

Breast cancer



Objectives:

Pathology of benign breast diseases.

- Know the ways that benign breast conditions can clinically present.
- Know the common inflammatory conditions of breast (mastitis and abscesses).
- Understand the pathology of fibrocystic change.
- Know the common benign breast tumours with special emphasis on fibroadenoma and phyllodes tumour.
- Know the risk of subsequent breast cancer in women with diagnosed benign breast tissue.

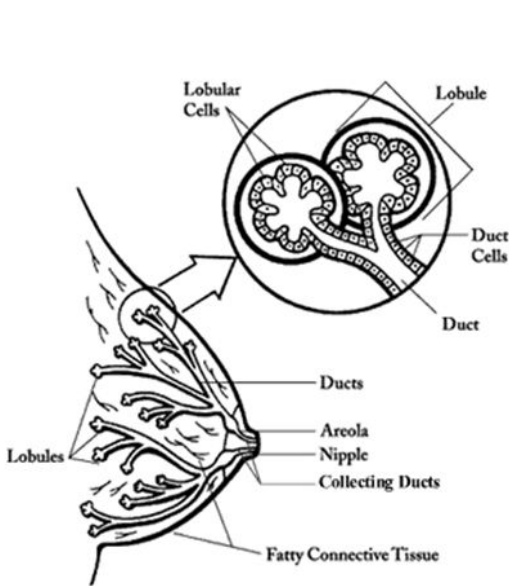
Breast cancer.

- 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.

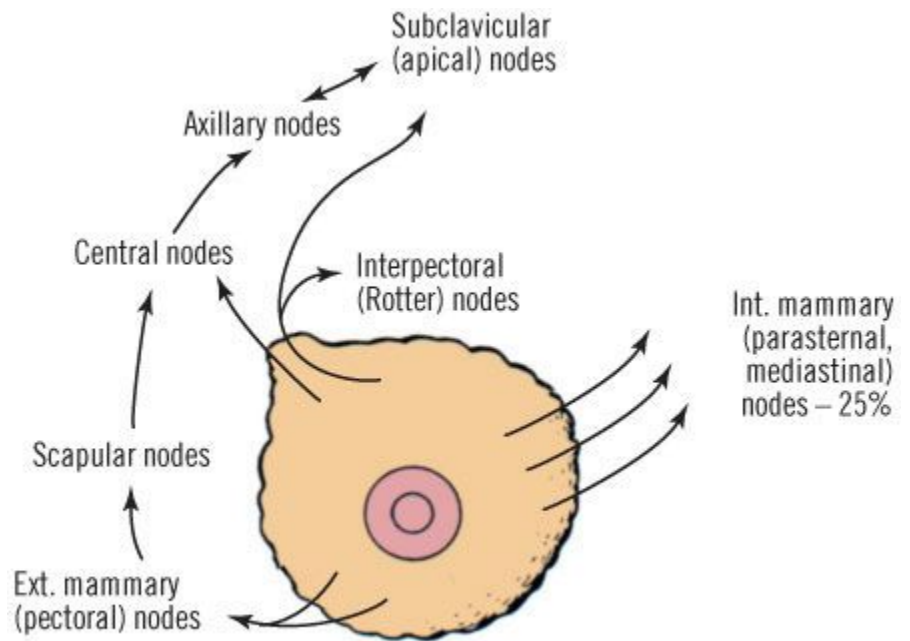
Important note: Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all or our work: [Pathology Edit.](#)

Grey = Extra
Red = Important

Introduction.



Anatomy of the breast



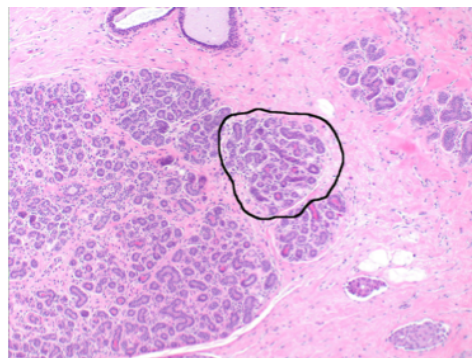
Lymphatic drainage of breast

Histology of breast:

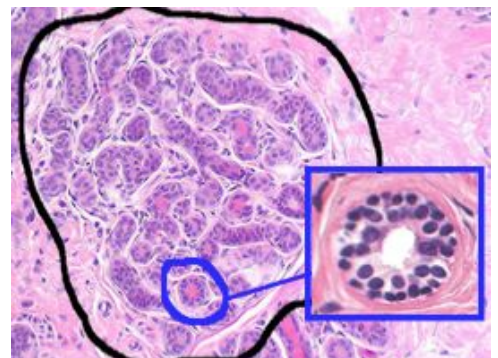
- **Lobes:** about 10 in whole breast
- **Lobules**
- **Acini/Alevoli:** Each acini is lined by a **bilayered epithelial and myoepithelial cells.**
- **Ducts:** (eventually leads to the lactiferous duct which opens → nipple)
 - Six to ten major ductal systems originate at the nipple .
 - Branching of the large ducts leads to the terminal duct lobular units.
 - The TDU branches into grapelike clusters of small acini to form the lobule.



Lobe

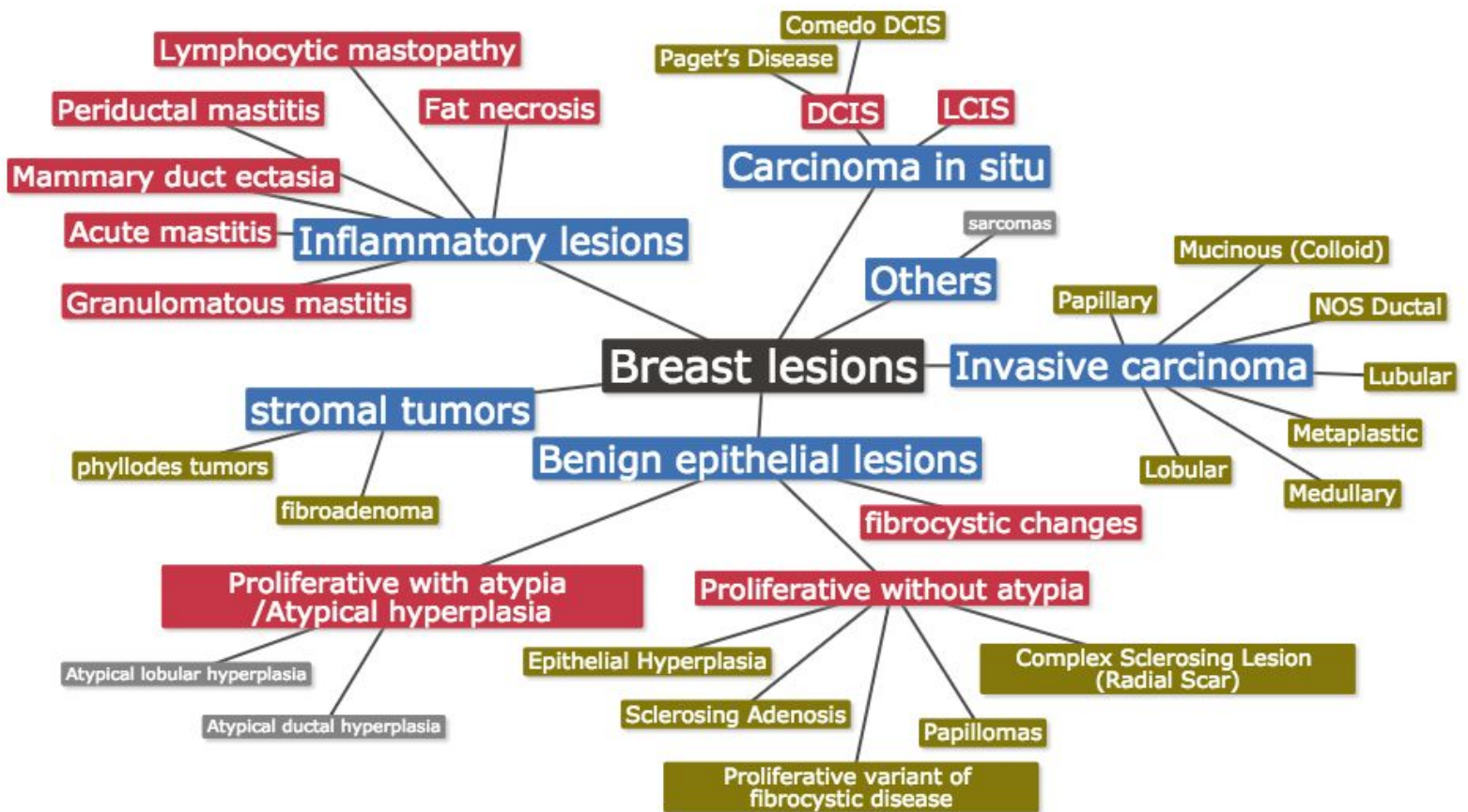


Lobule



Acini

Mind Map.



Clinical Presentation of Breast Diseases.

Prefix | **mast-** : Relating to a breast or nipple. (e.g. Mastitis, Mastalgia.. Etc.)

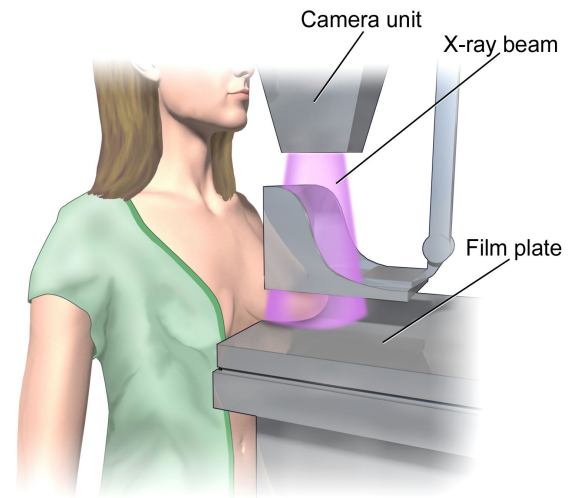
- 1) **Pain (mastalgia):** is the most common breast symptom. May be cyclical (with menses) or noncyclical. Diffuse cyclical pain¹ has no pathologic significance. **Non-cyclical pain** can be caused by **ruptured cysts or areas of prior injury or infection**, or no specific cause. *Although the great majority of painful masses are **benign**, about 10% of breast cancers present with pain.*
- 2) **Palpable mass. (Lumps)**
- 3) **Nipple discharge:**
 - **Milky discharge:** **not** associated with malignancy.
 - **Bloody or serous discharges:** commonly associated with **benign** lesions but can rarely be due to a malignancy.



¹is the most common type of breast pain, It may be caused by the normal monthly changes in hormones. This pain usually occurs in both breasts.

Mammographic screening.

- Mammographic screening was introduced in the 1980s as a means to detect small, nonpalpable, asymptomatic breast carcinomas.
- The value of mammography lies in its ability to identify *small, nonpalpable cancers*.
- Mammographic screening is generally *recommended to start after age 40*. Younger women undergo mammography is done only if they are at **high risk** for developing carcinoma e.g. first degree history.



Benefits of mammography:

1. number of women with invasive/advanced cancer is markedly decreased.
2. The mortality rate have started to decline. Currently only 20% of the women with breast cancer are expected to die of the disease.

The principal mammographic findings of breast carcinoma are densities/masses and calcifications:

1. **Densities (mass):** Most tumors appear radiologically denser than the normal breast. Invasive carcinomas, *Fibroadenomas*, or cysts etc. can also present as densities. (doesn't have to be malignant)
2. **Calcifications:** Calcium gets deposited in secretions, necrotic debris, or hyalinized stroma. It can be seen in **benign and malignant** conditions.
 - Calcifications in malignancy are usually *small, irregular, numerous, and clustered*.
 - **Ductal carcinoma in situ (DCIS)** (*non invasive and nonpalpable*) is most commonly detected as *mammographic calcifications*. Mammographic screening has increased the diagnosis of DCIS.

(Note: generally calcifications are more serious than densities, with a higher possibility to indicate cancer)

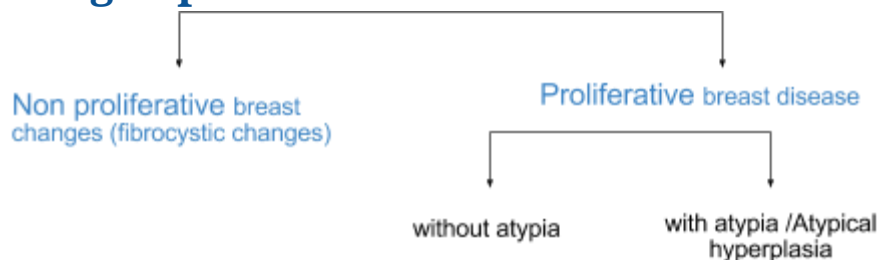
Breast lesions.

Inflammatory lesions.

Mastitis is an infection of the breast tissue that results in breast pain, swelling, warmth and redness. You also might have fever and chills.

- **Acute mastitis:** Almost all cases of acute mastitis occur during the first month of breastfeeding. ***Staphylococcus aureus*** is the most common causative organism. The breast is erythematous and painful, and fever is often present.
- **Periductal mastitis:** not associated with lactation. There is a strong association with **cigarette smoking**.
- **Mammary duct ectasia:** means dilated ducts disease beneath the nipple.
- **Fat necrosis:** is usually due to **mechanical trauma, surgical** or otherwise.
- **Lymphocytic mastopathy:** (sclerosing lymphocytic lobulitis) seen in **diabetics**.
- **Granulomatous mastitis:** sarcoid, TB, etc., but mostly idiopathic.

Benign epithelial lesions.



1- Non proliferative Breast Changes (fibrocystic changes).

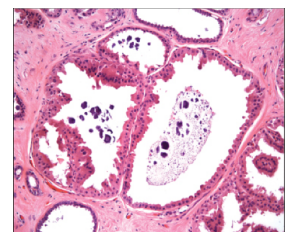
- Are the **most common** disorder of the breast.
- Age: 20-55yrs (premenopausal women) that's why it's thought to be caused by hormonal imbalances.
- Decreases progressively after menopause.
- **No increased risk for cancer (fibrocystic changes).**

Clinical presentation:

- Present as vague irregularity of breast tissue (**lumpy breast**) usually in the upper outer quadrant.
- Mammographic densities, calcifications, or nipple discharge.
- May also present with cyclical pain.

Histology: Three patterns are seen:

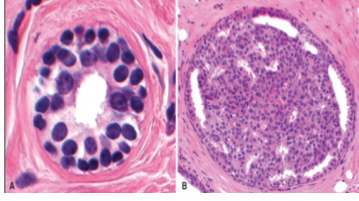
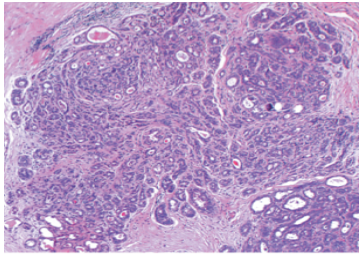
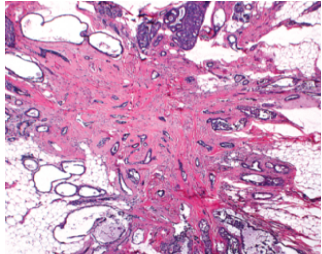
1. **Cysts formation with apocrine metaplasia:** Cysts are lined by benign flattened to columnar epithelium with focal apocrine metaplasia. Apocrine cysts (see pic) are large polygonal cells with abundant eosinophilic cytoplasm, resembling the cells of *normal apocrine sweat glands*. The secretions **within** cysts may calcify and can be **detected in mammograms**. The cysts can rupture and cause inflammation.
2. **Fibrosis:** Increase in fibrous stroma → contribute to the palpable firmness of the breast
3. **Adenosis:** Increase in the number of acini per lobule (adenosis can also be seen in pregnancy).

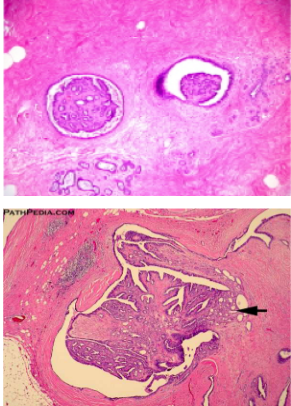


2- Proliferative Disease without Atypia.

- Rarely form palpable masses
- Detected as small mammographic densities.
- Incidental finding
- Increased Risk for cancer is 1.5 – 2 times

The following entities are included in this category:

<p>Epithelial Hyperplasia (usual epithelial hyperplasia)</p>	<p>Epithelial hyperplasia is defined as the presence of more than 2 layers. While the Normal breast has 2 layers of cells:</p> <ol style="list-style-type: none"> 1. epithelial or luminal cells 2. myoepithelial cells <ul style="list-style-type: none"> ● Hyperplasia can range from mild, moderate to severe/florid. ● Both epithelial and myoepithelial cells proliferate. ● It can be seen in the ducts and the lobules. ● When it is seen in fibrocystic disease: it is called as proliferative type/variant of fibrocystic disease. 	 <p>A. Normal. B. Epithelial hyperplasia characterized by</p> <ul style="list-style-type: none"> ● Lumen is filled with heterogeneous cells both luminal & myoepithelial cell types. ● Irregular slit-like fenestrations are prominent at the periphery.
<p>Sclerosing Adenosis</p>	<ul style="list-style-type: none"> ● Commonly seen as an incidental microscopic finding but may occasionally present as a palpable mass → <i>that's why mistaken by cancer.</i> ● It is almost always associated with other forms of fibrocystic change. ● Calcification is commonly seen in the lesion, so even on mammography it can mimic cancer. ● Grossly: hard, rubbery consistency and similar to breast cancer ● <u>The presence of double layers of epithelium and myoepithelium are helpful in correct diagnosis</u> 	 <p>adenosis (proliferation of luminal spaces) lined by epithelial cells and myoepithelial cells yielding with stromal fibrosis (masses of small glands within the struma) in the lobule which leads to compression and distortion of the lobule.</p>
<p>Complex Sclerosing Lesion (Radial Scar)</p>	<ul style="list-style-type: none"> ● Radial scars are stellate lesions characterized by a central nidus of entrapped glands in a hyalinized stroma ● They typically present as an irregular mammographic density and closely mimic an invasive carcinoma both mammographically and grossly. ● The word "scar" refers to the morphologic appearance, not a prior inflammation, trauma or surgery. 	 <p>There is a central nidus consisting of small tubules entrapped in a densely fibrotic stroma surrounded by radiating arms of epithelium with varying degrees of cyst</p>

		formation and hyperplasia.
Papillomas	<p>Is a papillary tumor (finger like projection) that arises from the ductal epithelium. Has two forms:</p> <ul style="list-style-type: none"> ● Large duct papillomas (central papillomas): usually solitary and situated in the lactiferous duct at the nipple. Patients present with bloody nipple discharge and sometimes a subareolar palpable mass. It's more common ● Small duct papillomas: commonly multiple and located deeper within the ductal system. Small duct papillomas have been shown to increase the risk of subsequent carcinoma. 	
Proliferative variant of fibrocystic disease	-	

3- Proliferative breast disease with atypia (Atypical hyperplasia).

-
- Risk for cancer is **4-5 times** normal (**↑ risk for cancer**)
- **Atypical hyperplasia** is a cellular proliferation resembling **ductal carcinoma in situ (DCIS)** or **lobular carcinoma in situ (LCIS)** but **lacking sufficient qualitative or quantitative features for a diagnosis of carcinoma in situ.**
- **Include two entities:**
 - a. Atypical ductal hyperplasia (ADH)
 - b. Atypical lobular hyperplasia (ALH)
- Atypical hyperplasia has **some** of the architectural and cytologic features of carcinoma in situ but **lack the complete criteria** for that diagnosis and is categorized as ductal or lobular in type

Carcinoma in situ.

- a) DCIS
- b) LCIS

Invasive carcinoma.

- a) Ductal carcinoma
- b) Lobular carcinoma

Others/stromal tumors: e.g. fibroadenoma, phyllodes tumors, sarcomas.

Breast Cancer.

- Carcinoma of the breast is one of the **most common cancer in women**.
- Women who live to age 90 have a one in eight chance of developing breast cancer

Breast cancer risk factors:

- ★ The etiology of breast cancer 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).

Age	Increased incidence in older women Majority >50 yrs of age. Rare before 25 years (except in familial forms).
Estrogen Exposure	<p>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:</p> <ul style="list-style-type: none"> ● 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	<ul style="list-style-type: none"> ● 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 <p>★ NOTE: majority of cancers occur in women without such history.</p>
Race & Geographic influence	<ul style="list-style-type: none"> ● 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.
Radiation exposure	Higher rate of breast cancer
History of breast cancer	In Same breast cancer or have cancer in the other breast are at increased risk of developing a second primary breast cancer .
History of Other Cancer	Example: ovarian or endometrial cancer are at high risk .
Certain Breast Disease	Benign breast disease are at risk. Especially a breast biopsy diagnosis of atypical hyperplasia increases the risk for breast cancer .
Dietary factors	Example: high fat intake and excessive alcohol consumption , and exposure to ionizing radiation .
Obesity	-

Environmental toxins	pesticides ² .
Exercise	Lower risk with exercise.
Breast feeding	The longer the women breastfeed, the lower the risk.
Tobacco	Not associated with breast cancer, but associated with the development of <i>peri-ductal mastitis, or sub-areolar abscess.</i>

Classification depending on etiology:

1- Hereditary Breast Cancer. (family history or germ line mutation)

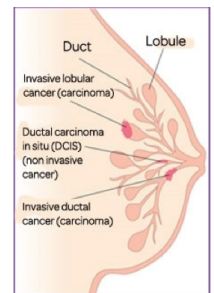
- ★ A family history of breast cancer in a **first-degree relative**.
- ★ About 25% of familial cancers (or around 3% of all breast cancers) can be attributed to two autosomal-dominant genes: **BRCA1 and BRCA2**

2- 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 **overexpression of estrogen**

Classification Depending on the site and extension:

Almost all (majority) are adenocarcinoma				
Types	Ductal		lobular	
Subtypes	Carcinoma in situ (non-invasive)	Invasive carcinoma	Carcinoma in situ (non-invasive)	Invasive carcinoma



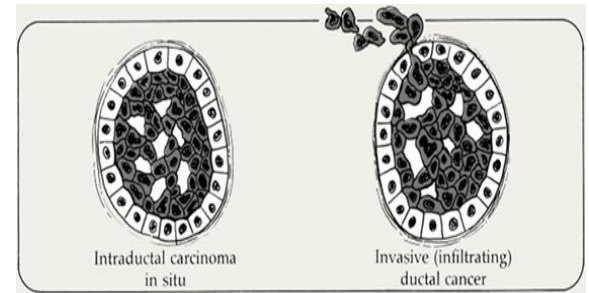
² Pesticides are substances meant for attracting, seducing, and then destroying any pest (insects).

Carcinoma in situ.

This is epithelial proliferation that is still confined to the TDLU³, 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%).

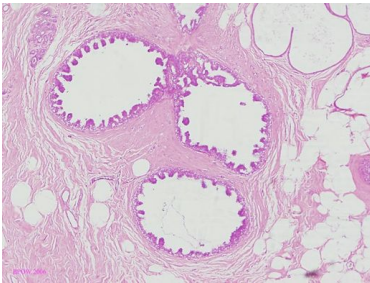


Ductal Carcinoma In Situ (DCIS).

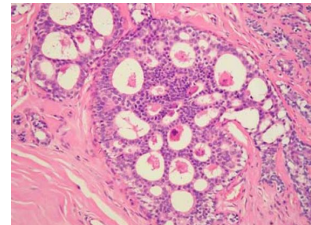
DCIS is the **non-invasive** proliferation of malignant cells within the duct system **without** breaching the underlying **basement membrane**.

Different patterns/subtypes

- **Comedo (central necrosis)** has essentially a **100%** chance of becoming invasive if left untreated. **It** 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*** (cells arranged around “punched-out” spaces)
 - **papillary, Micropapillary***
 - **solid**(cells fill spaces)
- *Pure cribriform/micropapillary carries only a **30%** chance of becoming invasive carcinoma.



Micropapillary DCIS.



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

Diagnosis

- On mammography DCIS frequently shows microcalcifications and it's sensitive diagnostic procedure for detecting DCIS → the reason of the increased diagnosis of DCIS in the last two decades.
- majority of DCIS are not palpable → due not spreading to basement membrane Less frequently they can present as a mammographic density or a vaguely palpable mass or nipple discharge.

³ Terminal ductal-lobular unit.

Prognosis

- They have a **very high risk** of development of subsequent invasive carcinoma.
- The tumor distends and distorts⁴ the ducts.
- Often **multifocal—malignant**⁵ cells can spread widely through the ductal system **without** breaching the **basement membrane**
- Women with DCIS are at risk of **recurrent** DCIS following treatment.

Treatment

Wide local excision⁶& Mastectomy⁷

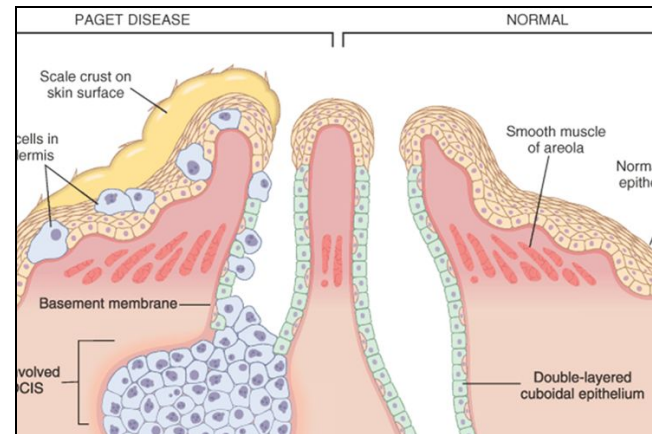
Comedo DCIS.

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*.

Paget's Disease.

Paget's disease of the breast is DCIS that extends into skin nipples. which characterized by a **red, scaly eczematous, unilateral lesion on the nipple and surrounding areola**.

- Paget's disease may be subtle or appear as an **eroded and weeping erythematous eruption**. **Pruritus** is common and it might be **mistaken for eczema**.
- In almost all cases, an underlying carcinoma is present.
- Malignant cells are called **Paget cells** and are found **scattered in the epidermis**

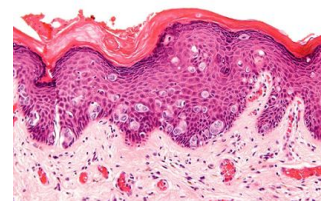
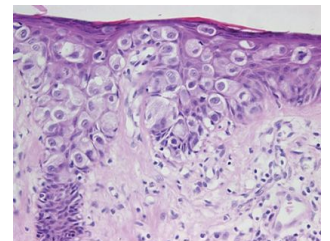


Histology

- The hallmark of Paget's disease is the infiltration of the epidermis by **large ductal neoplastic 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**.

Gross: Palpable mass can be seen in 50% of women with Paget disease indicating an underlying **invasive** carcinoma near by.

Prognosis: based on the underlying carcinoma and is not affected by the presence of Paget disease .



⁵ If there is more than one tumor in the breast, the breast cancer is described as multifocal, tend to develop in the same quadrant of the breast.

⁶ Only the lump or area of cancer removed

⁷ The whole breast removed

Lobular Carcinoma in Situ (LCIS).

LCIS is malignant proliferation of cells lobules and is always an **incidental** finding in breast biopsy performed for another reason, because:

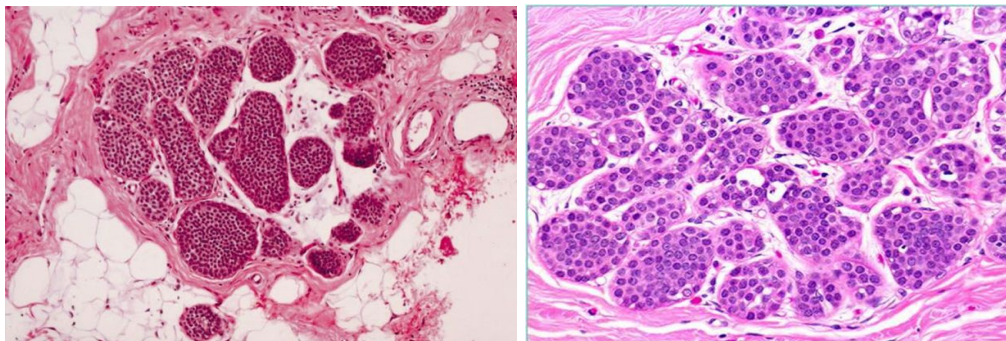
1. LCIS **does not** form a palpable mass and cannot be detected clinically on palpation or on gross pathological examination
 2. Microcalcifications in LCIS are **infrequent** and so mammography is not useful for detection.
- LCIS is uncommon and there's no invasion of basement membrane
 - LCIS tends to be **multicentric and bilateral** and therefore subsequent carcinomas can occur both breasts. And $\frac{1}{3}$ of women with LCIS will eventually develop invasive carcinoma (lobular (mostly) or ductal).

Histology:

- **monomorphic** (uniform appearance) population of **small, rounded** cells fills & expands the acini of lobules. The underlying lobular **architecture can still be recognized**.
- Intracellular mucin vacuoles (sometimes forming **signet ring cells**) are common.

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 risk of carcinoma in both breasts and a direct precursor of some cancers.



Invasive Breast Carcinoma.

Invasive breast carcinoma is tumor that has extended **across the basement membrane** → This **permits access** to lymphatics and vessels → potential to **metastasize**.

Invasive breast carcinoma is subdivided into:

1. **NOS Ductal** 70-80% (NOS= no otherwise specified)
2. **Lobular** 10%
3. **Lubular** 6%
4. **Mucinous (Colloid)** 2%
5. **Medullary** 2%
6. **Papillary** 1%
7. **Metaplastic Carcinoma** 1%



CLINICAL FEATURES OF INVASIVE BREAST CANCER:

- **Palpable mass.**
- When the tumor involves the **central portion** of the breast, **retraction of the nipple** may develop .
- Larger carcinomas may be **fixed** to the chest wall (pectoral muscles or deep fascia) or cause **dimpling of the skin** .

Regarding Lymph nodes:

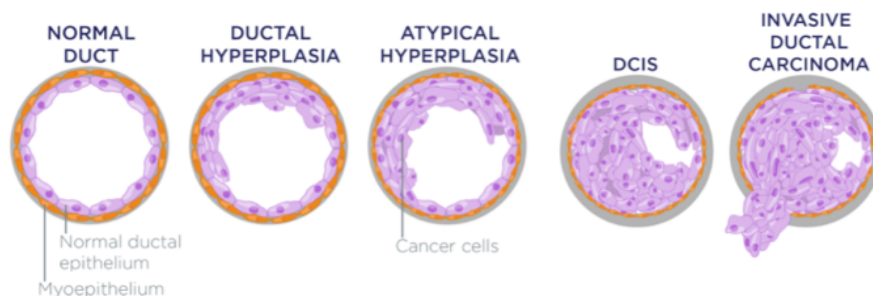
- About half of the patients will have **axillary lymph node metastases**
- Lymphatics may become involved and the lymphatic drainage of that area and the overlying skin gets blocked causing **localized lymphedema** and **thickening of the skin** of the breast with exaggerated hair follicles, a change referred to as **peau d'orange (orange peel)**.
- The term "**inflammatory carcinoma**" refers 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.

On mammography:

- Commonly present as a **density**.
- presenting as **mammographic calcifications** **without** an associated density are usually very small in size.

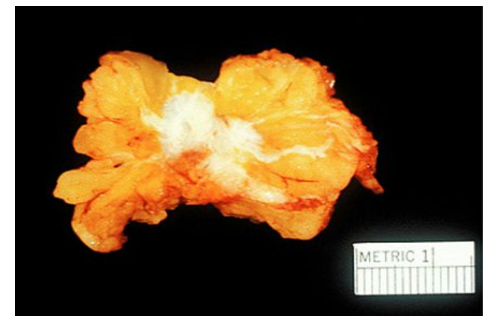
Invasive Ductal Carcinoma, NOS.

- The **commonest 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 hard consistency (scirrhous carcinoma)**. And therefore a hard 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**.
- Accompanied by varying amounts of DCIS.
- About Two third **Expresses Estrogen or Progesterone** Receptors , and the other One Third shows an **overexpression of HER2/NEU** genes .



Gross

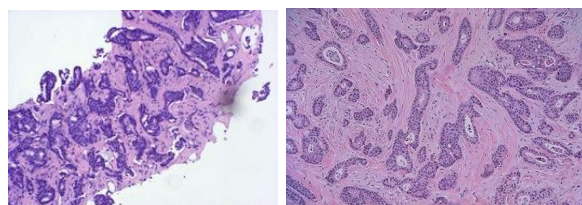
- Grossly: tumor is **firm, hard, with an irregular border**.
- Cut surface: gritty and shows irregular margins with **stellate infiltration** (sometimes it can be soft and well demarcated) and in the center there are small foci of **chalky white stroma** and occasionally **calcifications**.
- Characteristic **grating sound** when cut or scraped.



Histology

- **Large and pleomorphic** cells 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.

Treatment: Carcinomas associated with a large amount of DCIS require large excisions with wide margins to reduce local recurrences

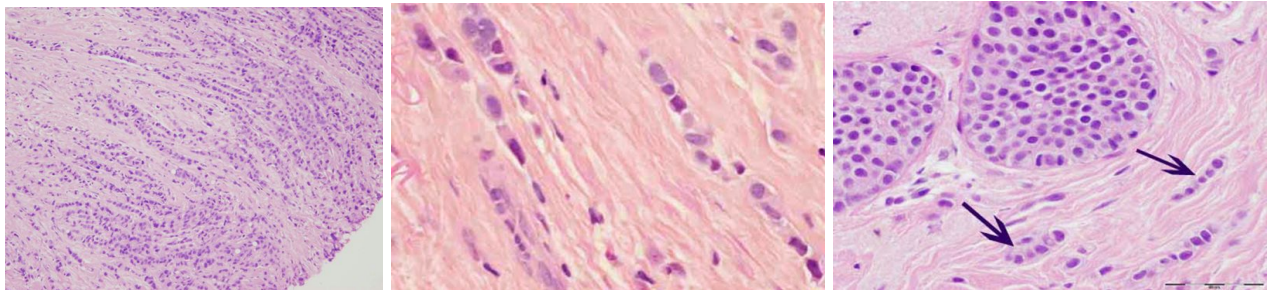


Invasive Lobular Carcinoma.

- It is the **second most common type** of invasive breast cancer forming up to 10% of breast cancers.
- Cells are morphologically identical to LCIS
- The tumor may occur alone or in combination with ductal carcinoma.
- It tends to be **bilateral and multicentric**.
- 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**
- This type of cancer, unlike other breast tumors exhibits a **unique type of metastases**, they spread to CSF, GI tract, serosal surfaces & Bone marrow as well as ovary & uterus.

Histology:

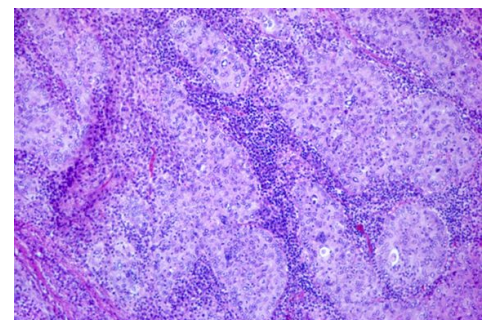
- single infiltrating malignant cells, forming a **line often one cell width** (called as **indian file pattern**). **No** tubules or papillary formation.
- The Cells invade the stroma individually and aligned in a **“Single File”** strands , often correlates with the presence of mutations that abrogate the function of **E-Cadherin** (which is a surface protein that contributes to the adhesion of normal breast epithelial cells)



Invasive lobular carcinoma with area of lobular carcinoma in situ also

Medullary Carcinoma.

- This subtype of breast cancer presents as a well **circumscribed mass**.
- May be **mistaken** clinically and **radiologically for fibroadenoma**.
- Increase risk in women with **BRCA1 mutations**.
- **No expression** of Estrogen and progesterone receptors and **No overexpression of HER2/NEU** (usually referred as **Triple-Negative**).
- It does not produce any fibroblastic (desmoplastic) reaction and therefore is soft and fleshy.



Histology:

- **solid sheets of malignant** cells surrounded by **many lymphocytes and plasma cells**.
- There is scant fibrous stroma.

Colloid Carcinoma/ Mucinous carcinoma.

- Tends to occur in **older women**.
- It is **sharply circumscribed**, lacks fibrous stroma and is slow growing.
- **Most express hormone receptors**
- Is soft 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**.



Treatment: Wide local excision OR Radical mastectomy.

Major prognostic factors of breast carcinoma.

TNM (Tumor size, lymph Node metastasis, distant Metastasis)

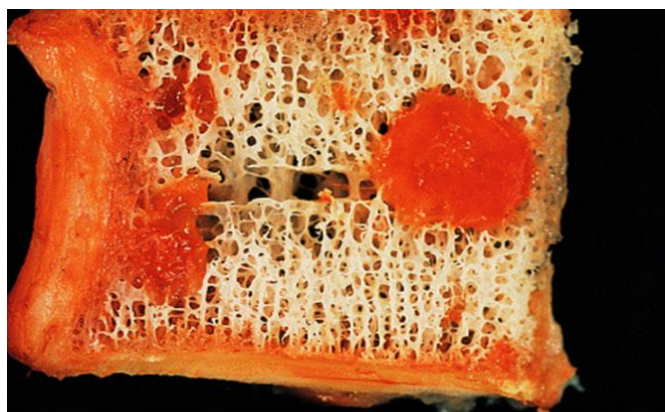
1. **Invasive or In situ disease:**
 - A. Invasive carcinoma has poorer prognosis as **it can metastasize**.
 - B. In-situ carcinoma is confined to the ductal/lobular system and **cannot metastasize**, so it has better prognosis.
2. **Distant metastasis:** Once distant metastases is present, **cure is unlikely**, although long-term remissions and palliation can be achieved. Favored sites for dissemination are the lungs, bones, liver, adrenals, brain, and meninges.
3. **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.
4. **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.

Note: all the above parameters are used to stage the tumor. Stage is a combination of size, lymph node status and distant metastasis. 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 and 4 or more positive nodes have the worse prognosis.

5. **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.
6. **Inflammatory Carcinoma:** Women presenting with the clinical appearance of breast swelling and skin thickening have a poor prognosis.

Minor prognostic factors of breast carcinoma.

1. **Histologic Subtype:** Infiltrating ductal and lobular carcinomas have the **worst prognosis**. Medullary and mucinous have intermediate prognosis. And tubular and cribriform have the **most favorable** prognosis
2. **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.
3. **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 chemotherapy drugs e.g. **Tamoxifen**. Therefore it is mandatory to identify which tumors are **ER/PR positive as they respond well to chemotherapy** and have **better prognosis** when compared to ER/PR negative tumors.
4. **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 called 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.
5. **Lymphovascular invasion:** is strongly associated with the **presence of lymph node metastases** and is a poor prognostic factor.
6. **Proliferative rates:** ki67 index, the **faster** it grows the **worse** the result is.

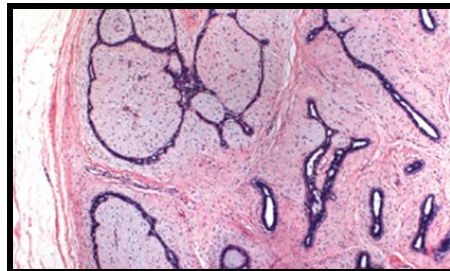


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Metastasis to vertebra

STROMAL TUMORS.

	Fibroadenoma (FA)	Phylloides tumor
Incidence	<ul style="list-style-type: none"> ● Any age, most common before age 30. ● The most common benign tumor of the female breast. ● It is composed of benign proliferation of both <u>epithelial</u> and <u>stromal</u> elements (completely benign and almost never malignant) 	<ul style="list-style-type: none"> ● tumor can occur at any age, but most present in the 40s and 50s, that is 10 to 20 years later than the average presentation of a fibroadenoma ● less common than fibroadenomas ● They are usually benign or low-grade tumors that may recur locally. ● High-grade Phyllodes tumors are uncommon and they behave aggressively, with frequent local recurrences and distant metastases.
Clinical presentation	<ul style="list-style-type: none"> ● Firm, mobile lump (“breast mouse”). ● It may increase in size during pregnancy. It may stop growing & regress after menopause. 	
Grossly	<ul style="list-style-type: none"> ● Spherical nodules, sharply demarcated and circumscribed from the surrounding breast tissue ● freely movable and can be shelled out. ● Size vary (1cm to 10 cm in diameter). Cut surface: pearl-white and whorled ● solitary (might multiple and involves both breasts) 	Most present as large palpable masses (usually 3 to 4 cm in diameter)
Histology	Tumor is composed of a mixture of ducts and fibrous connective tissue	They are fibro epithelial tumors arranged in leaf like pattern with cellular stroma.
Treatment	lumpectomy (only the lump is removed)	excised with wide margins to avoid the chances of local recurrences.



Fibroadenoma: The lesion consists of a proliferation of intra-lobular stroma surrounding and often pushing and distorting the associated epithelium. The border is sharply delimited.

Summary.

Inflammatory lesions	Relation	Cause
Acute mastitis	1st month of breastfeeding	Staph infection
Periductal mastitis	not associated with lactation	cigarette smoking
Fat necrosis	-	mechanical trauma, surgical
Lymphocytic mastopathy	diabetics	-
Granulomatous mastitis	-	sarcoid, TB, but mostly idiopathic

Benign Epithelial Lesions	Cancer risk	Histology	Comment
Non proliferative	No	Cysts with apocrine metaplasia & Fibrosis & Adenosis	<ul style="list-style-type: none"> ● ↓↓ after menopause ● Produce palpable breast mass
Proliferative without atypia			
Form palpable masses rarely & incidental finding and detected as small mammographic densities			
Epithelial Hyperplasia	1.5 – 2	Irregular slit-like fenestrations	<ul style="list-style-type: none"> ● presence of more than 2 layers ● Both cells proliferate ● Seen in ducts & lobules
Sclerosing Adenosis		Adenosis stromal fibrosis	<ul style="list-style-type: none"> ● Associated with other forms of fibrocystic change ● Calcification ● Can mimic cancer
Complex Sclerosing		Central nidus	<ul style="list-style-type: none"> ● Mimic an invasive carcinoma
Papillomas			
Arises from ductal epithelium and more common in large lactiferous ducts in central part			
Large duct	1.5 – 2	Solitary and in lactiferous duct	<ul style="list-style-type: none"> ● Bloody nipple discharge ● Subareolar palpable mass
Small duct		Multiple and deeper within ductal system	<ul style="list-style-type: none"> ● Increase the risk of subsequent carcinoma
Proliferative with atypia	4 – 5	Atypical hyperplasia	<ul style="list-style-type: none"> ● Resembling ductal & lobular carcinoma in situ ● Lacking sufficient features for a diagnosis of carcinoma in situ

Inflammation of breast	
<p>Acute mastitis :-</p> <ul style="list-style-type: none"> ❖ Purulent nipple discharge. ❖ Acute mastitis due to <i>S. aureus</i> ❖ Usually occurs during lactation or breast-feeding. 	<p>Silicone breast implant :- EXTRA</p> <ul style="list-style-type: none"> ❖ Polymer of silica, oxygen, and hydrogen. ❖ Silicone gel can leak, or the implant can rupture <ul style="list-style-type: none"> ➢ Silicone produces foreign body giant cells and chronic inflammation. ➢ Association with autoimmune disease has not been proved.
<p>Mammary duct ectasia (plasma cell mastitis):-</p> <ul style="list-style-type: none"> ❖ Affects 25% of women in menopause. ❖ Main ducts fill up with debris. <ul style="list-style-type: none"> ➢ Causes dilation, rupture, and inflammation. ➢ Greenish brown nipple discharge. ❖ May produce skin and nipple retraction simulating cancer. ❖ No increased risk for breast cancer. ❖ Treatment : Antibiotics if infection is present, Surgical removal of blocked duct. 	<p>Traumatic fat necrosis:-</p> <ul style="list-style-type: none"> ❖ Trauma to breast tissue. ❖ Microscopic findings:- <ul style="list-style-type: none"> ➢ Lipid-laden macrophages with foreign body giant cells. ➢ Fibrosis, dystrophic calcification. ❖ Painless (Painful in acute stage) , indurated mass. ❖ May produce skin retraction simulating cancer
Factors that increase and decrease the risk for breast cancer.	
Factors that increase the risk for breast cancer	Factors that decrease the risk for breast cancer
<ol style="list-style-type: none"> 1. Prolonged estrogen stimulation 2. Family history and genetics <ol style="list-style-type: none"> a. Increased risk if breast cancer involves first-generation relatives(Mother, sister) b. Genetic basis is involved in <10% of cases. <ol style="list-style-type: none"> i. Autosomal dominant BRCA1 and BRCA2 association ii. Li-Fraumeni multicancer syndrome (Inactivation of p53 suppressor gene) iii. Other gene relationships (RAS oncogene, ERBB2, RB1 suppressor gene) 3. Atypical ductal hyperplasia. 4. Endometrial cancer, ionizing radiation, smoking cigarettes. 	<ol style="list-style-type: none"> 1. Breast-feeding 2. Moderate or vigorous physical training 3. Healthy body weight

Benign breast tumors and fibrocystic changes

TYPE	COMMENT
Fibroadenoma	Most common breast tumor in women <30 years old.
	Most commonly diagnosed breast tumor.
	Develop in 50% of women who receive cyclosporine after renal transplantation.
	Discrete movable, painless or painful mass. Multiple lesions may be present (10%–15% of cases).
	Benign tumor derived from the stroma <ul style="list-style-type: none"> ❖ Stroma proliferates and compresses the. ❖ Duct epithelium is not neoplastic.
	Increases in size during pregnancy(Estrogen sensitive).
	May spontaneously disappear or involute during menopause.
	Do not progress into cancer; however, breast cancer may secondarily develop within duct epithelial cells as a separate event (3% of cases).
	Diagnosis: Fine needle or core needle biopsy. Treatment : Surgical removal and Cryoablation.
Phyllodes tumor	Bulky tumor derived from stromal cells.
	Most often benign but can be malignant in some cases(Hypercellular stroma with mitoses are signs of malignancy).
	Phyllodes tumor: benign, borderline, or malignant stromal tumor; depends on stromal cellularity.
	Lobulated tumor with cystic spaces containing leaf-like extensions.
	Treat by wide excision because it is Often reach a massive size.
Intraductal papilloma	Most common cause of a bloody nipple discharge in women <50 years old
	Develop in the lactiferous ducts or sinuses
	No increased risk for cancer
	Surgically remove the duct or sinus.
Fibrocystic change	Small and large cysts <ul style="list-style-type: none"> ❖ Some cysts hemorrhage into the cyst fluid. (Called “blue-domed” cysts). ❖ Vary in size with the menstrual cycle. ❖ No malignant potential. ❖ May have to surgically remove if recurrent.
	Fibrosis.
	Sclerosing adenosis <ul style="list-style-type: none"> ❖ Proliferation of small ductules/acini in the lobule. <ul style="list-style-type: none"> ➢ Pattern is often confused with infiltrating ductal cancer. ❖ Often contain microcalcifications.
	Ductal hyperplasia <ol style="list-style-type: none"> 01. Ducts are estrogen sensitive. 02. Pathologic findings. <ol style="list-style-type: none"> a. Papillary proliferation is called papillomatosis. b. Apocrine metaplasia refers to the presence of large, pink-staining cells. c. Atypical ductal hyperplasia.

Types of Breast Cancer	
Type	Comment
Noninvasive	
Ductal carcinoma in-situ (DCIS)	Nonpalpable.
	Patterns: cribriform (sieve-like), comedo (necrotic center).
	Commonly contain microcalcifications; cannot be detected by mammogram unless microcalcifications are present.
	One-third eventually invade.
Lobular carcinoma in-situ (LCIS)	Treated with lumpectomy.
	Nonpalpable; virtually always an incidental finding in a breast biopsy for other reasons; cannot be identified by mammography (no calcifications).
	Lobules are distended with bland neoplastic cells; one-third eventually invade; usually positive for estrogen and progesterone receptors.
invasive	
Infiltrating ductal carcinoma	Increased incidence of cancer in the opposite breast (20%–40% of cases).
	Stellate morphology (noted in the gross specimen and mammogram), indurated, gray-white tumor.
	About Two third Expresses Estrogen or Progesterone Receptors , and the other One Third shows an overexpression of HER2/NEU genes (One third have amplification of the <i>ERBB2</i> oncogene)
Paget disease of nipple	Gritty on cut section; induration is caused by reactive fibroplasia (desmoplasia) of the stroma to the tumor.
	Extension of DCIS into the lactiferous ducts and skin of the nipple producing a rash, with or without nipple retraction.
	Palpable mass is present in 50%–60% of cases.
Medullary carcinoma	Associated with <i>BRCA1</i> mutations.
	Majority are negative for estrogen and progesterone receptors.
	Bulky, soft tumor with large cells and a lymphoid infiltrate.
Inflammatory carcinoma	Erythematous breast with dimpling like an orange (peau d'orange) due to fixed opening of the sweat glands, which cannot expand with lymphedema.
	Plugs of tumor blocking the lumen of dermal lymphatics cause localized lymphedema.
	Very poor prognosis.
	Combination chemotherapy followed by surgery and irradiation.
Invasive lobular carcinoma	Neoplastic cells are arranged linearly or in concentric circles (bull's-eye appearance) in the stroma; invasive carcinoma develops in contralateral breast in 5%–10% of cases.
Tubular carcinoma	Develops in terminal ductules.
	Increased incidence of cancer in opposite breast (10% of cases).
Colloid (mucinous) carcinoma	Usually occurs in elderly women.
	Neoplastic cells are surrounded by extracellular mucin.

MCQ's.

- 1) Which of the following is NOT a risk factor in the development of breast cancer in women?
- A) Age
 - B) Age of menarche
 - C) Race
 - D) Long periods of breastfeeding
- 2) Which of the following breast lesions are non-invasive malignancies?
- A) Intraductal carcinoma
 - B) Tubular carcinoma and mucinous carcinoma
 - C) Infiltrating ductal carcinoma and lobular carcinoma
 - D) Medullary carcinoma, including atypical medullary lesions
- 3) Which of the following is the most common benign tumor of the female breast.
- A) Fibroadenoma
 - B) Phyllodes tumor
 - C) Intraductal papilloma
 - D) Fibrocystic change
- 4) After intraductal papilloma, unilateral bloody nipple discharge from one duct orifice is most commonly caused by which of the following pathologic conditions?
- A) Paget's disease of the nipple.
 - B) Intraductal carcinoma.
 - C) Inflammatory carcinoma.
 - D) Subareolar mastitis.
- 5) 28. Which of the following statement is true concerning the histologic variants of invasive breast carcinoma?
- A) The presence of an in situ component with invasive ductal carcinoma adversely affects prognosis
 - B) Mucinous or colloid carcinoma is one of the more common variants of invasive ductal cancer
 - C) Invasive lobular carcinoma is associated with a higher incidence of bilateral breast cancer
- 6) 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. 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

Answers: 1-D 2-A 3-A 4-B 5-C 6-B

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com

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Ask us: www.ask.fm/Pathology434

GOOD LUCK !!

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منى القحطاني
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**PUSH YOURSELF
BECAUSE, NO ONE
ELSE IS GOING
TO DO IT FOR YOU.**