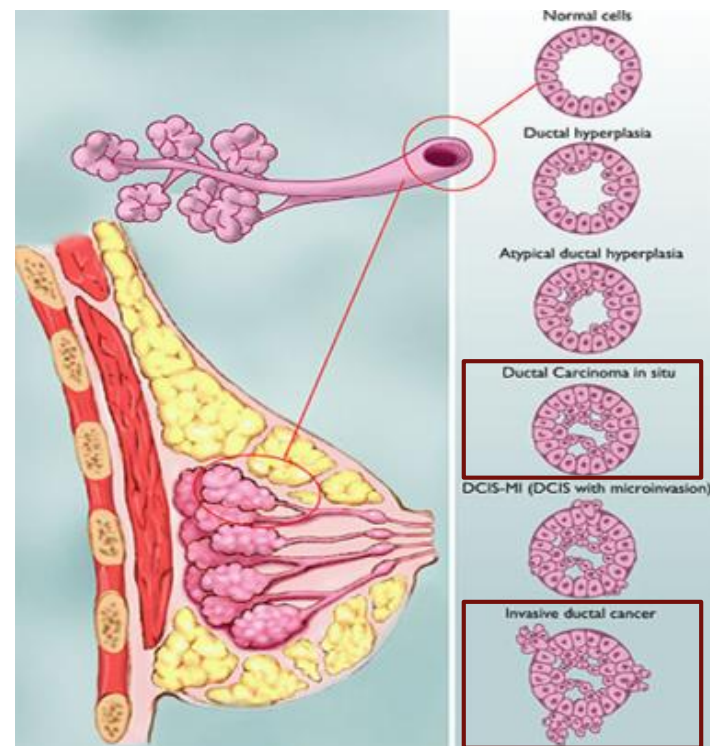
- Palpable mass (over half the patients will have axillary lymph nodes metastases)
- Might be fixed to the chest wall OR cause dimpling of the skin. (the breast is not completely round but has some depressions in it)
- Lymphatics may become involved: blockage of the local area of skin causes lymphedema and thickening of skin (**peau d'orange**)
- Nipple retraction (**inverted nipple**): if the tumor is in the center of breast.
- Older ladies mammography: invasive carcinomas are present as a density.
- Invasive carcinomas presenting as mammographic calcifications without an associated density are usually very small in size
- Inflammatory Carcinoma: a term used to refer to the clinical presentation of a carcinoma extensively involving dermal lymphatics, resulting in an enlarged erythematous breast. The diagnosis is made on clinical grounds and does not correlate with a specific histologic type of carcinoma

## Invasive Ductal Carcinoma, NOS :

- **Commonest breast cancer (80%)**
- Most of these tumors excite a pronounced fibroblastic stromal reaction to the invading tumor cells producing a palpable mass with hard consistency (scirrhous carcinoma), which 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.

### Morphology:

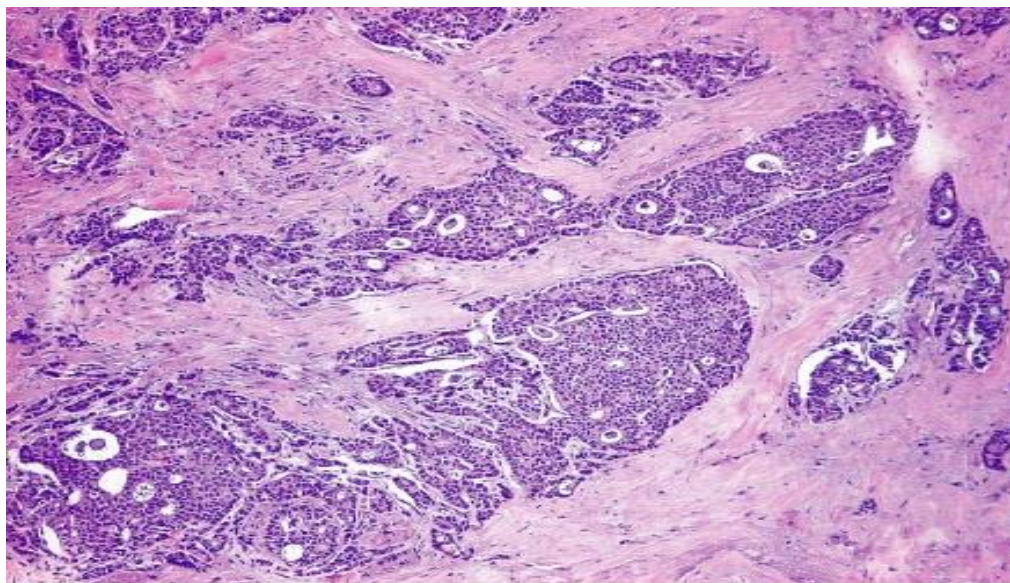
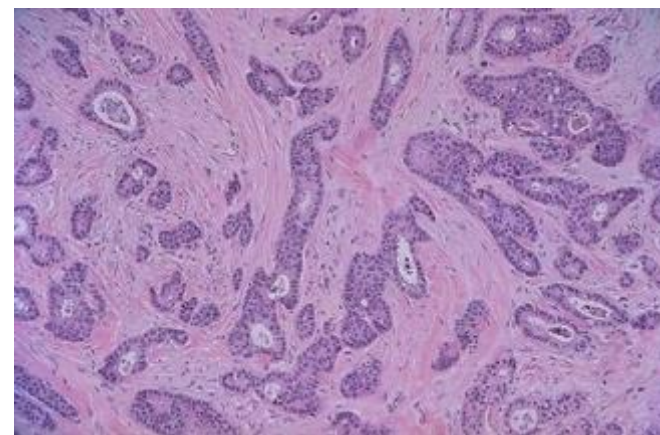
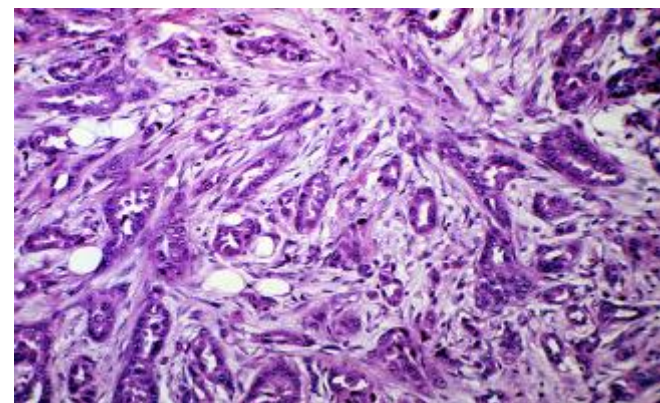
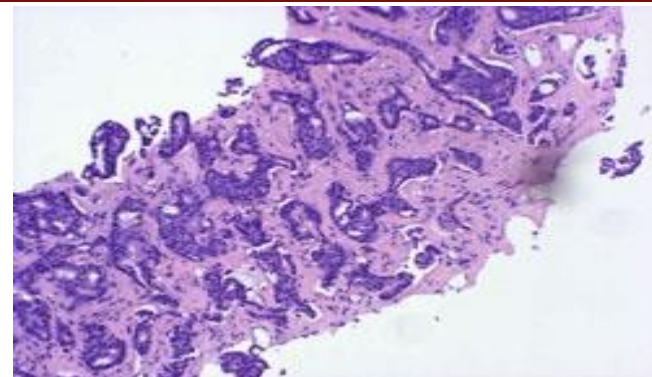
- **Grossly:**
- A firm hard mass, with irregular borders.
- **Stellate infiltration.**
- In the center there are small foci of chalky white stroma and occasionally calcifications
- **Characteristic grating sound when cut**
- Could be soft and well demarcated
- Accompanied by varying amounts of DCIS



## Invasive Ductal Carcinoma, NOS :

### Morphology:

- **Histologically:**
- Tumor cells are larger than normal epithelium
- Can form variety of patterns (Glandular formation, cords of cells, broad sheets, or mixed within usually within a dense stroma.
- Tumor cells range from well differentiated ( in which there is glandular formation) to poorly differentiated (Solid sheets of pleomorphic neoplastic cells)
- **Carcinomas associated with a large amount of DCIS require large excisions with wide margins to reduce local recurrences.**



## Invasive Lobular Carcinoma :

- 2<sup>nd</sup> most common if invasive breast cancer – 10%
- May occur alone or with ductal carcinoma
- Tends to be bilateral and multicentric
- The amount of stromal reaction to the tumor varies from dense **desmoplasia** to little reaction and therefore the presentation varies from a discrete mass to a subtle, diffuse indurated area

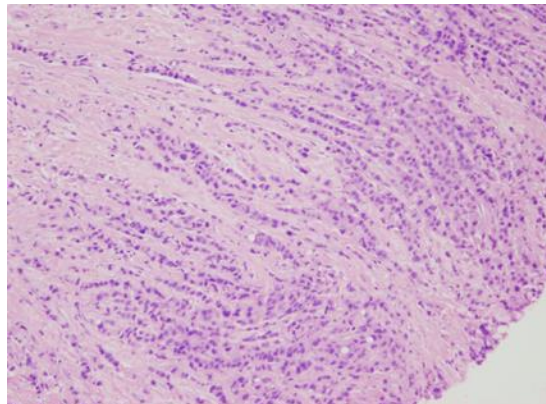
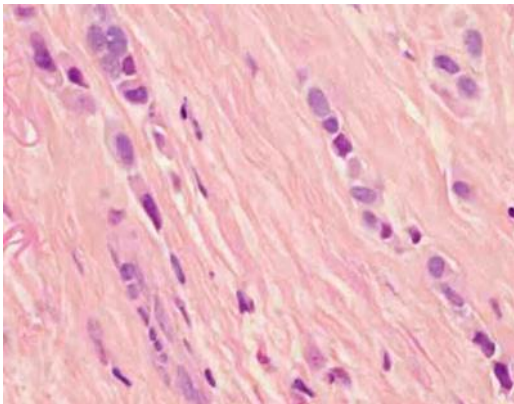
### Morphology:

- **Grossly:**

- Most are firm to hard with irregular margins

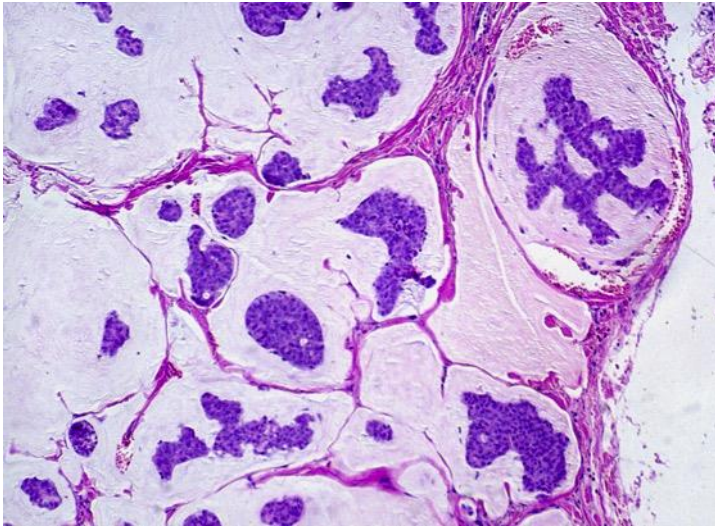
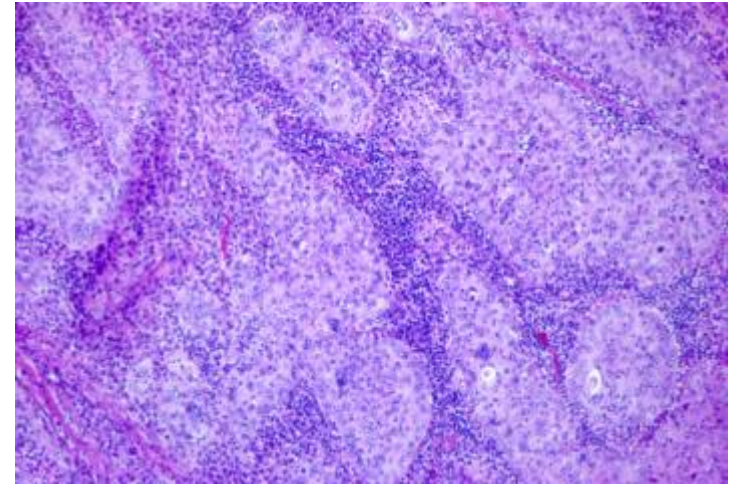
- **Histologically:**

- Single infiltrating cells (**one row of cells which is one cell width**) this is called: **Indian File Pattern**
- No tubules or papillary formation
- In 10% of the cases the tumor have mixed features of invasive ductal and lobular carcinomas.



## Medullary Carcinoma :

- Present as a well circumscribed mass,
- May be mistaken clinically and radiologically for fibroadenoma
- It does not produce any fibroblastic (**desmoplastic**) reaction and therefore is soft and fleshy (**encephaloid**). On section foci of necrosis and hemorrhage are evident.
- Microscopically, the tumor is composed of solid sheets of malignant cells and frequent mitoses. There is scant fibrous stroma. **Lymphocytes** and plasma cells surround the tumor cells.



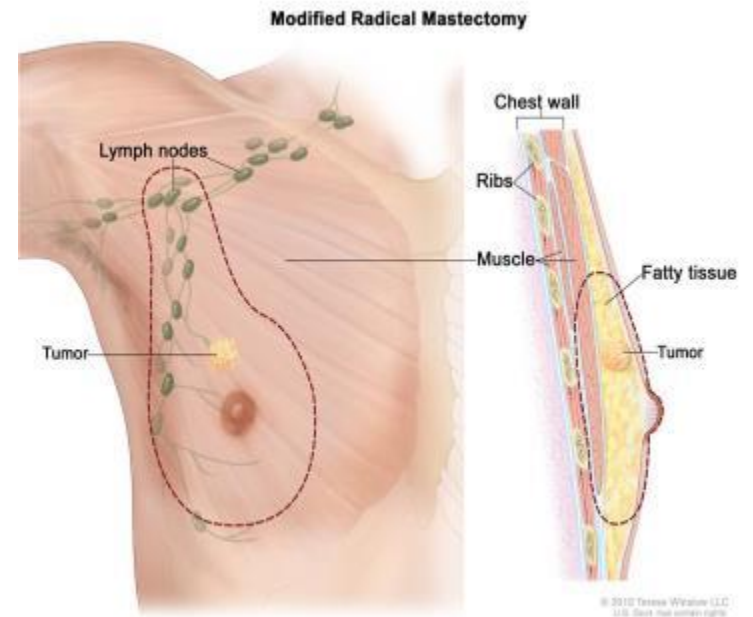
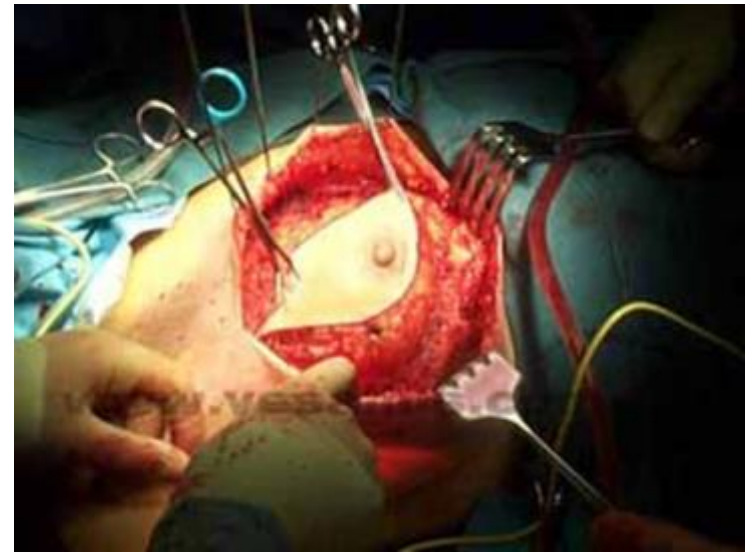
## Colloid (Mucinous) Carcinoma :

- Tends to occur in older women.
- It is sharply circumscribed, lacks fibrous stroma and is slow growing.
- Is soft and **gelatinous** and has a glistening (**shiny**) cut surface.
- It may be in pure mucinous or mixed in which it is associated with other types of invasive breast carcinoma.
- The mucinous tumor is composed of small islands of tumors cells (occasionally forming glands), and isolated tumor cells floating in pools of extracellular mucin



## Treatment :

- Wide local excision  
(Wide: to decrease the risk of recurrence)
- Radical Mastectomy  
(Removal of breast, underlying muscle, and lymph nodes.)



## Major Prognostic Factors

### 1. Invasive or in situ disease:

In situ carcinoma **cannot metastasize**. Breast cancer deaths associated with DCIS are due to the subsequent development of invasive carcinoma or areas of invasion undetected at the time of diagnosis. The great majority of women with adequately treated DCIS will be cured. In contrast, at least half of invasive carcinomas will have metastasized locally or distantly at the time of diagnosis.

### 2. Distant Metastases:

Once distant metastases are 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.**

### 3. Lymph node metastases:

**Axillary lymph node status is the most important prognostic factor** for invasive carcinoma in the absence of distant metastases. The clinical assessment of nodal involvement is very inaccurate; therefore, biopsy is necessary for accurate assessment. With no involvement, the 10-year disease-free survival rate is close to 70% to 80%; the rate falls to 35% to 40% with one to three positive nodes and 10% to 15% in the presence of more than 10 positive nodes.

### 4. Tumor size:

The size of the carcinoma **is the 2nd most important prognostic** factor. The risk of axillary lymph node metastases increases with the size of the carcinoma.

### 5. Locally advanced disease:

Tumors invading into skin or skeletal muscle are frequently associated with distant disease

### 6. Inflammatory Carcinoma:

Women presenting with the clinical appearance of breast swelling and skin thickening have a particularly poor prognosis with a 3-year survival rate of only 3% to 10%.

These 4 parameters are used to stage the tumor

## Minor Prognostic Factors

### 1. **Histologic Subtype:**

Infiltrating ductal and lobular carcinomas have the worst prognosis. Medullary and mucinous have intermediate and tubular and cribriform have the most favorable prognoses.

### 2. **Tumor Grade:**

This is calculated by the pathologist. Grading separates tumors into three categories according to the amount of well formed tubules, the degree of nuclear pleomorphism, and the mitotic rate. The most commonly used grading system to assess the degree of tumor differentiation (Bloom Richardson). There are three grades with grade 1 having better prognosis and grade 3 having poorer prognosis.

### 3. **Estrogen and Progesterone receptors:**

50% to 85% of carcinomas express estrogen receptors; such tumors are more common in postmenopausal women. Such hormone positive cancers have better prognosis. They respond well to specific chemotherapeutic drugs e.g. Tamoxifen. Therefore reporting of ER/PR positivity is important when reporting breast cancer

### 4. **HER/NEU:**

(Human epidermal growth factor receptor 2 or c-erb B2 or neu) is a glycoprotein overexpressed in 20% to 30% of breast carcinomas. Many studies have shown that overexpression of HER2/neu is associated with a poor prognosis. In addition, ongoing studies have shown that HER2/neu-overexpressing tumors respond very well to hormonal or anthracycline chemotherapy regimens e.g. Trastuzumab (Herceptin). Therefore evaluation of HER2/neu is important when reporting breast cancer in order to help decide the chemotherapy plan.

### 5. **Lymphovascular invasion:** Tumor cells may be seen within vascular spaces (either lymphatics or small capillaries) surrounding tumors. This finding is strongly associated with the presence of lymph node metastases and is a poor prognostic factor in women without lymph node metastases.

### 6. **Proliferative Rates** (Faster growth = worse result)

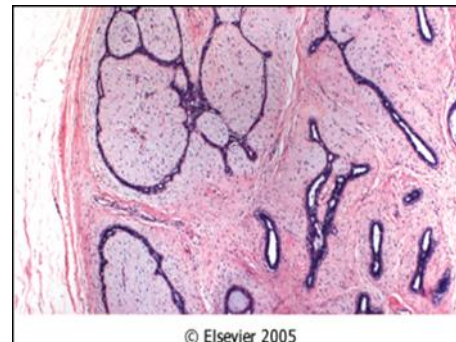
# Stromal Tumors

## Fibroadenoma :

- Common-usually Solitary. (**Most common neoplastic process of the breast**).
- **Completely benign** proliferation of both epithelial and stromal elements.
- Common before age **30** (**young Females**).
- Firm, mobile lump ("**breast mouse**"), Giant forms can occur, especially in younger patients.
- It may **increase in size during pregnancy** and **regress after menopause**.
- Rarely, carcinoma may arise within a fibroadenoma. The predominant type has been **lobular carcinoma**.

### Grossly:

Spherical nodules, well-circumscribed, movable (breast mouse)  
Cut surface is pearl-white and whorled.



**Histologically:** The tumor is composed of a mixture of ducts and fibrous connective tissue

## Phylloides Tumor :

- Phyllodes tumors, like fibroadenomas, arise from intralobular stroma. Although they can occur at any age, most present in the **sixth decade**.
- Most present as large palpable masses
- They are **fibroepithelial** tumors arranged in leaf like pattern with cellular stroma. They can be myxoid too.
- **Must be excised with wide margins to avoid the high risk of local recurrences**.
- The majority are low-grade tumors that may recur locally but only rarely metastasize.
- Rare are high-grade lesions which behave aggressively, with frequent local recurrences and distant hematogenous metastases in about one third of cases.

# Summary (from Robbin's basic pathology)

## SUMMARY

### Breast Carcinoma

- The lifetime risk of developing breast cancer for an American woman is 1 in 8.
- A majority (75%) of breast cancers are diagnosed after the age of 50.
- Risk of developing breast cancer is related to estrogen exposure, genetic factors, long duration between menarche and menopause, atypical proliferative lesions, and family history of breast cancer in a first-degree relative, particularly if the disease was multifocal or in a premenopausal woman.
- About 10% of all breast cancers are caused by inherited mutations; *BRCA1* and *BRCA2* genes account for one third of the cases associated with single-gene mutations.
- Ductal carcinoma in situ (DCIS) is a precursor to invasive ductal carcinoma and typically is found on mammographic examination as calcifications. When carcinoma develops in a woman with a previous diagnosis of DCIS, it usually is an invasive ductal carcinoma in the same breast.
- Lobular carcinoma in situ (LCIS) frequently is an incidental finding and usually is not associated with calcifications. When carcinoma develops in a woman with a previous diagnosis of LCIS, it may occur in the affected or unaffected breast and usually is invasive lobular carcinoma but may be invasive ductal carcinoma.
- The natural history of breast carcinoma is long, with metastases sometimes appearing decades after the initial diagnosis.
- Prognosis is most dependent on tumor size, lymph node involvement, distant metastasis at presentation, tumor grade, and histologic type.
- Estrogen and progesterone receptor status and expression of HER2/NEU are used primarily to determine response to treatment. Estrogen receptor-expressing tumors are more likely to respond to tamoxifen. HER2/NEU-overexpressing tumors often are treated with trastuzumab.

# Thank You!

We hope you found this helpful and informative.

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