

**Breast
Surgery**

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هذا العمل صدقة عن روح والدي حسان حزيني، وعن روح زميلنا وأخونا باشق جهاد صباح، وعن روح معلمتنا الفاضلة ايناس شطناوي، وابنائها عمر ومبين -رحمهم الله جميعا-.

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في حال وجود ملاحظات او اخطاء يرجى التواصل معنا.

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Introduction

Anatomy of the breast

▪ Location

The breasts are paired specialized accessory glands that secrete milk. They are located on the ventral thorax below the subcutaneous tissue in superficial fascia of pectoral region, and on the muscles of ventral thorax (pectoralis major, rectus abdominis and serratus anterior). The base of the breast extends from **the 2nd to 6th rib** and from the lateral margin of **the sternum to the mid-axillary line**. They are divided into four quadrants: upper lateral, upper medial, lower lateral, and lower medial, and the axillary tail (axillary tail of **Spence**) which extends upward and laterally, piercing the deep fascia and enters the axilla.

▪ General structure

1. **Mammary glands (parenchyma):** They are modified sweat glands with the function of milk production. Mammary glands are organized into 15-20 lobes that drain the milk to the nipple. Mammary glands are rudimentary and usually not-functioning in men.

2. **The stroma:** The gland has no capsule. It has a stroma which is divided into:

- **Adipose tissue:** Forms the main bulk of the gland.
- **Fibrous stroma:** Consists of the suspensory ligaments of the breast (**Cooper** ligaments) which are strong bands of connective tissue that run between the dermis and the pectoral fascia* (deep fascia) to support the form of the breasts and separate the secretory lobules.

*Pectoral fascia is located dorsally to the breast and it is connected to the breast through loose connective tissue (retromammary space). This loose connective tissue allows the free mobility of the breast over the deep fascia.

3. **Nipple-areolar complex**

- **Nipple:** Conical projection from just below the center of the breast. It lies in the **4th** intercostal space and carries the opening of lactiferous ducts.
- **Areola:** Pigmented area of skin that surrounds the base of the nipple. It is rich in modified sebaceous gland. It enlarges during pregnancy and lactation to form raised tubercles "tubercles of Montgomery". Oily secretions of these glands are of great importance to lubricate the nipple and the areola and prevent them from cracking during lactation.

▪ Vasculature and innervation

1. **Arterial supply**

▪ Medial breast

- **Medial mammary branches** of the internal thoracic artery (internal mammary artery) from the subclavian artery.
- **Anterior intercostal arteries** from **2-6**

- **Lateral breast**
 - **Lateral thoracic and thoracoacromial branches** from the axillary artery
 - **Lateral mammary branches of the posterior intercostal arteries 2-6**

2. Venous drainage

- Internal thoracic vein → subclavian vein
- Lateral thoracic vein → axillary vein
- Intercostal veins → azygos vein
- Areolar venous plexus → axillary vein

3. Innervation (sensory and autonomic fibers)

- Supraclavicular nerves of the cervical plexus
- Lateral and medial branches from intercostal nerves 2–6

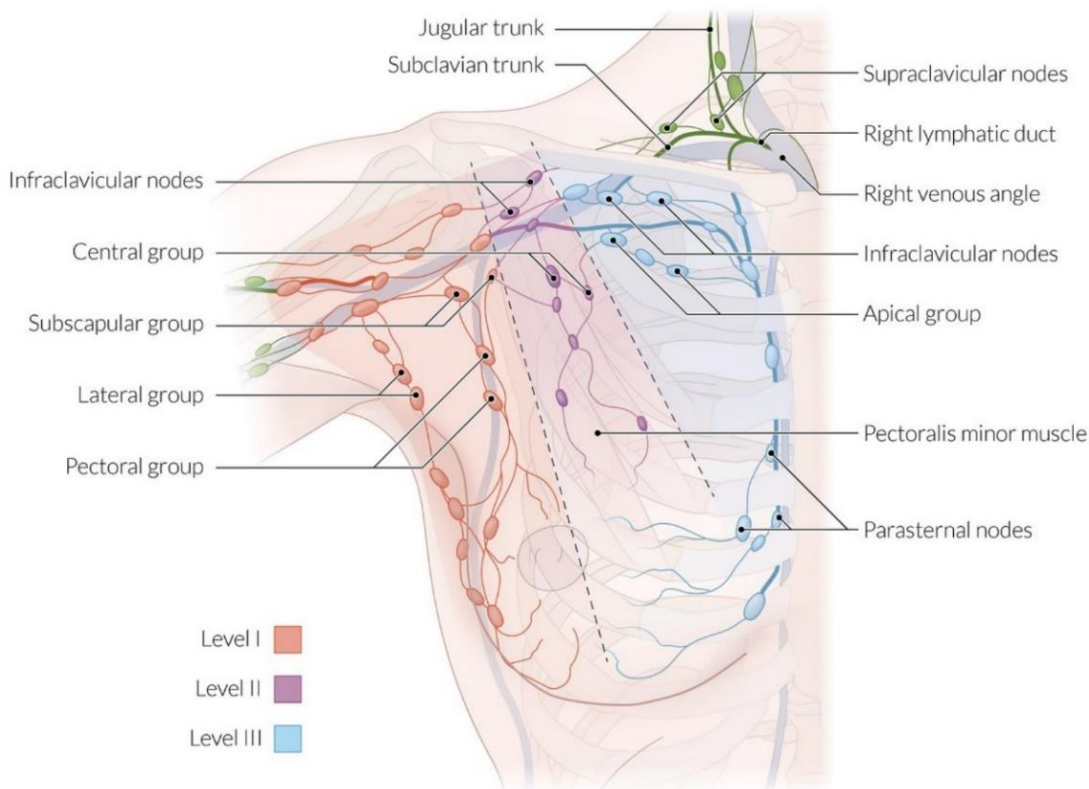
Note: Secretion of milk is not mediated by the nerves but by the hormone prolactin.

4. Lymphatic drainage

Area	Lymph Group
Central and lateral parts	pectoral (anterior) group of axillary lymph nodes
Upper part	apical group of axillary lymph nodes
Medial part	internal thoracic (parasternal) lymph nodes Or anastomosis with the opposite breast
Inferomedial part	lymphatics of the rectus sheath, linea alba and subdiaphragmatic lymphatics

Notes about lymphatic drainage:

- **Axillary lymph nodes:** Consist of 30-60 nodes that are divided into 3 levels in relation to the pectoralis minor muscle.
 - **Level I:** lateral to the lateral border of the pectoralis minor.
 - **Level II:** behind the pectoralis minor.
 - **Level III:** medial to the medial border of the pectoralis minor.
- **Axillary lymph nodes Provide 75% of the lymphatic drainage of the breast** (nipple, upper and lower lateral quadrants).
- Parasternal (internal thoracic) lymph nodes: Drain most of the medial parts of the breast and lie along the internal thoracic arteries.
- Efferent lymphatics travel to the supraclavicular nodes and terminate in the thoracic duct on the left or the right lymphatic duct on the right.



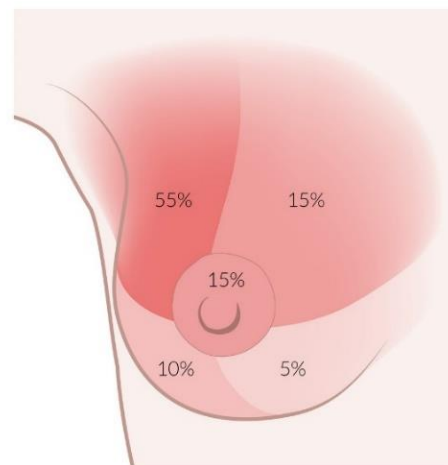
Lymphatic drainage of the breast

Notes:

- A tumor infiltrating the breast tissue can deform, shorten, and retract the Cooper ligaments and lead to dimpling of the skin. Tumorous infiltration and blockage of the lymphatics manifest as lymphedema and thickening of the skin, which is known as peau d'orange because of the resemblance to orange peel. Retraction of the nipple can be a sign of a tumor within the ducts (Paget disease).
- Carcinomas of the breast metastasize early on through the lymph pathways. As most carcinomas of the breast develop in the upper lateral quadrant, lymph node metastases often occur in the axilla of the same side.



Breast cancer: local findings



Breast cancer: location

Development of the breasts (Embryology)

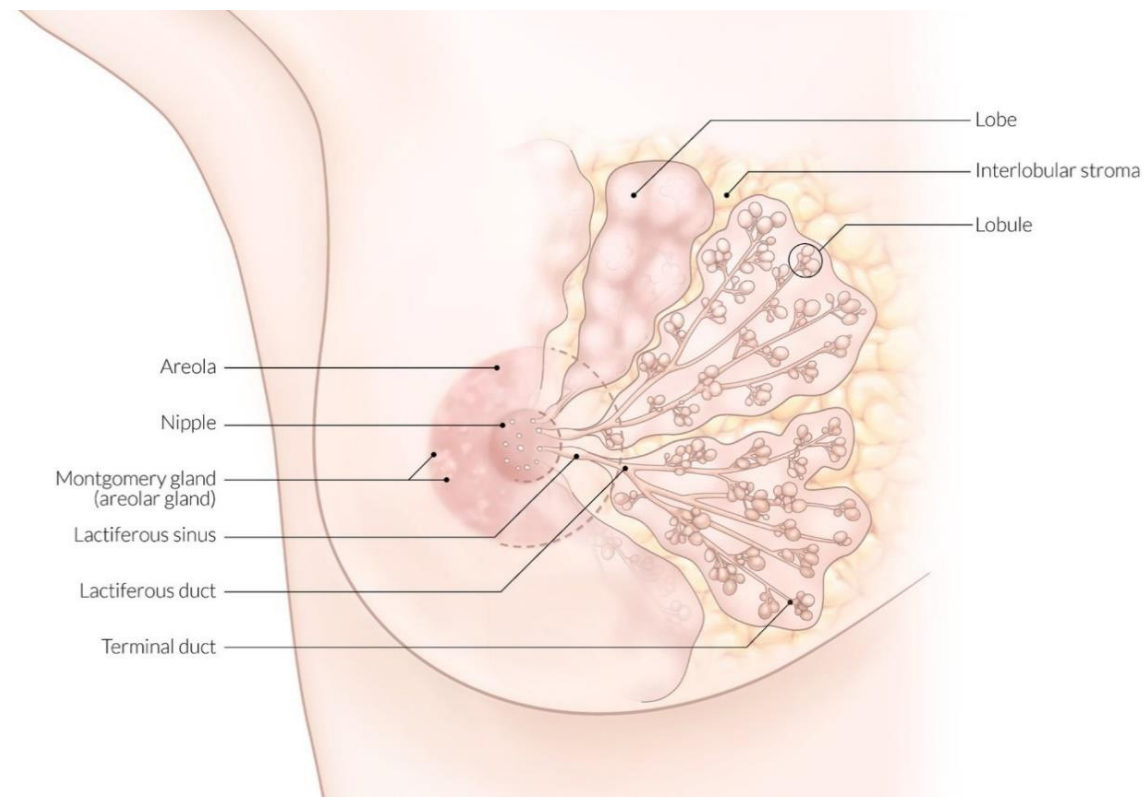
The mammary glands initially develop as a linear thickening from the embryonic surface ectoderm known as mammary ridges (**milk ridges**). Mammary ridges are cutaneous crests from which multiple glandular buds originate. They develop vertically on both sides from the axilla to the groin from the 5th week on. These ridges regress except for a small part in the pectoral region. This localized area thickens, becomes slightly depressed, and sends off 15 to 20 solid cords, which grow into the underlying mesenchyme. The underlying mesenchyme then proliferates, and the depressed ectodermal thickening becomes raised to form the nipple. At the fifth month, the areola is recognized as a circular pigmented area of skin around the future nipple.

Notes:

- If the regression of the mammary ridge is impaired, more than two epithelial buds may remain. In this case, accessory nipples (**polythelia**) or breast tissue (**polymastia**) may develop. Total regression of nipples (**athelia**) and breast tissue (**amastia**) can also occur.
- The development of the breasts is identical in all sexes until puberty. Glandular tissue only begins developing at puberty which is sex-specific. Breast development in women during puberty is also called thelarche.
- ↑ **Estrogen stimulates the development of breast tissue**. Because men do not have the same hormonal influxes of estrogen, their mammary glands remain rudimentary. Nevertheless, men can also develop carcinoma of the breast!

Histology of the breast

- The breast parenchyma is made up of 15-20 lobes with interlobular stroma in between. Each lobe is made up of multiple lobules, which are drained by a single lactiferous duct that opens onto the surface of the nipple. The lactiferous sinus is the terminal dilation of the lactiferous duct.



- **Terminal ductal lobular unit (TDLU):** The basic histopathological unit of the mammary gland which consist of lobule of the mammary gland and extralobular terminal duct.
- **Lobule of the mammary gland (functional unit of the breast)** consists of:
 - Intralobular terminal duct with multiple outpouching called acini, these acini consist of compound tubulo-alveolar glandular structure, with two-layered epithelium: outer myoepithelium cells which contract to route the milk to the ducts in lactating breasts, and inner layer of cubic apocrine glandular epithelial cells which can produce milk.
 - Intralobular stroma.
- **Milk duct system:** Intralobular terminal duct → extralobular terminal ducts (aka terminal ducts: excretory duct of a single lobule. Most breast tumors, benign and malignant develop at the terminal duct) → lactiferous ducts → lactiferous sinus (dilated end of lactiferous ducts, reservoir of milk) → nipple.
- After skin cancer, breast cancer is the most common malignancy in women. Depending on the tissue in which malignancy originates, breast cancers can be histologically differentiated into ductal carcinoma (originating from the milk duct epithelium) and lobular carcinoma (originating from the lobules). Invasive ductal carcinoma of the breast is the most common type.
- **Lactating breasts:** The transition from non-lactating to lactating breasts already begins in the first trimester of pregnancy. During this time, the mammary gland increases in size, and the production of breast milk is initiated.
 - Changes in the mammary gland:
 - Enlargement and differentiation of the lobules of the mammary gland.
 - Tubulo-alveolar glands of the lobules initiate lactation.
 - ↓ Interlobular stroma.
 - ↑ Vasculature.
 - Changes in the nipple:
 - ↑ Size, ↑ pigmentation.
 - Montgomery tubercles become visible.
 - Hormonal regulation of the transition of the glands:
 - Estrogen: ↑ cell proliferation and hypertrophy of the milk duct system.
 - Progesterone, estrogen, and prolactin: ↑ cell differentiation and proliferation of the lobules.
 - Prolactin: production of milk.
- **Age-dependent changes of the breasts:** Involution of the breasts with the onset of menopause due to a decrease in estrogen levels leading to:
 - Atrophy of mammary glands and connective tissue stroma.
 - The milk duct system is preserved (so development of carcinoma is still possible and even more frequent around the time of menopause).
 - Relative increase in fat percentage.
- **Menstrual cycle-dependent changes of the breasts:**
 - During proliferative phase: No changes.
 - During Secretory phase: ↑ estrogen and ↑ progesterone → cell proliferation, ↑ number of acini, edema of interlobular stroma. This edema can lead to an increase in size and may be accompanied by dragging pain (mastodynia).
 - During menstruation: Desquamation and regression.

Benign breast conditions

Inflammatory conditions

Inflammatory processes involving the breast are uncommon and are usually associated with pain and tenderness in the affected areas. Included in this category are several forms of mastitis and traumatic fat necrosis, none of which increase the risk of cancer.

1- Acute Mastitis

Definition & epidemiology:

Inflammation of the breast parenchyma. Most commonly caused by *staphylococcus aureus*. It affects up to 10% of nursing mothers (particularly 2–4 weeks postpartum).

Pathophysiology

- Most frequently in women during the early weeks of nursing, when the skin of the nipple is vulnerable to the development of fissures, prolonged breast engorgement (e.g., because of overproduction of milk or insufficient milk drainage (e.g., infrequent feeding, quick weaning, illness in either the baby or mother).
- Bacteria located in the nostril and throat of the infant or on the skin of the mother enter milk ducts during breastfeeding → pathogen flourishes in stagnant milk → tissue inflammation.

Clinical features:

- Tender, firm, swollen, erythematous breast (generally unilateral).
- Pain during breastfeeding.
- Reduced milk secretion.
- Flu-like symptoms, malaise, fever, and chills.
- In some cases, reactive lymphadenopathy.
- Purulent nipple discharge.

Diagnosis:

Clinical diagnosis mainly (may need breast milk cultures or imaging if there is no response to initial treatment)

Treatment

- In nursing mothers, frequent emptying of the breast; to reduce risk of breast abscess (appears as a fluctuant mass).
 - Breastfeeding with alternate breasts is recommended every 2–3 hours.
- Analgesics (e.g., ibuprofen).
- Cold compresses.

- **Antibiotic** treatment
 - Oral penicillinase-resistant penicillin or cephalosporin (e.g., **dicloxacillin** or **cephalexin**).
 - In the case of methicillin-resistant Staphylococcus aureus (MRSA): **clindamycin** or trimethoprim-sulfamethoxazole (TMP-SMX).
- In the case of inadequate response to initial treatment:
 - Initiate treatment according to breast milk culture results.
 - Consider an underlying breast abscess, which requires surgical drainage.

2- Periductal Mastitis

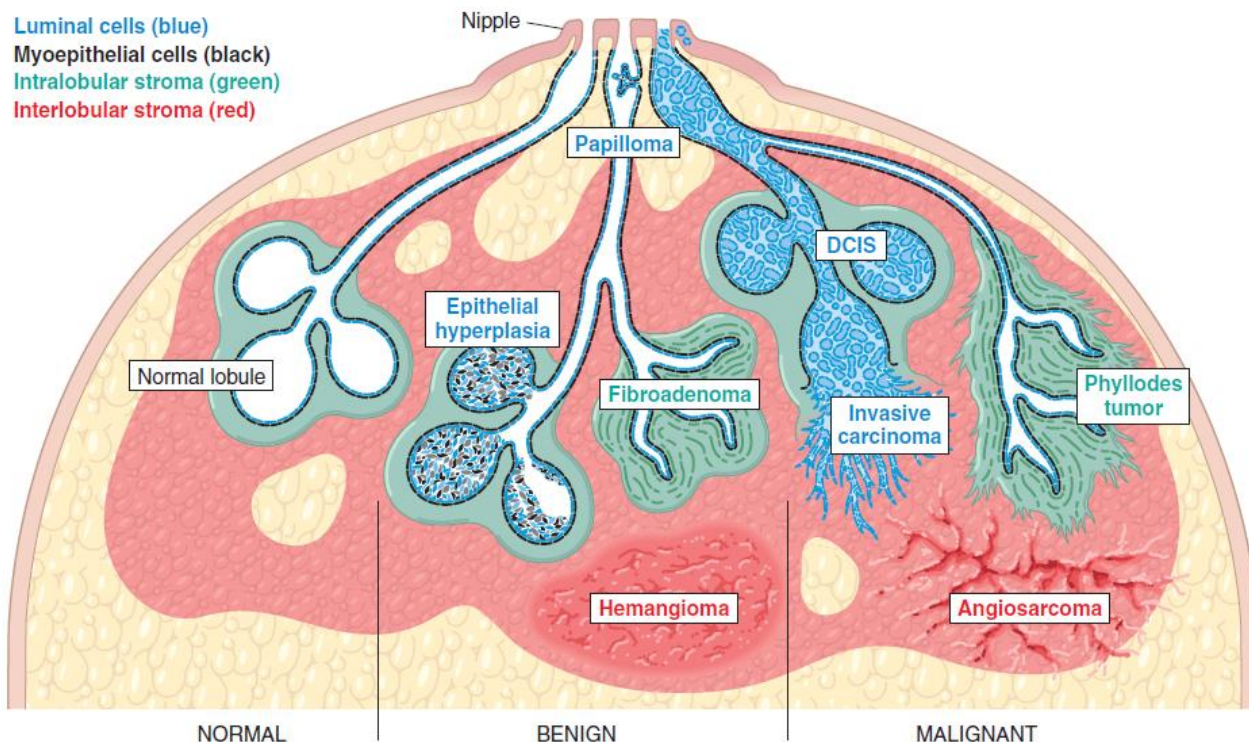
- It is an inflammation of the subareolar ducts usually seen in **smokers**. Present as a subareolar mass with nipple retraction.
- **Pathophysiology**: Smoking causes relative vitamin A deficiency that results in squamous metaplasia of lactiferous ducts, producing duct blockage and inflammation.

3- Mammary duct ectasia (plasma cell mastitis)

- Subareolar periductal chronic inflammatory condition defined by dilated mammary ducts which are eventually clogged. It is rare condition that affects multiparous postmenopausal women.
- Present as a peri areolar firm, painful mass with **green-brown nipple discharge (most common cause for green discharge)** and nipple retraction, mimicking the changes caused by some cancer. However, on biopsy it shows chronic inflammation with **plasma cells**.
- Most cases resolve spontaneously. May need to give antibiotics if it gets infected. Surgical excision for persistent lesions.

4- Fat Necrosis

- It's a nonsuppurative inflammatory lesion affecting breast adipose tissue causing necrosis of breast fat. Usually caused by **trauma**. It comprises < 3% of all breast lesions with peak incidence at 50 years.
- Present as irregularly defined and dense breast mass (generally peri areolar) causing skin retraction, erythema, or ecchymosis.
- Diagnosed by Mammogram and/or ultrasound: **fluid-filled cyst**, coarse rim calcification on mammogram (due to saponification).
- If any suspicious or inconclusive imaging findings → perform biopsy.
 - Shows **foam cells, multinucleated giant cells**, hemosiderin deposition, and chronic inflammation.
- Treatment is unnecessary



Origins of breast disorders. Benign epithelial lesions include intraductal papillomas that grow in sinuses below the nipple and epithelial hyperplasia that arises in lobules. Malignant epithelial lesions are mainly breast carcinomas, which may remain in situ or invade into the breast and spread by metastasis. Specialized intralobular stroma (green) cells may give rise to fibroadenomas and phyllodes tumors, whereas interlobular stroma (green) may give rise to a variety of rare benign and malignant tumors.

Fibrocystic changes

Definition & Epidemiology

Most common benign lesion of the premenopausal breast characterized by the formation of fibrotic and/or cystic tissue. Up to 50% of women are affected during their lifetime. It is thought to be hormone mediated.

Clinical features

- **Premenstrual bilateral breast pain.**
- Tender or nontender breast nodules/irregularity usually in upper outer quadrant.
- Clear or slightly milky nipple discharge.

Diagnosis

- Physical exam
- **First-line:** ultrasound and mammogram
 - Ultrasound: Findings range from normal appearance to focal regions of thick parenchyma; cysts may be present.
 - Mammogram (not recommended for women < 30 years): round or oval masses with clear borders; in some cases, dispersed calcifications is seen.

- Fine-needle aspiration (after imaging confirms a cystic lesion): indicated if the patient is symptomatic and/or requests the procedure. Aspiration of a clear, nonbloody fluid that results in complete resolution of the lesion confirms the diagnosis of a simple cyst.
- Biopsy: confirms diagnosis if imaging is inconclusive. Findings may include:

1- Non-proliferative disease

- Cysts: dilated, fluid-filled ducts (blue dome cysts on gross exam).
- Apocrine metaplasia.
- Stromal fibrosis: (no malignant potential).

2- Proliferative disease without atypia

- Sclerosing adenosis: proliferation of small ductules and acini in the lobules, calcifications (slightly increased risk of breast cancer).
- Ductal hyperplasia
 - Papillary proliferation (papillomatosis).
 - Epithelial hyperplasia of terminal duct cells and lobular epithelium.

3- Proliferative disease with atypia

- Atypical lobular hyperplasia (ALH).
- Atypical ductal hyperplasia (ADH).

Treatment

- If symptoms are mild, treatment is not required.
- In case of severe symptoms: oral contraceptives, tamoxifen, or progesterone.
- Fine-needle aspiration or surgery
 - If a cyst causes severe pain, discomfort, or disfiguration. Reevaluate the cyst after 4–6 weeks.
 - In case of proliferative lesions with atypical cells.

Prognosis: Depends on the histologic subtype:

- Nonproliferative disease → no increased risk of breast cancer.
- Proliferative disease without atypia → 2x increased risk of breast cancer.
- Proliferative disease with atypia → 5x increased risk of breast cancer. overall, 13% to 17% of women with these lesions develop breast cancer.

Benign breast neoplasms

1- Fibroadenoma

Definition & Epidemiology

Benign breast tumor of fibrous and glandular tissue. It is the most common benign tumor of the breast. Usually seen in premenopausal women with peak incidence of 15-35 years.

The etiology is unknown, but a hormonal relationship has been established; (increased estrogen, e.g., during pregnancy or before menstruation, may stimulate growth).

Clinical features:

- Mostly solitary, well-defined, non-tender, rubbery, and **mobile** mass.
- May be painful during the menstrual cycle.

Diagnosis:

- Ultrasound: well-defined mass.
- Mammogram: well-defined mass that may have **popcorn-like calcifications**.
- If imaging is inconclusive: fine-needle aspiration showing fibrous and glandular tissue.

Management: regular check-ups.

2- Phyllodes tumor

Definition & Epidemiology

Rare fibroepithelial tumor with histology similar to that of fibroadenoma. It is of unknown etiology with peak incidence of 40-50 years and comprise 1% of all breast tumor. It is most commonly a benign tumor. However, 25% are malignant.

Clinical features

- Painless, smooth, multinodular lump in the breast.
- Variable growth rate: may grow slowly over many years, rapidly, or have a biphasic growth pattern.
- Average size 4–7 cm.

Diagnosis

- Ultrasound and mammogram findings are similar to fibroadenoma, but phyllodes tumors tend to be larger and grow faster than fibroadenomas.
- Despite the fact that the lesion is typically benign, a suspected phyllodes tumor should be considered a suspicious mass until proven otherwise.
- If a phyllodes tumor is suspected (based on clinical or imaging findings) → core biopsy.
 - Biopsy: **Leaf-like architecture** with papillary projection of epithelium-lined stroma and varying degrees of atypia and hyperplasia.
- If a core biopsy is negative, but the mass continues to grow rapidly, an excisional biopsy should be performed.

Treatment

- Surgical excision.
- In case of recurrence: total mastectomy.

Prognosis

- After excision of benign tumors: excellent prognosis.
- Lesions that show signs of malignancy on histology may recur and metastasize.

3- Intraductal papilloma

Definition & epidemiology

Solitary or multiple benign lesions that arise from the epithelium of breast ducts. Peak incidence: 40–50 years (Solitary lesions: ~ 48 years, Multiple: ~ 41 years).

Clinical features

Features are related to size and location: Central papilloma is usually a large, subareolar located lesion. Peripheral papilloma, on the other hand, is characterized by multiple small lesions located on external areas of the breast.

- Solitary lesions
 - **Most common cause of bloody nipple discharge.**
 - Large, central lesion.
 - Palpable breast tumor close to or behind the nipple.
- Multiple lesions
 - Usually asymptomatic but may cause nipple discharge in rare cases.
 - Peripheral lesions; smaller than solitary papilloma.

Diagnosis

- If lesion is palpable: **Core needle biopsy** is confirmatory and rules out malignancy. Shows papillary cells with fibrovascular core.
- Otherwise: ductogram (A mammogram with contrast injection to visualize the breast milk ducts).

Treatment: surgical excision of the affected duct.

Prognosis

- For most of the lesions, there is no risk of malignant transformation. However, lesions with atypical hyperplasia are associated with an increased risk of breast cancer.

Other benign pathologies of the breast

1- Galactocele

Definition & Epidemiology

Milk retention cyst located in the mammary gland. It is the most common benign breast lesion in lactating women, frequently occurs during or **after lactation**.

Pathophysiology: obstruction of lactiferous duct → distention of the duct due to collection of milk and epithelial cells → cyst formation.

Clinical features:

- Soft, nontender mass; typically located in the sub-areolar region.
- Pain suggests secondary infection.

Diagnosis

- Primarily a **clinical diagnosis**.
- Fine needle aspiration: milky substance (diagnostic and therapeutic).
- Ultrasound: complex mass; findings depend on the fat and water content of the cyst.
- Mammography (rarely indicated): galactoceles may appear as an indeterminate mass or a mass with the classic fat-fluid level.

Treatment:

- Usually not necessary (**most cases resolve spontaneously**).
- Repeated needle aspiration or surgical excision for symptomatic cysts.

Prognosis: good; no increased risk of subsequent breast cancer.

2- Gynecomastia

Definition

It is a benign proliferation of mammary gland tissue in males due to increased estrogen/testosterone ratio (elevated estrogen levels, decreased testosterone levels, or both).

Types and pathophysiology

A. Physiological gynecomastia

- **Neonatal gynecomastia:** Occurs in up to 90% of neonates due to placental transfer of maternal estrogens. Neonatal gynecomastia is bilateral, gender independent, and spontaneously resolves within a few weeks or months.
- **Pubertal gynecomastia:** Occurs in up to 50% of adolescent boys. Caused by pubertal estrogen/androgen imbalance (In pubertal males, adult estrogen concentrations are reached before adult testosterone levels). Spontaneously resolve by 17 years of age (When adult testosterone levels are achieved, and the estrogen/androgen ratio is normalized).
 - Clinical features
 - Present as a small, mobile, firm plaques of breast tissue in the sub-areolar region, which develop during puberty.
Can be tender, unilateral/asymmetric, and associated with fatty development around the nipple.
 - Management
 - Most cases require only that the patient be reassured of the benign nature of the condition. surgical removal of the breast glandular tissue is indicated for pubertal gynecomastia which persists after 17 years of age (persistent pubertal gynecomastia).
- **Senile gynecomastia:** Occurs in ~ 50% of men > 50 years; due to relative hyperestrogenism caused by an age-related decrease in testosterone.

B. Pathological gynecomastia

- **Due to estrogen excess**
 - Malignancies: **Leydig cell tumor**, **Sertoli cell tumor**, ectopic hCG-producing tumors (e.g., lung cancer, hepatocellular cancer), adrenocortical tumors
 - **Liver cirrhosis.**
 - Hyperthyroidism.
- **Due to decreased testosterone**
 - Chronic kidney disease.
 - **Klinefelter syndrome.**
 - Mumps orchitis; castration; trauma to both testes.
- **Due to drugs (focus on the *bolded ones*)**
 - Inhibitors of testosterone receptors
 - **Antiandrogens** (e.g., bicalutamide, cyproterone acetate, flutamide).
 - High-dose **cimetidine** (H2 receptor blocker).
 - **Spirolactone.**
 - Inhibitors of testosterone synthesis
 - Spirolactone.
 - **Ketoconazole.**
 - Chemotherapy drugs (e.g., cyclophosphamide, methotrexate, bleomycin, cisplatin, vincristine).
 - Exogenous androgens and androgenic steroids.

The aromatase enzyme converts testosterone to estrogen. High levels of exogenous testosterone, (e.g., in androgen misuse in athletes) can cause high levels of estrogen and, therefore, gynecomastia.
 - Estrogen receptor stimulators.
 - Estrogens, digitalis compounds.
 - Marijuana 😊.
 - HAART drugs.

C. **Idiopathic gynecomastia.** Up to 25% of patients.

Clinical features of gynecomastia:

- Firm, concentric mass at the nipple areolar complex that may be tender.

Diagnosis

- Laboratory studies
 - Serum levels of testosterone, estradiol, luteinizing hormone, and hCG: indicated in patients with pathological/idiopathic gynecomastia.
 - Liver function tests, renal function tests, thyroid hormone assay: based on history and examination findings.
- Imaging
 - Mammography and ultrasound-guided biopsy: indicated in patients with suspected breast cancer.
 - Testicular ultrasound: indicated in patients with abnormal findings on testicular examination, signs of undervirilization, features of primary hypogonadism, or ↑ hCG levels.

Treatment

- **Treat the underlying cause:** discontinue the offending drug (if possible); treat hyperthyroidism, hypogonadism, chronic liver or kidney disease.
- **Observation:** indicated in physiological and recent-onset (< 6 months) pathological gynecomastia.
- **Medical therapy:** indicated for cosmesis or tender gynecomastia in select patients (Patients with large (> 5 cm) gynecomastia affecting self-confidence or tender gynecomastia, both present for < 1 year).
 - **Testosterone replacement:** in patients with hypogonadism.
 - **Selective estrogen receptor modulators (e.g., tamoxifen):** in patients with severe pubertal gynecomastia or idiopathic gynecomastia > 3 months that causes substantial breast enlargement with tenderness and/or affects self-confidence.
- **Surgery (subcutaneous mastectomy):** indicated for cosmesis in persistent gynecomastia (> 1 year).

3- congenital anomalies of the breast

The mammary ridge regresses in the 7th–8th week of embryonal development. Disorders during this stage of development may lead to the following anomalies:

- **Amastia:** absence of breast tissue and nipples.
- **Polymastia:** presence of accessory breast tissue.
- **Athelia:** absence of nipples.
- **Polythelia:** presence of accessory nipples.

Breast cancer

Epidemiology

Breast cancer is the most common non-skin malignancy in biologically female individuals (~ 30% of all malignancies in women) with peak incidence in post menopause. It is the second cause of cancer death in women.

Note: the incidence of breast cancer for women is 1:8 (The lifetime risk of developing breast cancer for women is approx. 12%).

Predisposing factors

- **Biologically female individuals** (Rare in biologically male individuals).
 - **Age:** cancer usually arises in postmenopausal women, with the notable exception of hereditary breast cancer.
 - **Breast cancer in the contralateral breast** (the highest risk), history of ovarian, endometrial, or colorectal cancer.
 - **Increased estrogen exposure:**
 - High number of total menstrual cycles: early menarche, late menopause, nulliparity, first full-term pregnancy after age 35 years. (Each pregnancy and breastfeeding period lower the lifetime risk for a woman to develop breast cancer. Also, first live birth <20 years is protective).
 - Exogenous estrogen intake: hormone replacement therapy after menopause (Invasive lobular carcinoma is more commonly associated with hormone replacement therapy).
 - **Genetic mutation:** most importantly **BRCA1** and **BRCA2** gene mutations.
 - BRCA: tumor suppressor gene that codes for a DNA repair gene.
 - Autosomal-dominant inherited gene mutation.
 - Associated with an increased risk for breast cancer (~ 70%) and ovarian cancer.
 - BRCA-positive women develop breast cancer approx. 15–20 years earlier than women without the mutation.
 - BRCA mutations are found in 5–10% of all women with breast cancer.
 - **Positive family history** (several relatives with breast or ovarian cancer and/or early onset of disease).
 - **Benign breast disease.**
 - Proliferative disease without atypia (relative risk* is 1.5-2).
 - Proliferative disease with atypia (relative risk is 4-5).
 - Carcinoma in situ (relative risk is 8-10).
- *Relative risk is the likelihood of developing cancer compared to a woman with no risk factors whose relative risk is 1.
- **Lifestyle factors:** low-fiber and high-fat diet, smoking, alcohol consumption, obesity in postmenopausal women (Lipocytes convert a prohormone of testosterone to estrogen using the aromatase enzyme.)

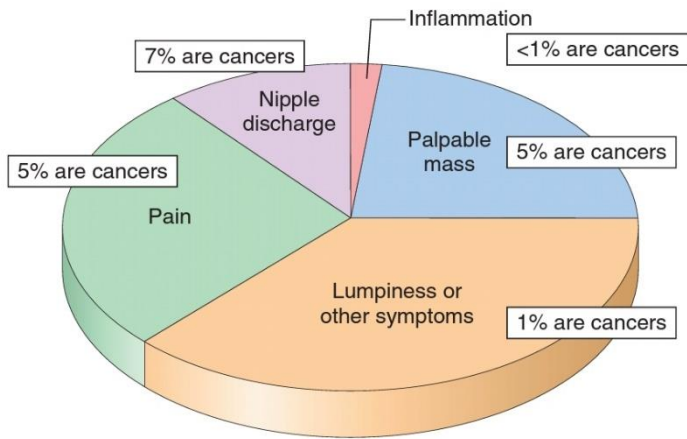
- **Previous radiation treatment** to the chest in childhood (while the breast is still developing).
- **Increased mammographic density.**
- **Genetic syndromes:**
 - Li-Fraumeni syndrome: Autosomal dominant inherited mutation of the p53 tumor suppressor gene.
 - Peutz-Jeghers syndrome

Clinical presentation

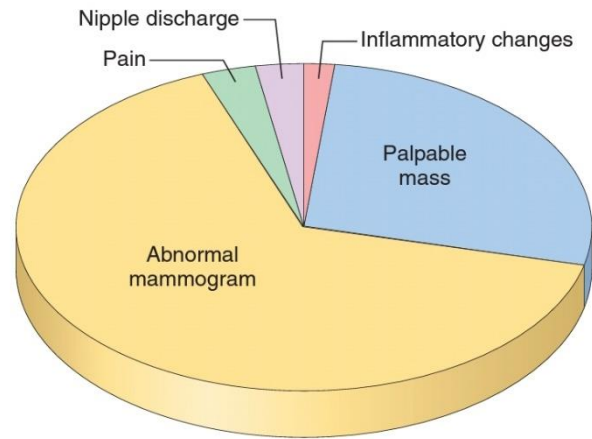
- **Abnormality in a screening test**, e.g. mammogram. (Most common cause of presentation).
- **Changes in breast size and/or shape; asymmetric breasts** (Always compare findings with the contralateral breast!)
- **Palpable mass:** generally detected when they are 2-3 cm in size. The usual presentation of a malignant mass is a single, nontender, firm mass with poorly defined margins, most commonly in the upper outer quadrant (all palpable masses require evaluation).
- **Skin changes:**
 - **Retractions or dimpling** (due to tightening of the Cooper ligaments).
 - **Peau d'orange:** skin resembling an orange peel (due to obstruction of the lymphatic channels). Presenting signs: Redness, edema, and pitting of the hair follicles.
- **Nipple changes:** inversion, discharge (discharges that are spontaneous, unilateral, and bloody are of greatest concern for malignancy).
- **Pain:** although most painful masses are benign, a small fraction of cancers cause pain.
- **Inflammation:** most often caused by infections that occur during lactation and it is rare to be caused by malignancy (an important mimic of inflammation is inflammatory breast carcinoma).
- **Lumpiness:** diffuse nodularity throughout the breast, usually it is a result of normal glandular tissue (imaging may help to determine whether a discrete mass is present).
- **Axillary lymphadenopathy:** firm, enlarged lymph nodes (> 1 cm in size), that are fixed to the skin or surrounding tissue (the parasternal, supraclavicular, and infraclavicular lymph nodes may also be involved and should also be examined!)
- Ulcerations in advanced stages.

Notes:

- Most symptomatic breast lesions (>90%) are benign. Of women with cancer, about 45% have symptoms, whereas the remainder come to attention through screening tests.
- Patients with breast cancer develop clinical symptoms rather late at advanced tumor stages.



A SYMPTOMS OF PATIENTS



B PRESENTATIONS OF BREAST CANCERS

Presenting symptoms of breast disease. (A) Common breast-related symptoms that bring patients to clinical attention. (B) Presentations of breast cancer.

Morphological classification of Breast Cancer

- Most breast cancers are adenocarcinomas, arising from ductal tissue (80%) or lobular tissue (20%).

Noninvasive (in situ) carcinomas

Ductal carcinoma in situ (DCIS)	Lobular carcinoma in situ (LCIS)
~ 25% of all newly diagnosed breast cancers.	1–5% of all newly diagnosed breast cancers.
Localization: unifocal.	Localization: multifocal and bilateral.
Often detected as grouped microcalcifications on mammography; DCIS does not usually produce a mass.	LCIS does not produce a mass or calcifications and is usually discovered incidentally on biopsy.
Higher risk of subsequent invasive carcinoma (ipsilateral).	LCIS is both a marker of an increased risk of carcinoma in both breasts and a direct precursor of some cancers.

Notes

- The noninvasive carcinomas are characterized by the absence of stromal invasion! (no invasion of the basement membrane).
- The terms ductal and lobular are misleading, as both types of CIS are thought to arise from cells in the terminal duct that give rise to lobules. LCIS usually expands involved lobules, whereas DCIS distorts lobules into ductlike spaces.
- Mammographic calcifications can also be associated with benign conditions such as fibrocystic changes (especially sclerosing adenosis) and fat necrosis, so biopsy of calcifications is often necessary to distinguish between benign and malignant conditions.
- Histologic subtypes of DCIS are based on architecture:
 - Comedo type is characterized by high-grade cells with necrosis and dystrophic calcification in the center of ducts.
 - Noncomedo (cribriform, papillary, solid).
- LCIS is characterized by dyscohesive cells lacking E-cadherin adhesion protein.
- Treatment of LCIS is tamoxifen (to reduce the risk of subsequent carcinoma) and close follow-up; low risk of progression to invasive carcinoma.

Invasive (infiltrating) carcinomas

Invasive ductal carcinoma (most common)	Invasive lobular carcinoma
70–80% of all invasive breast carcinomas, usually associated with DCIS.	10–15% of all invasive breast carcinomas, two-thirds of the cases are associated with LCIS.
Unilateral localization.	Unilateral or bilateral.
Mostly unifocal tumors.	Frequently multifocal.
More aggressive, early metastases.	Less aggressive, slower metastasis.
Forms duct-like structures.	Grows in a single-file pattern (No duct formation due to lack of E-cadherin). May exhibit signet-ring morphology.

Notes

- Most invasive ductal carcinomas produce a desmoplastic response, which replaces normal breast fat (resulting in a mammographic density) and eventually leads to the appearance of a hard, palpable irregular mass.
 - Clinically detected masses are usually 2 cm or greater.
 - Mammographically detected masses are usually 1 cm or greater.
 - Advanced tumors may result in dimpling of the skin or retraction of the nipple.
- Although most invasive lobular carcinomas manifest as palpable masses or mammographic densities, a significant subgroup invade without producing a desmoplastic response; such tumors may be clinically occult and difficult to detect by imaging.

Subtypes and Variants

1. Paget disease of the breast

- Definition: a ductal carcinoma (usually adenocarcinoma- either in situ or invasive) that infiltrates the nipple and areola.
- Clinical features:
 - Erythematous, scaly, or vesicular rash affecting the nipple and areola.
 - Pruritus, burning sensation, nipple retraction.
 - The lesion eventually ulcerates → blood-tinged nipple discharge.
- Diagnostics:
 - Nipple scrape cytology: large, round cells with prominent nuclei.
 - Punch or wedge biopsy.
- Differential diagnosis: mamillary eczema.
- Treatment: surgical treatment, using a breast-conserving procedure if possible.

2. Inflammatory breast cancer

- Definition: a rare form of advanced, invasive carcinoma, characterized by dermal lymphatic invasion of tumor cells. Most commonly a ductal carcinoma.
- The underlying invasive carcinoma is generally poorly differentiated and diffusely infiltrates and obstructs dermal lymphatic spaces, causing the “inflamed” appearance; true inflammation is absent.
- Clinical features:
 - Erythematous and edematous (peau d'orange) skin plaques over a rapidly growing breast mass.
 - Tenderness, burning sensation, blood-tinged nipple discharge.
 - Axillary lymphadenopathy.
 - 25% of patients have metastatic disease at the time of presentation.
- Differential diagnosis: mastitis, breast abscess, Paget disease of the breast.
- Treatment: chemotherapy + radiotherapy + radical mastectomy.
- Poor prognosis: 5-year survival with treatment: ~ 50% (without treatment: < 5%).

3. Tubular carcinoma

- 1–2% of invasive carcinomas.
- Typically occurs in women in their late 40s.
- Special subtype of invasive ductal carcinoma.
- Characterized by well-differentiated tubules that lack myoepithelial cells.
- Excellent prognosis.

4. Mucinous (colloid) carcinoma

- < 5% of invasive carcinomas.
- More common in older women.
- Special subtype of invasive ductal carcinoma.
- Characterized by carcinoma with abundant extracellular mucin (tumor cells floating in a mucus pool).
- The tumors usually are soft and gelatinous because of the presence of mucin pools that create an expansile circumscribed mass.
- Relatively good prognosis.

5. Medullary carcinoma

- 5% of invasive carcinomas.
- Special subtype of invasive ductal carcinoma.
- characterized by large, anaplastic, high-grade cells growing in sheets with associated T lymphocytes and plasma cells (the presence of lymphocytes is associated with a favorable prognosis).
- Grows as a well-circumscribed mass that can mimic fibroadenoma on mammography.
- Increased incidence in BRCA1 carriers.
- Relatively good prognosis.

Note: the term “**Invasive ductal carcinoma**” is a term used for all carcinomas that cannot be subclassified into one of the specialized types described above.

Additional classification systems

1. **Classification of Breast cancer based on the expression of hormone receptors—estrogen receptor (ER) and progesterone receptor (PR)—and the expression of the human epidermal growth factor receptor 2 (HER2).** The most clinically useful classification system. Breast cancers are divided based on this system into three major groups:
 - a. **ER positive** (HER2 negative; 50%–65% of cancers). Arises most commonly in individuals with germline BRCA2 mutations. Common examples are invasive lobular, mucinous and tubular carcinomas.
 - b. **HER2 positive** (ER positive or negative; 10%–20% of cancers). Usually associated with germline TP53 mutations.
 - c. **Triple negative** (ER, PR, and HER2 negative; 10%–20% of cancers). Typically, **more aggressive**, high-grade tumors. These cancers have loss of BRCA1 and TP53 function and are genomically unstable. Common example of triple negative is medullary carcinoma.

Notes

- **Human epidermal growth factor receptor 2 (HER2)** is a growth factor receptor with intracellular tyrosine-kinase activity that controls cellular growth and differentiation. (It promotes cell proliferation and opposes apoptosis).
 - Estrogens stimulate the production of growth factors which may promote tumor development. In addition, ER regulates dozens of other genes in an estrogen dependent fashion, some of which are important for tumor development or growth.
2. **Classification of Breast cancer based on gene expression profiling (defined by mRNA profiling).** This system which is currently used mainly in the context of clinical research, divides breast cancers into four major types:
 - a. **Luminal A:** The majority are lower-grade ER, PR positive cancers that are HER2 negative
 - b. **Luminal B:** The majority are higher-grade ER, PR positive cancers that are either HER2 positive or negative
 - c. **HER2-enriched:** The majority overexpress HER2 and do not express ER nor PR
 - d. **Basal-like:** The majority by gene expression profiling resemble basally located myoepithelial cells and are ER, PR and HER2-negative

- Don't memorize the details in the following table, just read it and understand the general ideas about each type.

Summary of the Major Biologic Types of Breast Cancer

Feature	ER Positive/HER2 Negative	HER2 Positive (ER Positive or Negative)	Triple Negative (ER, PR, and HER2 Negative)
Overall frequency	50%–65%	20%	15%
Typical patient groups	Older women; men; cancers detected by screening; germline BRCA2 mutation carriers	Young women; germline TP53 mutation carriers	Young women; germline BRCA1 mutation carriers
Grade	Mainly grade 1 and 2	Mainly grade 2 and 3	Mainly grade 3
Complete response to chemotherapy	Low grade (<10%), higher grade (10%)	ER positive (15%), ER negative (>30%)	30%
Timing of relapse	May be late (>10 years after diagnosis)	Usually short (<10 years after diagnosis)	Usually short (<8 years after diagnosis)
Metastatic sites	Bone (70%), viscera (25%), brain (<10%)	Bone (70%), viscera (45%), brain (30%)	Bone (40%), viscera (35%), brain (25%)
Similar group defined by mRNA profiling	Luminal A (low grade), luminal B (high grade)	Luminal B (ER positive), HER2- enriched (ER negative)	Basal-like
Common special histologic types	Lobular, tubular, mucinous, papillary	Apocrine, micropapillary	Carcinoma with medullary features

Diagnostics

• Approach to suspected breast cancer

Most patients present with abnormalities detected during routine mammography screening. Alternatively, young women (who are not routinely screened) present with a self-palpated breast mass. The diagnostic approach involves clinical assessment, radiographic imaging, and biopsy.

Clinical scenario	First step
<ul style="list-style-type: none"> • Women < 30 years with a self-palpated breast lump 	<ul style="list-style-type: none"> • Clinical assessment • Ultrasound in women with a high probability of malignancy (Young women have higher density breast tissue and more nodular tissue architecture which makes the detection of breast abnormalities in mammogram more difficult.) • In women with low probability of malignancy (if there are no obvious signs of malignancy) reexamine within 3–10 days after the onset of their menstrual period for reexamination!
<ul style="list-style-type: none"> • Women > 30 years with self-palpated breast lump or mammographic abnormalities detected during breast cancer screening 	<ul style="list-style-type: none"> • Clinical assessment and mammography (ultrasound if mammography is inconclusive)

• **Clinical assessment**

Certain constellations of patient characteristics should raise suspicion for malignancy in a breast lump, warranting further assessment.

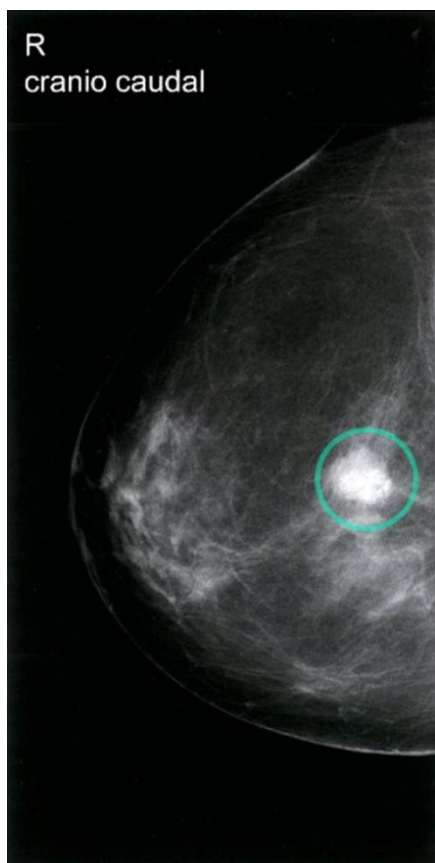
Nonsuspicious	Suspicious
<ul style="list-style-type: none"> • Age < 35 years • No family history • Soft, movable mass • Size changes with menstruation cycle 	<ul style="list-style-type: none"> • Age > 35 years • Positive family history • Firm, rigid mass with irregular borders • Skin changes • Axillary adenopathy • Asymmetry to the contralateral breast, fixation to the skin or chest wall

• **Radiographic imaging**

1. **Mammography**

- Although mammography does not confirm the diagnosis, it is primarily useful for early detection of breast abnormalities!

Benign	Malignant
<ul style="list-style-type: none"> • Well-defined, circumscribed mass • Radiolucent ring surrounding the lesion (halo sign) • Diffuse microcalcification or coarse calcification 	<ul style="list-style-type: none"> • Focal mass or density with poorly defined margins • Spiculated margins • Clustered microcalcifications

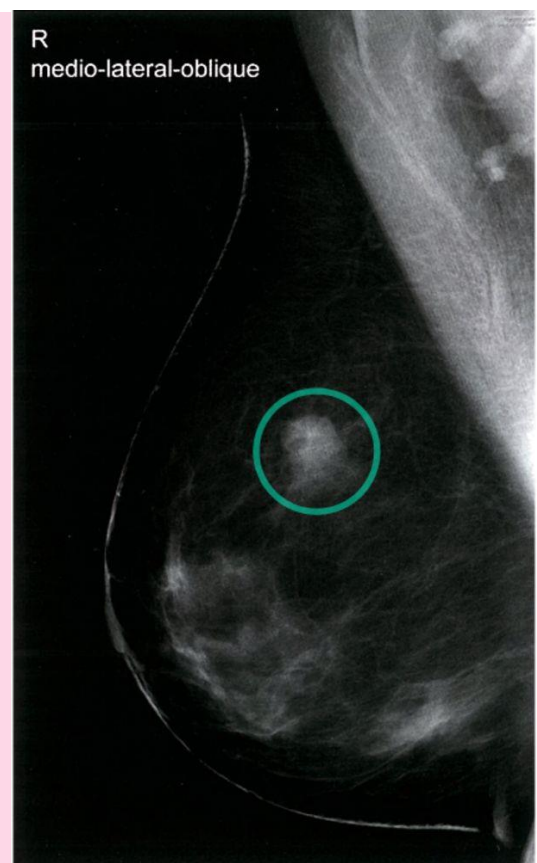


Mammography in Breast Cancer

Photo on the left: craniocaudal view. Notice the poorly defined, round lesion with radial protrusion behind the nipple.

Photo on the right: mediolateral oblique view. Notice the poorly defined lesion with radial protrusion.

Diagnosis: breast cancer.



2. Breast Ultrasound

- Distinguish between solid lesions and benign cysts.
- Evaluate axillary, supraclavicular, and infraclavicular lymph nodes.
- Provide guidance in interventional procedures (fine needle aspiration, core needle biopsy).

3. Magnetic resonance imaging

- To distinguish scar from recurrence in women who have had previous breast conservation therapy for cancer.
- To assess multifocality and multicentricity.
- It is the best imaging modality for the breasts of women with implants.
- As a screening tool in high-risk women (because of family history).

• Biopsy

1. Core needle biopsy (CNB)

- Stereotactic vacuum-assisted CNB is suitable for evaluating microcalcifications and masses < 1 cm
- Performed under image guidance using sonography, mammography, or MRI.
- Confirms the diagnosis (preferred test) and can distinguish between noninvasive and invasive carcinoma based on histology.
- Indicated for a suspicious breast mass on ultrasound or mammography.

2. Fine needle aspiration

- A quick procedure with high sensitivity and specificity. An experienced pathologist is required in order to accurately interpret the results of FNA.
- Preferred tool for assessing a breast mass with a low probability of being malignant (Even if a palpable breast mass appears nonsuspicious on radiographic imaging, biopsy is performed if the mass is symptomatic or to reassure the patient and definitively rule out a malignant process.)
- FNA cannot distinguish between noninvasive and invasive carcinomas (FNA yields a limited number of cells for analysis. Biopsy of more tissue is required to assess whether stromal invasion has occurred.)
- if cytology is suspicious for malignancy, a core needle biopsy is required to confirm the diagnosis.

3. Surgical excision

- If CNB is not feasible or if results of CNB are inconclusive.

• Triple assessment

In any patient who presents with a breast lump or other symptoms suspicious of carcinoma, the diagnosis should be made by a combination of clinical assessment (history and physical examination), radiological imaging and a tissue sample taken for either cytological or histological analysis.

- **Workup of diagnosed breast cancer**

- 1. Receptor testing of biopsy samples**

- Immunohistochemical staining for estrogen and progesterone receptor status.
- FISH or immunohistochemical staining for HER2/neu.

- 2. Tumor markers: CA 15-3, CA 27-29.**

- 3. (Axillary) lymph node status:** clinically suspicious lymph nodes require workup with CNB prior to surgical management of the breast cancer. Axillary lymph node involvement suggests that hematogenic spread has already occurred!

- 4. Further tests**

- **Bone metastasis**

- 1st: contrast-enhanced MRI (in patients with localized bone pain or elevated ALP).
- 2nd: bone scan: if MRI detects metastatic lesion to identify additional occult lesions.

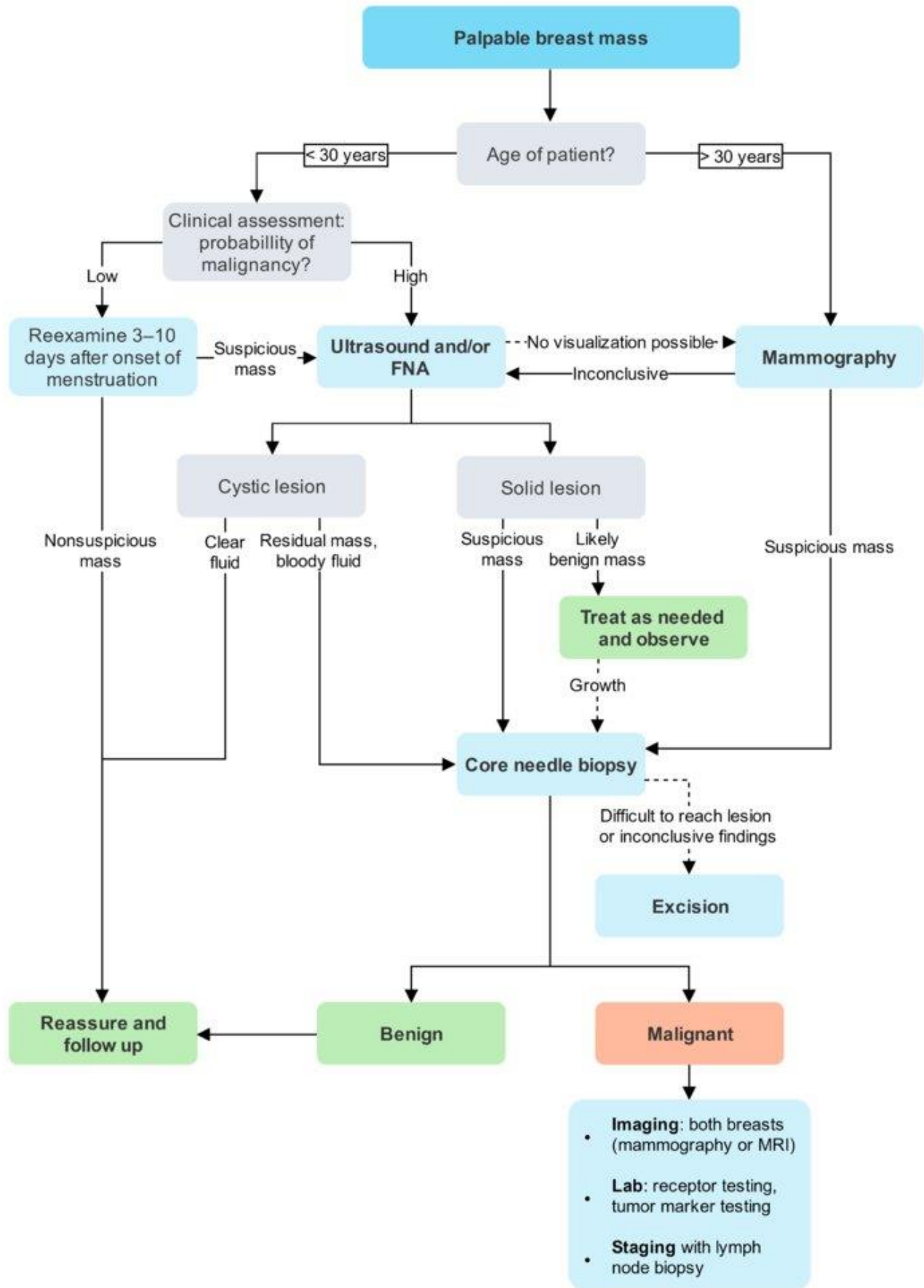
- **Liver metastasis:** abdominal CT.

- **Lung metastasis**

- CXR or chest CT: usually multiple lesions, mostly unilateral pleural effusion.
- Thoracentesis in the case of pleural effusion: malignant cells in the fluid (blood-tinged).

- **Brain metastasis:** Neuroimaging (head CT, MRI).

• Evaluation of palpable breast masses



Histopathology of breast cancer

• Noninvasive carcinomas

Type	Characteristics	Growth pattern
DCIS	<ul style="list-style-type: none"> • Macroscopic: firm mass may be visible. • Microscopic <ul style="list-style-type: none"> ○ Enlarged ducts lined with atypical epithelium. ○ Intact basal membrane. ○ Microcalcifications are noted occasionally, resulting from calcification of necrotic debris or secretory material. 	<ul style="list-style-type: none"> • Two growth patterns <ul style="list-style-type: none"> ○ Comedo necrosis: DCIS with central necrosis due to rapid intraductal proliferation of cells; associated with an increased risk of malignancy ○ Noncomedo (cribriform, papillary, solid)
LCIS	<ul style="list-style-type: none"> • Macroscopic: not visible. • Microscopic <ul style="list-style-type: none"> ○ The lobules are filled with monomorphic cells. ○ Intact basal membrane. 	<ul style="list-style-type: none"> • Diffuse.

• Invasive carcinomas

Type	Characteristics	Growth pattern
Invasive ductal	<ul style="list-style-type: none"> • Macroscopic: firm tumor, fibrous, grayish-white cut surface. • Microscopic: disorganized, small duct-like glandular cells with stromal invasion, microcalcifications, and fibrosis in surrounding tissue. 	Unilateral.
Invasive lobular	<ul style="list-style-type: none"> • Macroscopic: solid. • Microscopic <ul style="list-style-type: none"> ○ Malignant cells in lobules. ○ Monomorphic cells in a single file pattern ("Indian file" pattern) due to a decrease in E-cadherin expression. 	Unilateral or bilateral .
Medullary	<ul style="list-style-type: none"> • Well circumscribed tumor • Poorly differentiated cells with syncytial growth with lymphocytic infiltrates. (There may be no lymphoid infiltrates). 	Rapid growth.
Mucinous	<ul style="list-style-type: none"> • Well circumscribed tumor. • Extracellular mucus. 	Slow growth.
Tubular	<ul style="list-style-type: none"> • Well-differentiated tubular structures, stromal invasion (radial pattern). 	Slow growth.
Inflammatory	<ul style="list-style-type: none"> • Dermal lymphatic invasion, angioinvasion. 	Rapid growth.

Staging of breast cancer

1. TNM staging system (staging of the cancer based on the **size of the primary lesion “T”**, its **extent of spread to regional lymph nodes “N”**, and the **presence or absence of bloodborne metastases “M”**).

Stage	Primary tumor	Nodes	Metastases
Stage IA	≤ 20 mm	None	None
Stage IB	≤ 20 mm	Nodal micrometastases (>0.2 mm and <2.0 mm)	None
Stage IIA	≤ 20 mm > 20 mm and ≤ 50 mm	N1 None	None
Stage IIB	> 20 mm and ≤ 50 mm > 50 mm	N1 None	None
Stage IIIA	≤ 50 mm > 50 mm	N2 N1 or N2	None
Stage IIIB	Extension to chest wall and/or skin	N0 – N2	None
Stage IIIC	Any size	N3	None
Stage IV	Any size	Any involvement	Detectable

N0 = no regional lymph node metastasis.

N1 = 1-3 axillary lymph nodes involved and/or internal mammary nodes with metastases detected by biopsy.

N2 = 4-9 axillary lymph nodes involved or clinically detected internal mammary nodes in the absence of axillary nodal involvement.

N3 = ≥10 axillary lymph nodes involved, or infraclavicular lymph nodes, or clinically detected mammary lymph nodes with axillary involvement, or > 3 axillary nodes with internal mammary nodes detected by biopsy, or in ipsilateral supraclavicular lymph nodes.

Source: American joint committee on cancer 7th edition. Breast cancer staging.

2. A pragmatic staging of breast cancer (classify patients according to the treatment that they require).

	Description
Early stage disease	<ul style="list-style-type: none"> ▪ Localized tumor (< 5 cm) ▪ ≤ 3 nodes involved, including the sentinel lymph node
Locally advanced disease	<ul style="list-style-type: none"> ▪ Large tumor (> 5 cm) ▪ Regional lymph node involvement ▪ No distant metastases
Advanced metastatic disease	<ul style="list-style-type: none"> ▪ Distant metastases

Histopathological grading of Breast cancer

- Cancer cells are given a grade according to how different they are to normal breast cells (**the degree of differentiation**) and **how quickly they are growing**. According to **Nottingham grading system**, breast carcinoma is categorized into **3 grades** based on **3 variables: nuclear pleomorphism, mitotic count / mm², and tubular formation percentage**. Each variable is given a score of 1-3, and the tumor is given the grade according to the combined score.

Combined score	Tumor grade	Appearance of cells
3-5	Grade 1 tumor	Well differentiated. (appear normal, growing slowly, not aggressive)
6-7	Grade 2 tumor	Moderately differentiated. (semi-normal, growing moderately fast)
8-9	Grade 3 tumor	Poorly differentiated. (abnormal, growing quickly, aggressive)

- **Note:** The majority of HER2-positive and triple-negative carcinomas are highly proliferative, whereas ER-positive cancers show a wide range of proliferation.

Treatment: treatment of breast carcinoma is discussed in a separate topic.

Prognosis

- **Axillary lymph node status (most important prognostic factor):** Detection of tumor cells in axillary lymph nodes is associated with a higher risk of metastatic spread to other organs, lower survival rates, and increased rates of cancer recurrence (e.g., with 4–9 positive nodes, recurrence rates may be as high as 70%).
- **Tumor size.**
- **Patient's age:** Both patients who are younger and patients who are of advanced age at diagnosis are more likely to have a poorer prognosis. While women < 40 years of age are thought to suffer from more aggressive, high-grade tumors, women > 65 years old may experience overall frailty and are often multimorbid.
- **Receptor status (ER/PR-negative and triple-negative disease are associated with a worse prognosis):** Patients with a negative hormone receptor status cannot be treated with targeted hormone therapy. The limitations in treatment options are associated with a poorer prognosis. ER/PR-positive, HER2-negative tumors have the best prognosis, since they are responsive to hormone treatment and do not show features of increased malignancy.
- Histologic grade and subtype.

Complications

- **Metastatic disease:** bone metastasis > liver metastasis > lung metastasis > brain metastasis
 - Bone metastasis: bone pain, pathologic fractures, abnormal laboratory results (↑ alkaline phosphatase, ↑ calcium).
 - Liver metastasis: abdominal pain, abdominal distention, nausea, jaundice, abnormal liver function test.
 - Lung metastasis: cough, hemoptysis, dyspnea, chest pain.
 - Brain metastasis: headaches, cognitive deficits, focal neurological deficits, seizures.

- **Recurrence:** up to 40% are local (chest wall, lymph nodes). Relapse typically occurs within the first five years after completion of treatment!
- **Paraneoplastic syndrome*:** hypercalcemia of malignancy.
*Paraneoplastic syndromes: Symptom complexes that occur in patients with cancer and that cannot be readily explained by local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue of origin of the tumor.
- **Treatment-associated complications:**
 - **Lymphedema of the arm, angiosarcoma of the breast** (more details in the treatment topic).
 - **Endometrial cancer** is promoted by **tamoxifen therapy**.

Survival

- **Early-stage disease without lymph node involvement:** 10-year survival rate of 70%.
- **Node-positive disease:** high risk of recurrence.
- **Metastatic disease:** 3-year survival rate of 48–71%.

Prevention

- **Breast cancer screening**
 - **Mammography:**
 - every 2 years in average-risk women aged 50–74 years.
 - Two views of the breast are obtained: mediolateral oblique and craniocaudal.
 - Physical examination plays a **minor role in screening** for breast cancer. (Contrary to former recommendations, women should not be encouraged to perform self-examination.)

Notes:

- If the cancerous lesion is detectable by palpation, a stage II tumor or higher (size > 2 cm) is very likely!
- Mammography has greatly improved early detection of noninvasive carcinomas! While DCIS can occasionally be detected as a palpable lump, LCIS cannot be detected by clinical examination.

- **Prevention in high-risk women**

- **High risk women**

- BRCA1/BRCA2 mutation-positive women. These women have a $\geq 50\%$ life-time risk of developing breast cancer.
- Women with a first-degree relative with a BRCA1/BRCA2 gene mutation.
- Women who have a family history of breast cancer (several relatives with breast or ovarian cancer and/or early onset of disease).
- Women with a history of chest radiation therapy (between age 10–30 years).
- Women with personal or family history of familial cancer syndromes (e.g., Li-Fraumeni syndrome, Cowden syndrome).
- Women ≥ 35 years of age with previous invasive breast cancer or carcinoma in situ.

- **All women should be offered**

- Genetic counseling.
- Annual mammography and MRI (Starting at age 25 or earlier (depending on earliest age of onset of disease in a relative)).
- Prevention measures:
 - Prophylactic surgery:
 - ❖ Bilateral prophylactic mastectomy.
 - ❖ Bilateral salpingo-oophorectomy (BSO) by age 35–40 years and/or when childbearing is no longer desired (BSO decreases the risk for ovarian cancer and breast cancer but is a radical procedure which results in the premature onset of menopausal symptoms.)
 - Alternative: selective estrogen receptor modulator. (Tamoxifen can be offered to those who do not wish to undergo prophylactic surgery; but the benefit of tamoxifen use in this setting is currently uncertain.)
 - ❖ Tamoxifen: In high risk premenopausal women.
 - ❖ Aromatase inhibitors, Tamoxifen or Raloxifene: In high risk postmenopausal women. (Tamoxifen is more effective in risk reduction of breast cancer than Raloxifene. Raloxifene does not increase the risk of endometrial cancer and only marginally increases the risk of uterine sarcoma. Raloxifene shares the other effects and adverse effects of Tamoxifen.)

Treatment of breast carcinoma

The two basic principles of treatment are **to reduce the chance of local recurrence** and **the risk of metastatic spread**. The treatment approach primarily depends on the histopathologic classification and disease stage and involves a combination of surgical management and systemic therapy (chemotherapy, hormone therapy, targeted therapy). Patient preference for more or less aggressive management also plays a significant role in selecting the treatment approach.

Invasive carcinoma

➤ Early stage disease

Treatment of early breast cancer will usually involve surgery with or without radiotherapy. Systemic therapy such as chemotherapy or hormone therapy is added if there are adverse prognostic factors such as lymph node involvement, indicating a high likelihood of metastatic relapse. At the other end of the spectrum, locally advanced or metastatic disease is usually treated by systemic therapy to palliate symptoms, with surgery playing a much smaller role.

Local treatment of early breast cancer: Local control is achieved through surgery and/or radiotherapy.

- **Surgery:** Surgery still has a central role to play in the management of breast cancer but there has been a gradual shift towards more conservative techniques, backed up by clinical trials that have shown equal efficacy between mastectomy and local excision followed by radiotherapy. Types of surgeries:
 - **Mastectomy**
 - Mastectomy is the surgical removal of the entire breast tissue.
 - It is indicated for large tumors (in relation to the size of the breast), central tumors beneath or involving the nipple, multifocal disease, local recurrence or patient preference.
 - The radical Halsted mastectomy, which included excision of the breast, axillary lymph nodes and pectoralis major and minor muscles, is no longer indicated as it causes excessive morbidity with no survival benefit
 - The modified radical (Patey) mastectomy is more commonly performed, which includes the removal of the whole breast, a large portion of skin, the center of which overlies the tumor, but which always includes the nipple, all of the fat, fascia and lymph nodes of the axilla.

- **Conservative breast cancer surgery or Breast-conserving therapy (BCT):** wide local excision followed by radiation therapy.
 - This is aimed at removing the tumor plus a margin of normal breast tissue. This is commonly referred to as a **wide local excision**.
 - A **quadrantectomy** involves removing the entire segment of the breast that contains the tumor.
 - Surgical margins need to be tumor free (the margins of the resected tissue are marked with ink for histologic workup. The surgical margins are considered negative (i.e., tumor free) if there is no tumor at the inked margin). Otherwise, repeat resection or consider mastectomy.
 - 1 mm is considered as a safe margin. There is no need for wider margins than this.
 - The term **lumpectomy** should be reserved for an operation in which a benign tumor is excised and in which a large amount of normal breast tissue is not resected
 - These operations are usually combined with axillary surgery, usually via a separate incision in the axilla. There are various options that can be used to deal with the axilla, including sentinel node biopsy, sampling, removal of the nodes behind and lateral to the pectoralis minor (level II) or a full axillary dissection (level III)
 - **Contraindications to BCT:** large tumor-to-breast ratio, multifocal tumors, fixation to the chest wall, excision with negative tumor margins (> 2 mm) not guaranteed, clustered microcalcifications on imaging, involvement of the skin or nipple, a history of chest radiation
 - There is a somewhat higher rate of local recurrence following conservative surgery, even if combined with radiotherapy, but the long-term outlook in terms of survival is unaffected. Local recurrence is more common in younger women and in those with high-grade tumors and involved resection margins.
 - Patients whose margins are involved should have a further local excision (or a mastectomy) before going on to radiotherapy.
 - Local excision of a breast cancer without radiotherapy is associated with an unacceptably high local recurrence rate.
 - Consider mastectomy for anyone unable to undergo BCT or who requests a more aggressive management (mastectomy should be followed by radiation therapy in patients with a high risk of local recurrence (e.g., positive lymph nodes).
- **Axillary surgery**
 The role of axillary surgery is to stage the patient and to treat the axilla. The presence of metastatic disease within the axillary lymph nodes remains the best single marker for prognosis; however, treatment of the axilla does not affect long-term survival, suggesting that the axillary nodes act not as a 'reservoir' for disease but as a marker for metastatic potential. All patients (premenopausal and postmenopausal women) require axillary staging

- **Intraoperative lymph node evaluation:** The procedure depends on the preoperative lymph node status; clinically suspicious lymph nodes require workup prior to surgical management of the breast cancer, while clinically negative lymph nodes are assessed during surgery.
 - ❖ **Sentinel lymph node biopsy:** Assesses potential lymphatic spread of cancer cells to the axillary lymph nodes; indicated for all patients with clinically negative preoperative axillary lymph nodes. (This procedure helps to identify the axillary lymph node that initially drains the tumorous breast tissue. A blue dye with technetium tag is injected into the tissue surrounding the tumor. This radioactive colloid accumulates in the draining lymph nodes where it can be detected with a gamma probe or Geiger counter (preoperative lymphoscintigraphy). The blue dye allows the sentinel lymph node to be visually identified. Subsequent excision of the lymph node and intraoperative frozen section to detect lymphatic spread of malignant cells.)
 - ❖ **Axillary dissection:** Removal of ≥ 10 lymph nodes during surgery with subsequent histopathologic examination. It is indicated for patients with clinically positive preoperative axillary lymph nodes
- Axillary surgery should not be combined with radiotherapy to the axilla because of excess morbidity

- **Radiotherapy**

- It is conventional to combine conservative surgery with radiotherapy to the remaining breast tissue. Recurrence rates are too high for treatment by local excision alone
- Radiotherapy to the chest wall after mastectomy is indicated in selected patients in whom the risks of local recurrence are high. This includes patients with large tumors and those with large numbers of positive nodes or extensive lymphovascular invasion. There is some evidence that postoperative chest wall radiotherapy improves survival in women with node-positive breast cancer.

- **Adjuvant (after surgery) systemic therapy**

- Hormone and targeted biologic therapy in all **ER/PR+** or **HER2+** patients
- Chemotherapy in high-risk patients (see indications in the table below)
- The effect of combining hormone and chemotherapy is additive, although hormone therapy is started after completion of chemotherapy to reduce side effects.

➤ **Locally advanced disease**

- Neoadjuvant systemic therapy + surgical resection (BCT or mastectomy) + axillary lymph node dissection
- Followed by adjuvant systemic therapy ± radiation therapy
- Primary chemotherapy (neoadjuvant) is being used for large but operable tumors that would traditionally require a mastectomy (and almost certainly postoperative adjuvant chemotherapy). The aim of this treatment is to reduce tumor volume to enable breast-conserving surgery to be performed. It is important that tumors have a metallic clip placed into them at the onset of therapy as otherwise there will be uncertainty about which area to resect once chemotherapy has been completed. In patients with breast cancer strongly positive for hormone receptors, a similar effect can be seen following 3 months of endocrine treatment

➤ **Advanced metastatic disease**

- Systemic treatment followed by palliative surgery and/or radiation therapy (after systemic treatment has decreased tumor size or to resect solitary metastatic lesions)
- Hormone manipulation is often the first-line treatment because of its minimal side effects. It is particularly useful for bony metastases. However, only about 30% of these tumors will be hormone responsive and, unfortunately, in time even these will become resistant to treatment.
- Cytotoxic therapy is used particularly in younger women or those with visceral metastases and rapidly growing tumors. Although none prolongs survival, contrary to expectations, quality of life and symptom control is often better with more aggressive treatments
- Local treatment may also prove useful for some metastatic disease, such as radiotherapy for painful bony deposits and internal fixation of pathological fractures

Note: It is now widely accepted that the outcomes of treatment are predetermined by the extent of micrometastatic disease at the time of diagnosis. Variations in the radical extent of local therapy might influence local relapse but probably do not alter long-term mortality from the disease. However, systemic therapy targeted at these putative micrometastases might be expected to delay relapse and prolong survival.

Noninvasive carcinoma

- **DCIS:** breast-conserving therapy or mastectomy
 - Mastectomy plus sentinel lymph node biopsy (SNLB) if lumpectomy is not feasible (see "Contraindications" under breast-conserving therapy above)
- **LCIS:** life-long surveillance and chemoprevention with hormone therapy (e.g., tamoxifen)
- **Indications for prophylactic bilateral mastectomy**
 - A strong family history of breast cancer
 - Positive for mutations of BRCA 1 or BRCA 2
 - Patients who do not wish to take chemoprevention/hormone therapy

Gestational breast cancer

- Surgery is the treatment of choice (Radiation therapy is contraindicated during pregnancy, making mastectomy a more frequent option than breast conservation surgery)
- Adjuvant chemotherapy only in the second and third trimester.
- Most tumors are hormone receptor negative and so hormone treatment, which is potentially teratogenic, is not required.

Breast reconstruction

- Done after mastectomy
- immediate or delayed reconstruction of the breast can be done.
- Divided into volume displacement (e.g. a musculocutaneous flap using the latissimus dorsi muscle or using the transversus abdominis muscle) and volume replacement (e.g. silicone gel implant under the pectoralis major muscle)
- If the skin at the mastectomy site is poor (e.g. following radiotherapy) or if a larger volume of tissue is required, a musculocutaneous flap is preferred
- if a patient is likely to need postoperative radiotherapy then a delayed reconstruction using a flap often gives a better result. Radiotherapy onto a prosthesis often leads to a high incidence of capsular contracture and unacceptable results.

Lymphatic complications of breast cancer treatment

- **Lymphedema**

- Appears at any time from months to years after treatment using radical axillary dissection and/or radiotherapy
- Recurrent tumor should be excluded because neoplastic infiltration of the axilla can cause arm swelling as a result of both lymphatic and venous blockage (This neoplastic infiltration is often painful because of brachial plexus nerve involvement)
- An edematous limb is susceptible to bacterial infection following quite minor trauma and this requires vigorous antibiotic treatment
- Treatment of late edema is difficult but limb elevation, elastic arm stockings and pneumatic compression devices can be useful.

- **Lymphangiosarcoma**

- rare complication of lymphoedema with an onset many years after the original treatment
- It takes the form of multiple subcutaneous nodules in the upper limb and must be distinguished from recurrent carcinoma of the breast.
- The prognosis is poor

Systemic therapy

	Indications	Agents	Side effects and contraindications
Chemotherapy	High-risk patients: <ul style="list-style-type: none"> • Tumor size > 2 cm • Positive lymph nodes • Aggressive tumor histology • Triple negative breast cancer 	Anthracycline and taxane regimen (read the notes below the table)	<ul style="list-style-type: none"> • Side effects: <ul style="list-style-type: none"> ○ Myelosuppression ○ Alopecia ○ Hypersensitivity ○ Cardiotoxicity • Contraindicated during the first trimester of pregnancy
Hormone therapy	ER or PR positive tumors (The optimal duration is 5 years. Longer durations provide a small extra benefit but with increased toxicity)	Premenopausal <ul style="list-style-type: none"> • First-line treatment: tamoxifen: Selective estrogen receptor modulator (SERM) that acts as an antagonist on the estrogen receptors of the breast, and acts as an agonist on estrogen receptors in bone, uterus, 	<ul style="list-style-type: none"> • Side effects: <ul style="list-style-type: none"> ○ ↑ Risk of endometrial cancer: with Tamoxifen (Tamoxifen is a partial agonist in the endometrium) ○ ↑ Risk of uterine sarcoma ○ Hot flashes ○ Nausea ○ Skin rash ○ ↑ Risk of thromboembolic events

		<p>liver, and coagulation system.</p> <ul style="list-style-type: none"> • Aromatase inhibitors are contraindicated in women with intact ovarian function. • There are no data on the efficacy of raloxifene for breast cancer prevention among premenopausal women 	<ul style="list-style-type: none"> ○ Musculoskeletal pain, weakness (Tamoxifen has an estrogen-like effect leading to an increased bone turnover which may be painful.) ○ Decreases the risk of osteoporosis and fractures ○ Cataract (Patients should receive regular ophthalmologic examinations.) • Contraindicated during pregnancy
		<p>Postmenopausal Goal: Suppress extra-ovarian hormone production and block estrogen receptors.</p> <ul style="list-style-type: none"> • First line treatment: aromatase inhibitors (AIs), e.g., anastrozole, letrozole (Nonsteroidal AIs), exemestane (irreversible steroidal AI) • Alternative: selective estrogen receptor modulator (SERM); tamoxifen, or raloxifene. (raloxifene is a SERM that is approved as an agent for breast cancer prevention, and for the treatment of postmenopausal osteoporosis. Raloxifene has estrogenic effects on bone and lipids, but estrogen antagonist effects on the breast and uterus) 	<ul style="list-style-type: none"> • Side effects: <ul style="list-style-type: none"> ○ Hot flashes, night sweats ○ Arthralgia ○ Aromatase inhibitors: increase the risk of osteoporosis ○ Cardiovascular disease ○ Hypercholesterolemia ○ ↓ Libido, vaginal dryness ○ Fatigue, cognitive dysfunction ○ AIs do not predispose patients to endometrial cancer ○ Raloxifene: does not increase the risk of endometrial hyperplasia and carcinoma; has a lower risk of thromboembolic events and cataracts than tamoxifen
<p>Targeted therapy</p>	<p>HER2-positive tumors</p>	<p>Trastuzumab: monoclonal antibody that inhibits tumor growth by binding to the epidermal growth factor HER2</p>	<ul style="list-style-type: none"> • Cardiotoxic (e.g., dilated cardiomyopathy with systolic CHF): an echocardiogram is recommended prior to initiating treatment to evaluate cardiac function. (important: the cardiotoxic properties of trastuzumab are aggravated by simultaneous administration of anthracyclines, which are also cardiotoxic!) • Contraindicated during pregnancy

Notes

- **Anthracyclines:**

- A group of chemotherapeutic drugs including doxorubicin, daunorubicin, and idarubicin.
- Multiple mechanisms of action: inhibition of topoisomerase II, inhibition of DNA and RNA synthesis by intercalation with DNA, DNA strand excision, and generation of free radicals.
- Used to treat several cancers, including leukemias, lymphomas, breast, ovarian, and bone cancer (e.g., osteosarcoma).
- Adverse effects include cardiotoxicity (e.g., dilated cardiomyopathy, left ventricular dysfunction, heart failure, myocarditis) which can be limited with dexrazoxane, an iron chelating agent.

- **Taxanes**

- A group of chemotherapeutic agents that stabilizes polymerized microtubules of the mitotic spindle to stop mitosis (mitotic inhibitors) and thereby the process of cell division.
- Agents include paclitaxel and docetaxel.
- Commonly used in the treatment of ovarian, breast, prostate, lung, head and neck, and gastric cancer.
- Adverse effects include peripheral neuropathy, interstitial pneumonitis, myelosuppression, cardiotoxicity, alopecia, and skin changes.

- **Aromatase inhibitors (AIs)**

- The aromatase reaction is responsible for extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissues, including breast malignancies.
- Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women.

Mammogram

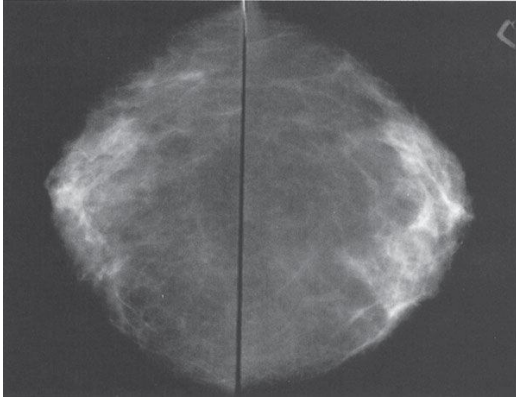
Introduction

- A mammogram is a breast X-ray used for screening and diagnosis of breast cancer and other breast pathologies. It is used as a screening tool in women who do not complain of any symptoms and perform it as part of their regular follow up. It is used as a diagnostic tool for patients who complain of symptoms and need a radiographic confirmation of the diagnosis.
- The indication for screening is the search for occult carcinoma in an asymptomatic patient.
- Indications for diagnostic mammography are
 - Palpable mass or other symptom or sign (e.g. skin dimpling, nipple retraction, or nipple discharge that is clear or bloody).
 - Radiographic abnormality on a screening mammogram.
- The primary purpose of breast imaging is to detect breast carcinoma. A secondary purpose is to evaluate benign disease, such as cyst formation, infection, implant complication, and trauma.
- It is almost universally acknowledged that women over 50 years of age benefit from periodic screening mammography. Several large population studies have shown a decrease in mortality of around 30% in this group.
- American Cancer Society Recommendations for Breast Cancer Detection in asymptomatic women:

Age group	Examination	Frequency
20 to 39	Breast self-examination	Optional
	Clinical breast examination	Every 3 years
40 and older	Breast self-examination	Optional
	Clinical breast examination	Annual
	Mammography	Annual
High risk (>20% life risk)	MRI	Annual
Moderate risk 15% to 20%	MRI	Talk with doctor about possible annual examinations
Risk <15%	MRI	Not recommended

Technique and normal anatomy

- The routine examination consists of two views of each breast, the craniocaudal (C-C) view and the mediolateral oblique (MLO) view, with a total of four films. The C-C view can be considered the “top-down” view, and the MLO an angled view from the side. the pectoralis muscle can be seen in MLO view.



C-C View

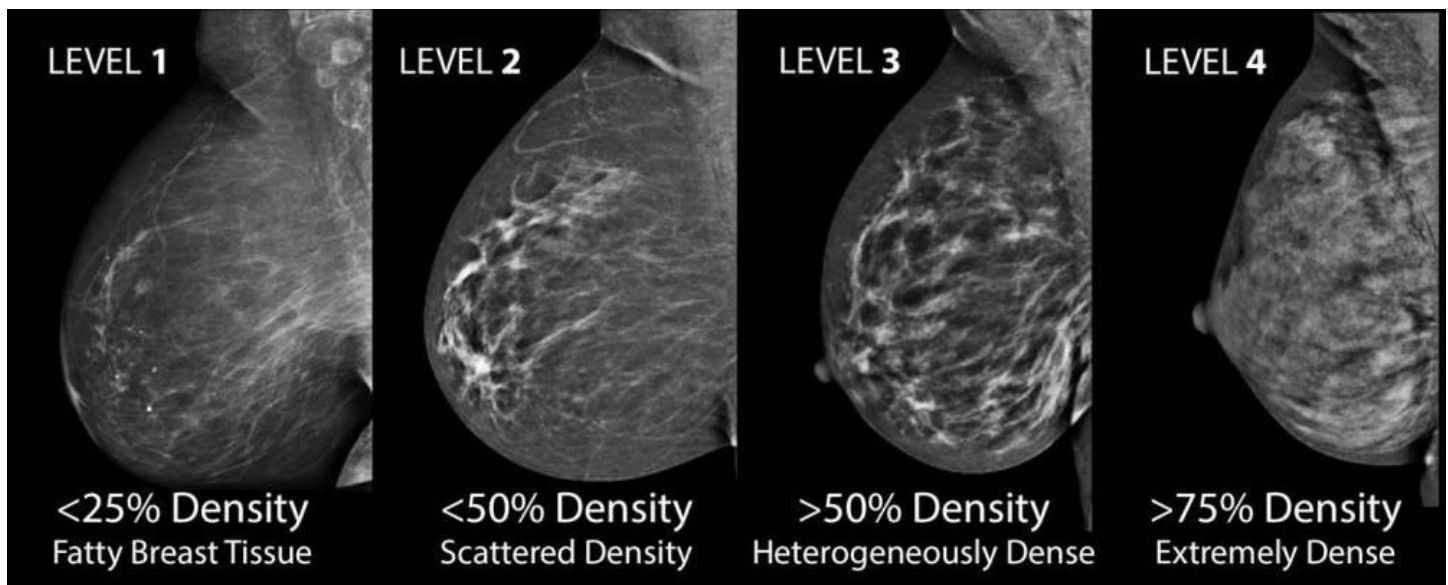


MLO View

- It is advised to schedule mammography when the breasts are least likely to be tender, which is usually during the week after menstrual period, to allow better compression. Advise the patient not to apply deodorants, powders, lotions or perfumes under the arms or on the breasts on the day of the test.
- The sensitivity of an image is measured based on the amount of fibroglandular tissue present in the breast. The more the fibroglandular tissue, the less sensitive the image. This is called the ACR system.

ACR system

- ACR1: fatty breast; usually in older females; <25% glandular tissue. Highly sensitive 85-90%.
- ACR2: low amounts of fibroglandular tissue; 25-50% fibroglandular tissue.
- ACR3: heterogenous breast; 50-75% fibroglandular tissue.
- ACR4: dense breast; >75% glandular tissue; sensitivity decreases to 60%.



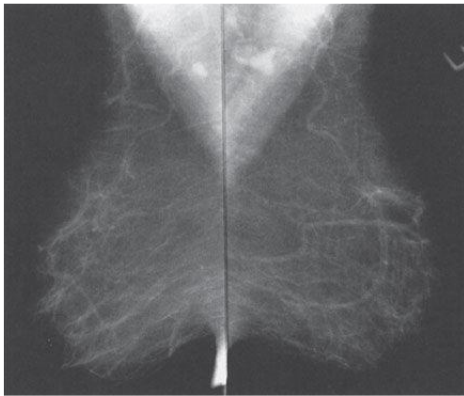
- Sensitivity is limited by three factors:
 1. The nature of breast parenchyma; In young women the breast parenchyma is more often dense and nodular. This condition decreases the sensitivity for detection for carcinoma and leads to more false-negative and false-positive results.
 2. The difficulty in positioning the organ for imaging.
 3. The nature of breast carcinoma.

Normal structures in the mammography

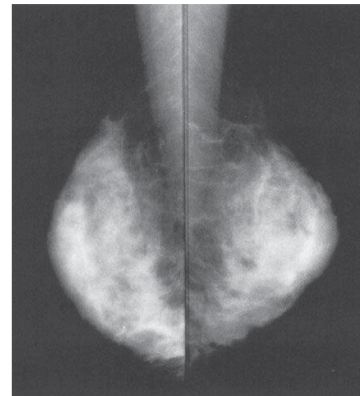
- Normal breast is composed mainly of parenchyma (lobules and ducts), connective tissue, and fat. Lobules are drained by ducts, which arborize within lobes. There are about 15 to 20 lobes in the breast. The lobar ducts converge upon the nipple.

DO NOT MEMORISE, JUST UNDERSTAND THE CONCEPTS

1. **Parenchyma:** The lobules are glandular units and are seen as ill-defined, splotchy opacities of medium density. Their size varies from 1 to several millimeters, and larger opacities result from conglomerates (تكتلات) of lobules with little interspersed fat. The amount and distribution of glandular tissue are highly variable. Younger women tend to have more glandular tissue than do older women.



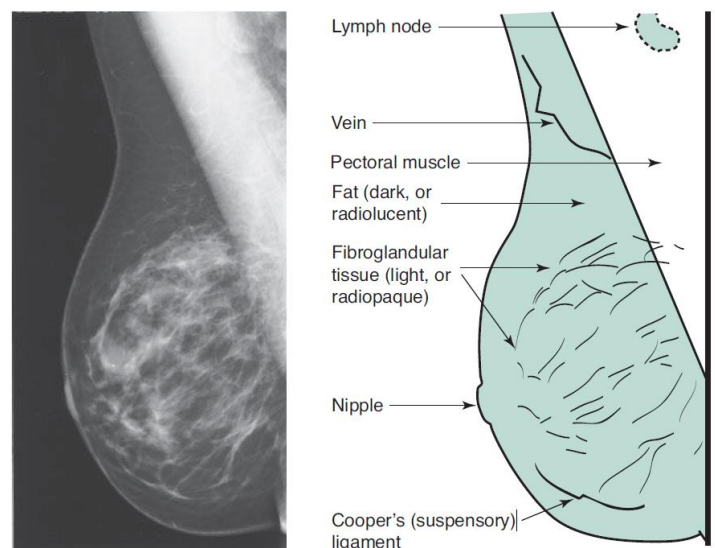
Fatty breast



Dense breast

2. **Connective Tissue:** Trabecular structures, which are condensations of connective tissue, appear as thin (<1 mm) linear opacities of medium to high density. Cooper's ligaments - the supporting trabeculae- are seen as curved lines around fat lobules along the skin-parenchyma interface within any one breast.

3. **Fat:** The breast is composed of a large amount of fat, which is lucent, or almost black, on mammograms. Fat is distributed in the subcutaneous layer, in among the parenchymal elements centrally, and in the retromammary layer anterior to the pectoral muscle.



4. **Lymph nodes:** Lymph nodes are seen in the axillae and occasionally in the breast itself. Intramammary Lymph nodes are kidney shaped (oval), microlobulated, with center fat (heterogeneous).
5. **Blood vessels: Veins:** Veins are seen traversing the breast as uniform, linear opacities, about 1 to 5 mm in diameter. **Arteries:** Arteries appear as slightly thinner, uniform, linear opacities and are best seen when calcified, as in patients with atherosclerosis, diabetes, or renal disease.
6. **Skin:** Skin lines are normally thin and are not easily seen without the aid of a bright light for film-screen mammograms.

Important note: Signs of malignancy in a lymph node:

- **Thickening of the cortex (>1cm)**
- **Loss of fatty medulla (hilum)**
- Increased in size (least important criterion)

Approach to the symptomatic patient

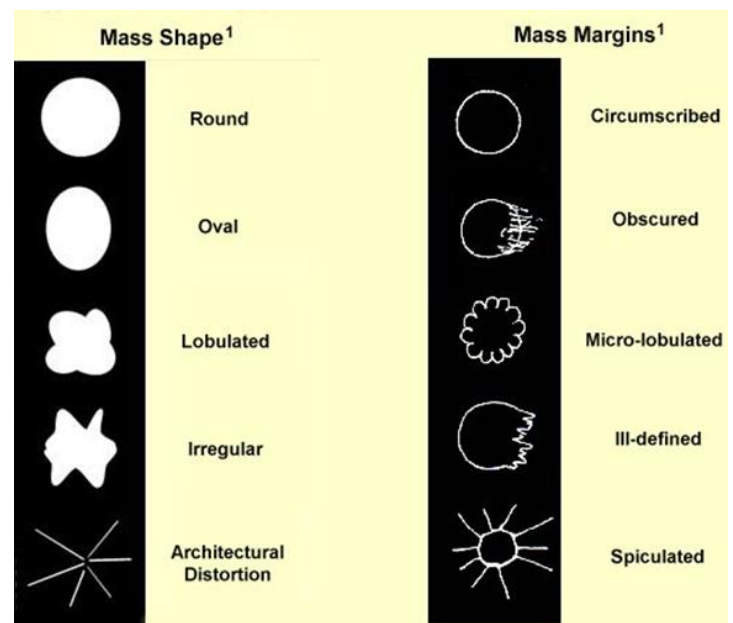
1. Masses

- When a breast lump is found, several questions must be answered before proceeding with breast imaging.
 - When is a lump significant?
Experts in CBE advise palpation with the flat surface of two to three fingers, and not with the fingertips. With this technique, nonsignificant lumps will disperse into background breast density, but a significant lump will stand out as a dominant mass.
 - Is the lump new or enlarged?
A new lump is more suspicious than a lump that has not changed over a few years.
 - How big is the lump?
Tiny pea-sized or smaller lumps, particularly in young women, are often observed closely with repeated CBE, because small breast nodules are extremely common, frequently resolve spontaneously, and are usually benign. Repeating CBE in 6 weeks allows for interval menses, which frequently causes waning or resolution of the lump. If the lump persists, diagnostic mammography is indicated.
 - **How old is the patient?**
If the patient > 35 years: breast imaging begins with a diagnostic mammogram at the time a lump is deemed to be significant.
If the patient < 35 years: a significant lump is usually first examined with ultrasonography to determine whether a simple cyst is present.
 - If there is no cyst, and the patient is below 30 years of age, then obtain a mammogram, but in this case the mammogram may be limited to one breast or to a single view because of breast density.

- For women between the ages of 30 and 40 years, judgment is needed as to whether other imaging is indicated. Several factors should be weighed, including age, family history of breast carcinoma, reproductive history, and findings at CBE.
- Possible scenarios: Choose from: (Screening mammography; Excisional biopsy; Ultrasonography; Diagnostic mammography; Needle aspiration) for each of the following cases:
 - 1) A 34-year-old woman noticed a new lump in her breast, it was 2 cm in diameter on CBE. She says it was definitely not present until recently. She has no risk factors for breast cancer. The mass is most likely to be? fibroadenoma or a cyst, but carcinoma cannot be excluded. Which test should be ordered first?
Ultrasound.
 - 2) A 60-year-old woman who, on the insistence of her children, went for her first routine physical examination in many years. Her doctor found a mass in her breast. on CBE; It is irregular and not freely mobile. The patient has never had a mammogram. Which test should be ordered first? Although the mass feels suspicious, she still needs a **diagnostic mammogram** prior to biopsy (FNA then excisional biopsy) to exclude other lesions such as multifocal carcinoma.
 - 3) A 53-year-old woman thinks she feels a hard nodule deep in her breast. Her breasts have always been difficult to examine because of their dense nodular texture -Spot compression view of the region of suspected abnormality may help in this case-. Results of screening mammography less than 1 year ago were normal. What test should be ordered first? being in a high-risk age group (over 50 years old), and having a dense parenchymal pattern, the patient needs another mammogram, this time a **diagnostic mammogram** of the involved breast only.
 - 4) A 78-year-old woman with a soft, rounded mass discovered during physical examination What test should be ordered first? She needs a **diagnostic mammogram** because of her age and the palpable findings.
- When you see a mass in a radio mammogram you have to check for its shape, margin, and density because these are important diagnostic features.

➤ **Shape:**

- **Round:** coin shaped lesion
- **Oval:** egg shaped
- **Lobulated:** up to 3 lobes; if more than 3 lobes are present, it is considered irregular
- **Irregular:** the presence of more than 3 lobes, an irregularly shaped mass, or a mass that looks different when viewed on CC and MLO views (ex looks round on CC and oval on MLO).



➤ **Margins:**

- **Well circumscribed (well defined)**
- **Obscured:** part of the margin is covered due to an overlap between the mass and the breast parenchyma.
- **Microlobulated**
- **Ill-defined:** the edges of the mass cannot be defined
- **Speculated:** sun-ray appearance; it is one of the most important signs of malignancy. The presence of a single speculation is highly suggestive of a malignant mass (invasive breast carcinoma).

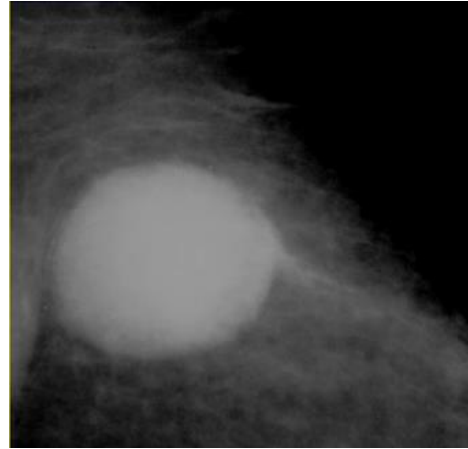
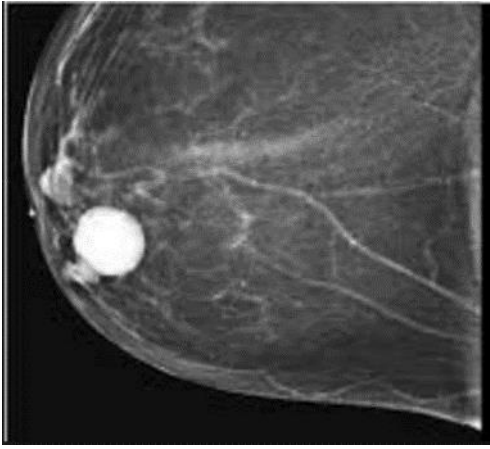
Besides carcinoma, the primary differential diagnosis for a **spiculated mass** includes postsurgical change, other trauma with hematoma, fat necrosis, infection, and radial scar (a complex, spontaneous benign lesion involving ductal proliferation, elastosis, and fibrosis).

➤ **Density:** the density of a mass is described in reference to the most hyperdense area in the breast.

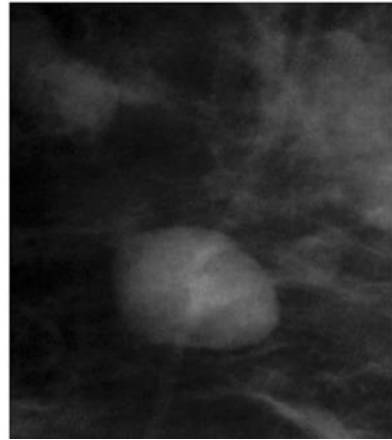
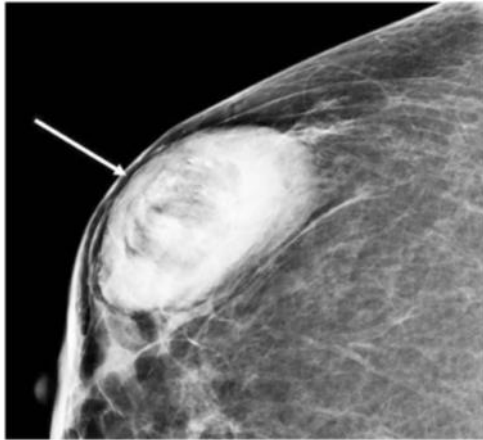
- **Hypodense**
- **Isodense**
- **Hyperdense**
- **Fat containing:** heterogenous with a rim of calcification called eggshell calcification. Another type of fat containing mass is a lymph node. Lymph nodes appear as kidney shaped with a hyperdense cortex and hypodense medulla (Fat).
- **Mixture of densities within the lesion.** If there are medium-density opacities interspersed with lucencies within a smoothly marginated mass. This appearance is **pathognomonic for a fibroadenolipoma**.

Notes

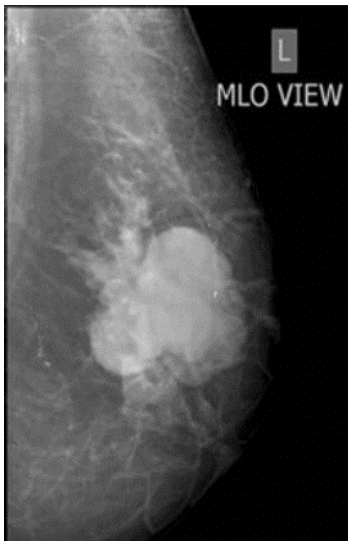
- **Round** and **oval** shaped masses are more likely to be **benign**. However, **irregular** masses are more likely to be **malignant**.
- **Well-circumscribed** margins are more likely to be benign. However, **ill-defined** or **speculated margins** are more likely to be malignant.
- **Hypodense** and **fat containing** masses are more likely to be benign.
- For final assessment & further management decisions, use descriptor(s) with MOST WORRISOME FINDINGS (e.g., if mass PARTLY CIRCUMSCRIBED & PARTLY INDISTINCT, take further action based on INDISTINCT MARGINS).



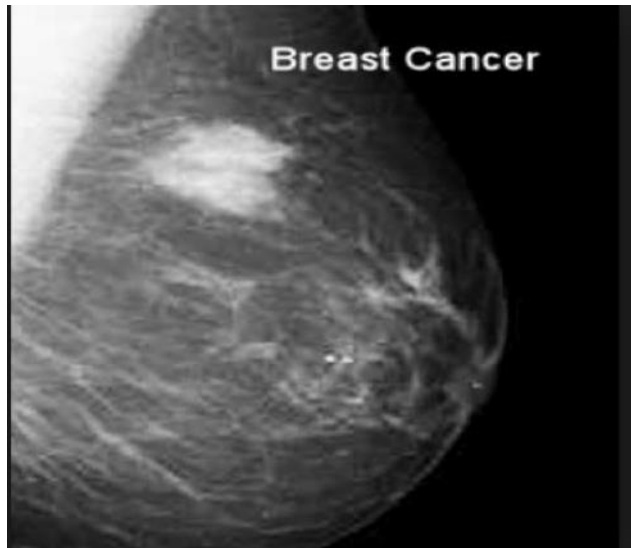
Mammogram images showing a round breast mass; well circumscribed margin



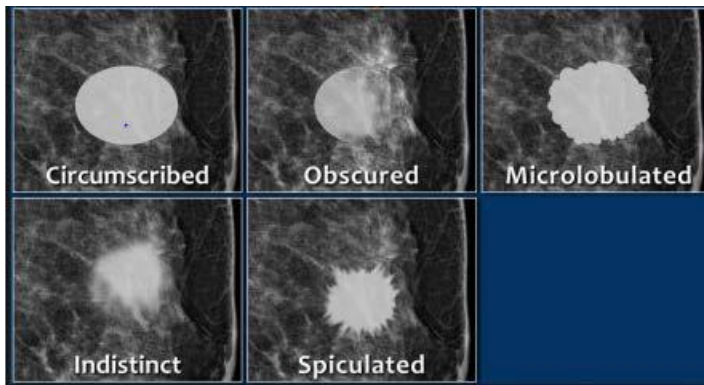
Mammogram images showing an oval breast mass



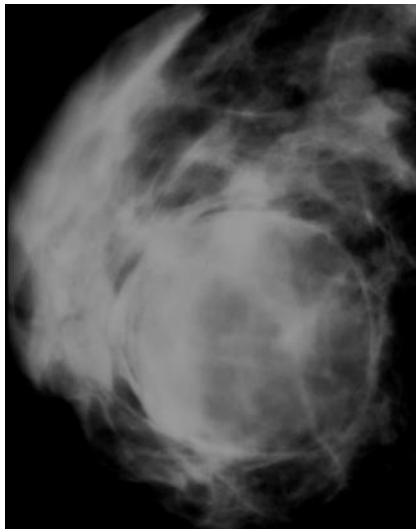
Mammogram showing a trilobed breast mass



Mammogram showing an irregular breast mass



A diagram showing different types of margins



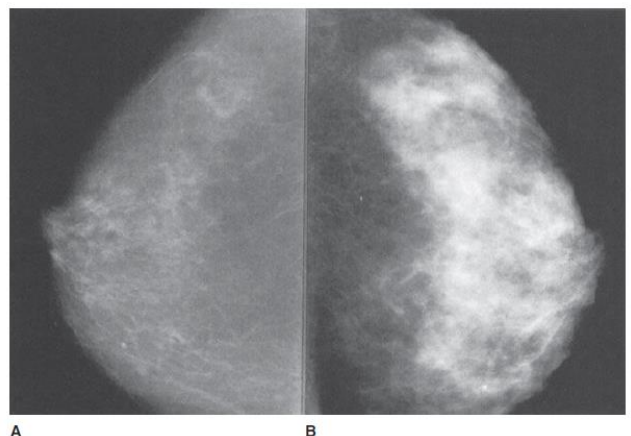
Mammogram showing a well circumscribed fatty lesion with eggshell calcification; suggestive of lipoma

2. Lumpiness, Nipple discharge, and pain

- Lumpy breasts are a variant of normal and, as such, require careful physical examination and mammography to avoid unnecessary surgery, as well as not to miss a carcinoma. Diffuse lumpiness is not a contraindication to screening mammography, but when a particular lump becomes dominant, a diagnostic study is indicated.

- Possible scenarios

1) An 82-year-old woman who complains of newly lumpy, painful breasts. The mammogram (A was taken 1 year before B), the most likely explanation for the patient's symptoms and mammographic changes is? These mammograms show a diffuse marked increase in mammographic density with a nodular character, this is probably due to **hormone effect**. Such changes can be seen asymmetrically or unilaterally, and it is useful to remember the estrogen effect when evaluating mammograms with interval changes. Correlation with clinical history is then needed.



Infectious mastitis and carcinoma are incorrect as both of these entities are usually **unilateral** and **focal**. Congestive heart failure (CHF), is incorrect because CHF causes bilateral changes that have a more linear pattern of trabecular thickening on mammography.

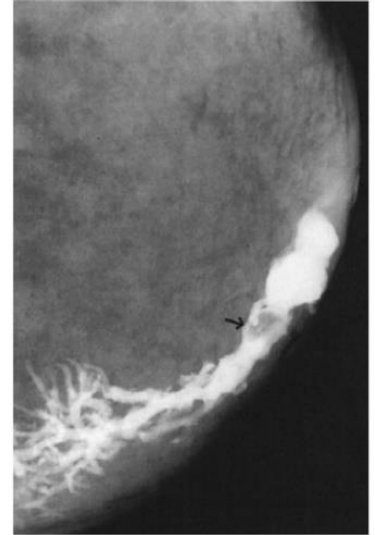
- 2) A 45-year-old woman with a serous nipple discharge. **Ductography** was done to guide the surgeon approach.

Most of the walls are smooth, as they should be. However, there is a filling defect in one of the major branches (arrow).

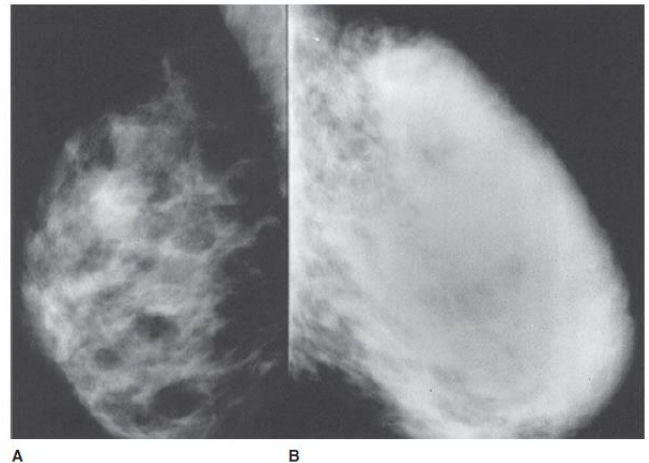
although approximately 90% of nipple discharges are due to benign causes, we cannot determine from these findings alone whether the defect is due to a benign or a malignant nodule. Whether or not a filling defect is seen on a ductogram, biopsy is needed to rule out carcinoma, and the ductogram may be helpful in showing the surgeon which area of the breast harbors the cause of discharge. The filling defect in this woman was a benign papilloma, the most common cause of bloody or serous discharge.

Note: Usually, ductography is not easily performed and is of limited usefulness when discharge is not spontaneous, profuse, and confined to a single duct. Therefore, **ductograms should not be performed on all patients with nipple discharge**. Only bloody or serous discharges are of concern.

A dark brownish or greenish fluid rather than a truly bloody or serous discharge is typical of fibrocystic changes. Milky discharge is normal.

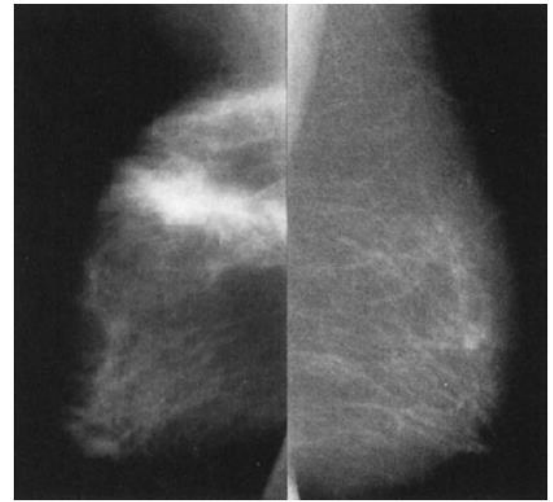


- 3) A 37-year-old woman who comes to the emergency department with a reddened, swollen, painful left breast. The right (A) and left (B) breast. The patient's entire left breast is abnormally dense. Infection and inflammatory carcinoma are both high on the differential diagnosis list. Breast carcinoma may incite an inflammatory response in the breast, mimicking a benign infectious process both clinically and radiographically. The patient turns out to have an elevated white blood cell count and fever with marked pain. This information now makes **infection** more likely than tumor, and a course of



antibiotics with follow up imaging to monitor resolution is appropriate. Infectious mastitis occurs more frequently in lactating women but is not uncommon in nonlactating women, particularly in diabetic patients. Imaging (mammography or ultrasound) is useful to exclude a drainable abscess collection and to provide a baseline for monitoring resolution to exclude carcinoma.

4) a 52-year old woman with soreness in the right breast. The patient was in a motor vehicle accident 2 months earlier and sustained a severe injury to the right side of her chest. Physical examination shows a resolving laceration and contusion that extends in a linear fashion over the right breast. The mammogram was done: This patient has pain, as in the last case, but her mammographic abnormality is much more localized and appears more like a malignant mass (being a high-density opacity with excessive speculation). However, this, too, is a benign process. These mammographic features are consistent with a resolving hematoma from acute trauma. Therefore, no further action is warranted at this time, other than **follow-up**. This case shows the **importance of correlation with history and physical examination**.



Approach to the asymptomatic patients

1. The first mammogram

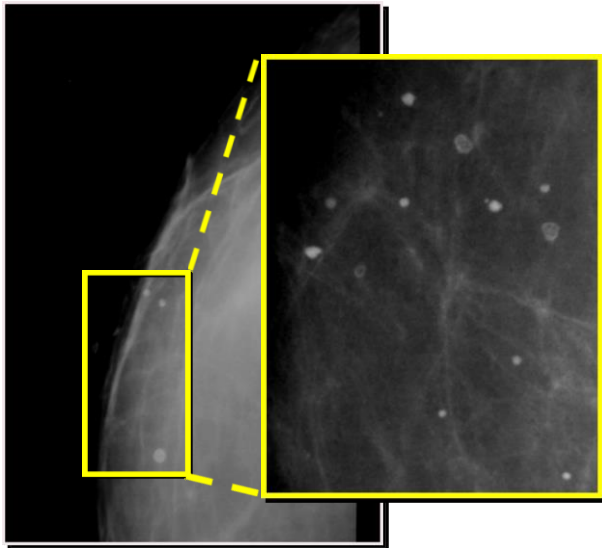
- The patient may have primary signs of malignancy (masses and calcification). However, these masses aren't palpable on CBE (small). We talked about the masses and now we'll talk about the calcifications.
- Diagnostic approach of calcification
 - Morphology:** The form of calcifications is the most important factor in the differentiation between benign and malignant.

Benign	Intermediate concern (suspicious)	Malignant
Skin (rounded or ring like)	Amorphous	Pleomorphic
Vascular		Fine linear and linear branching
popcorn		
Plasma cell mastitis (large rods)		
Fat necrosis (eggshell)/Milk of calcium		
round		
dystrophic		
suture		

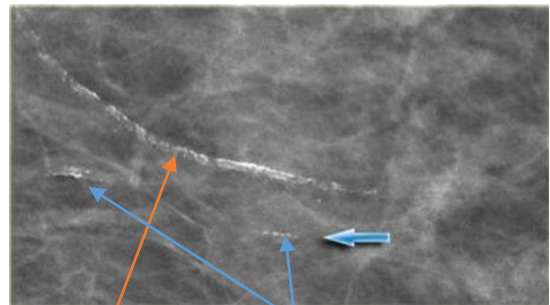
▪ **Benign:**

- Skin calcifications: round dense calcifications, sometimes eggshell, within 1 cm of the skin.
- Vascular calcifications: railroad appearance; they appear as either continuous or fragmented masses; increase with age.
- Round calcification away from the skin: Dense, scattered or clustered, with mixed sizes
- Eggshell calcifications away from skin: indicate calcified old cyst or sebaceous gland.
- Popcorn calcifications: also called coarse calcifications; the presence of a popcorn calcification inside an Isodense/hypodense well circumscribed mass **is diagnostic of an involuting fibroadenoma** which is a benign lesion.
- large rod calcifications: secretory calcification due to **Plasma cell mastitis**.
- Dystrophic: ill-defined calcifications usually following a surgery or a biopsy.
- Suture calcifications: calcifications at a suture site. Now rarely seen due to the use of absorbable sutures.

Skin calcification

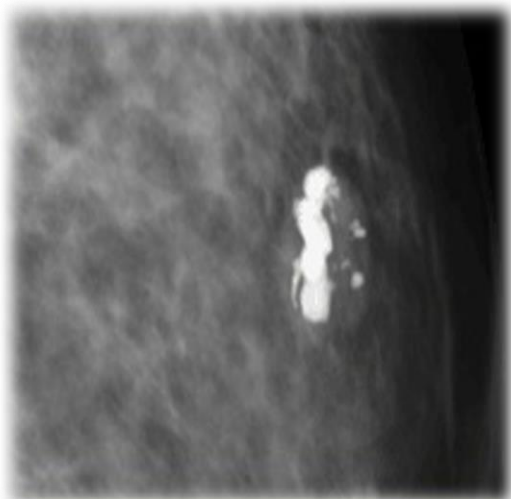


Vascular calcifications

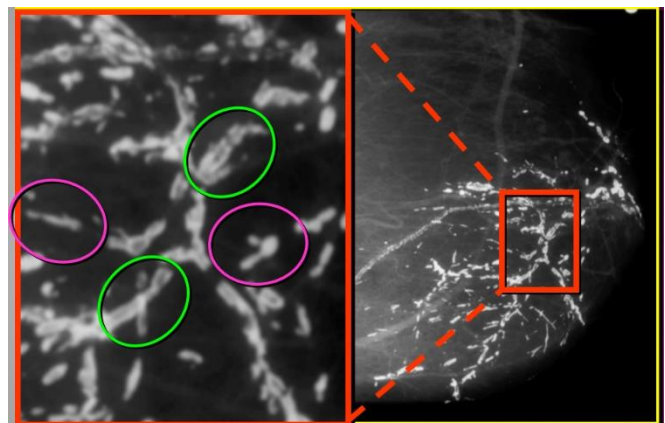


Continuous vs fragmented

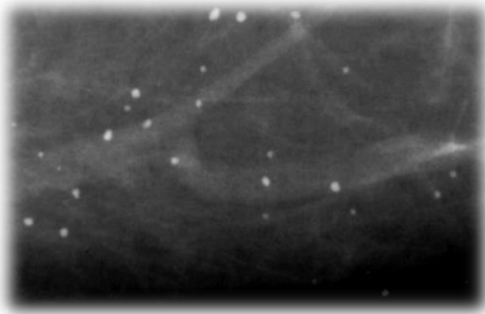
Coarse or 'Popcorn-like'



Large rods



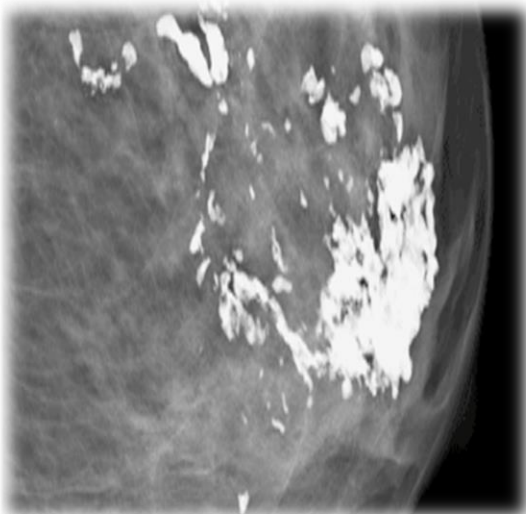
Round calcification



Eggshell or rim calcifications



Dystrophic calcifications



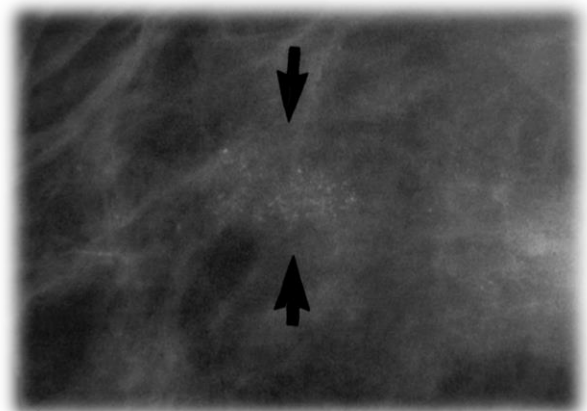
Suture calcification



- **Intermediate risk:**

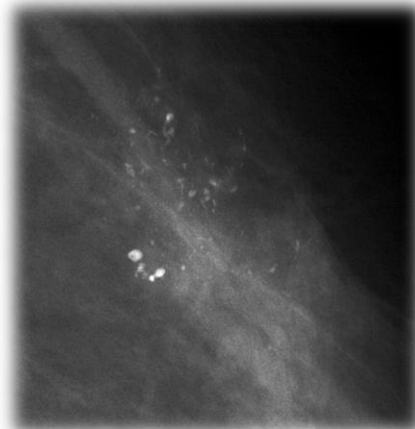
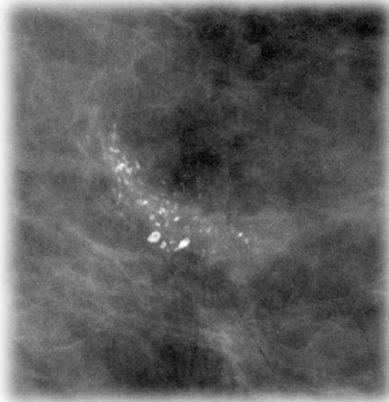
- Amorphous calcifications: powder like cluster calcifications; can indicate **low-grade DCIS** (malignant). They need to be biopsied. Hard to distinguish from sclerosing adenosis (**diffuse** and bilateral) and fibrocystic changes

Amorphous calcifications

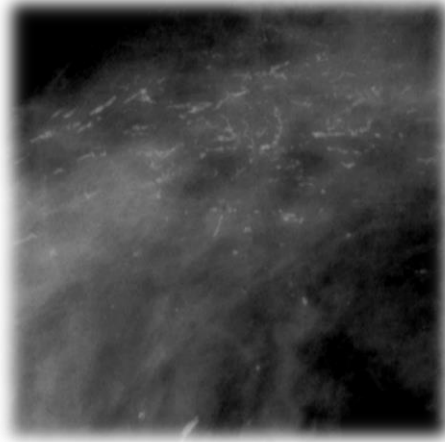
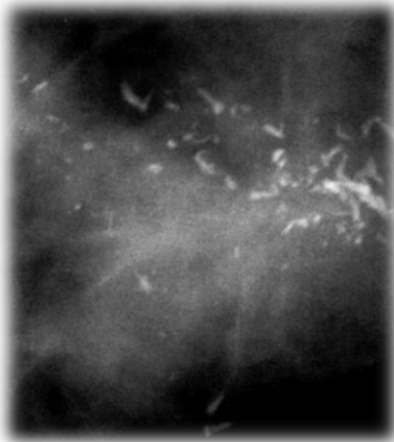


▪ **Malignant calcifications:**

- Pleomorphic, granular (“crushed stone”): multiple calcifications often mixtures of various sizes and shapes. Indicate high grade DCIS
- Fine linear branching calcifications (casting); indicate high grade DCIS (Comedo carcinoma).



High Grade
DCIS: **Granular**

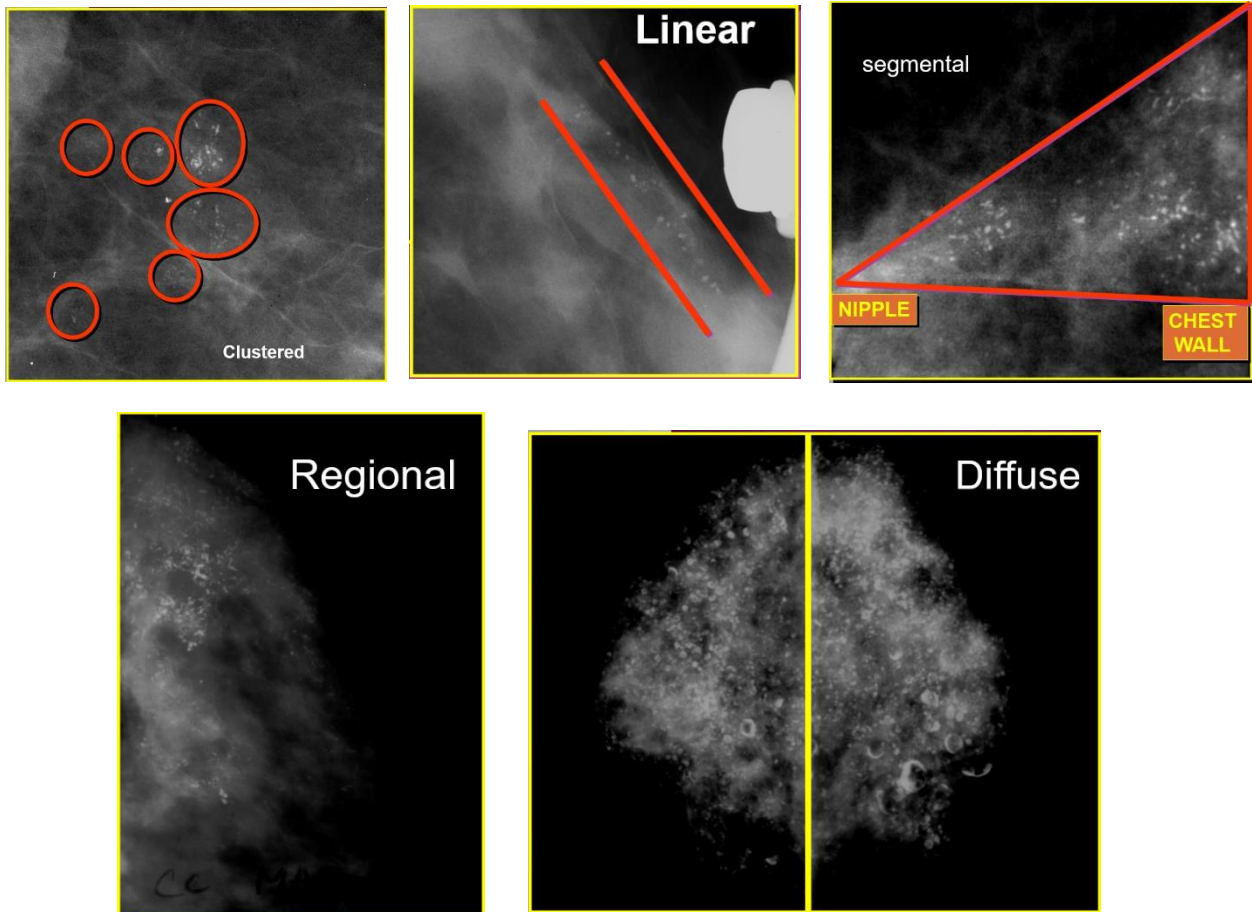


High-grade
DCIS:
Comedoform

B. Distribution

- Clustered: the calcifications are close to each other (1-2 cm apart)
- Linear calcifications: can be localized within two imaginary lines.
- Segmental: triangular distribution; the base of the triangle is towards the chest wall and the apex is at the nipple
- Regional: calcifications occupying 2-3 quadrants of the breast
- Diffuse: calcifications distributed throughout the breast; mostly seen post-radiation due to fat necrosis.

- **Note: Regional, loosely grouped or diffuse calcifications are usually benign. However, Segmental and cluster calcifications are usually malignant.**



2. The follow-up mammogram

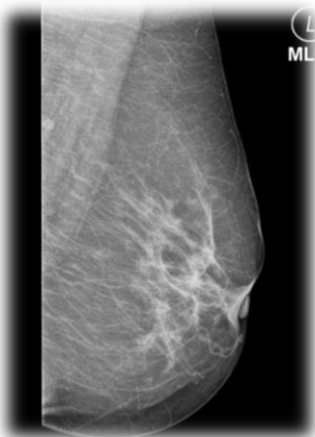
A. Developing densities.

- Any density that increases in size or density over time.
- All such opacities should be evaluated critically, as they can be signs of carcinoma. This concept is based on the natural behavior of breast cancer, which generally grows slowly. With periodic screening, the early tumor will be imaged but unrecognized on early images and may not be detected until 1, 2, 3, or more years later. Tumors 5 mm or smaller are very difficult to differentiate from normal breast tissue, but masses larger than 1 cm are more easily detected.
- **The spiculated margins, the rate of growth, and the patient's age group** all make the lesion a very suspicious lesion, thus a biopsy is warranted.

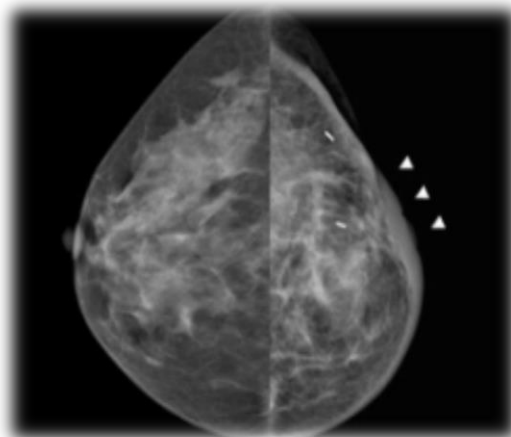
B. A new finding after a previous normal screening.

Secondary signs of cancer on mammogram

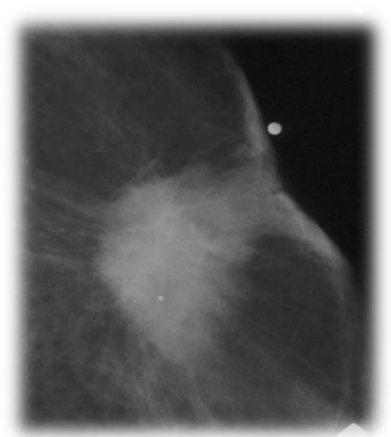
- Nipple inversion (nipple going inside).
- Thickened skin.
- Axillary lymphadenopathy.
- Skin retraction.
- Tissue asymmetry: differences in fibroglandular tissue distribution between the two breasts.
- Architectural distortion:
 - Although normal breast tissue is remarkably symmetric, it is never exactly the same on both sides. So, we have to recognize normal variation and to be able to distinguish non-pathologic asymmetry from disease. Once asymmetry is noted mammographically, a careful, focused breast examination is needed. If no suspicious areas are detected and if the radiographic features suggest fibroglandular tissue, then follow-up alone is adequate. If any suspicious areas are detected, then biopsy is strongly recommended.
 - The lines of tension appear to pull to a central focus (picture below). This is a classic appearance of **invasive lobular carcinoma**. **Surgical biopsy** may result in such distortion of the architecture (**benign**).
 - Studies have shown that a high percentage of carcinomas “missed” at mammography appear as architecture distortion or asymmetric density.
 - Previous mammograms are definitely useful in evaluating architecture distortion and asymmetric density. If the finding is unchanged over time, no further action may be needed.



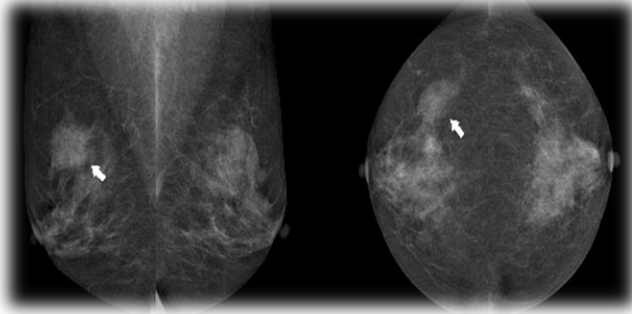
Nipple inversion



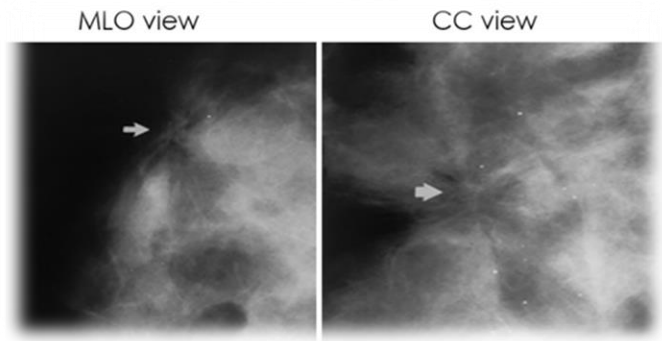
Skin thickening



Skin retraction



Focal asymmetry



Architectural distortion

BI-RADS classification (Breast mammogram report)

- **BI-RADS 0:** needs additional imaging and further evaluation; cannot assess the image.
- **BI-RADS 1:** negative findings: there is nothing to comment on (no positive findings).
- **BI-RADS 2:** benign finding; no need for short interval follow up; ex. Involuting fibroadenoma.
- **BI-RADS 3:** probably benign finding; <2% malignancy; follow up at 6,12,24 months (Initial short-interval follow up) ex. Fibroadenoma without a calcification.
- **BI-RADS 4:** suspicious finding (amorphous calcification); needs biopsy; 2-95% malignancy.
- **BI-RADS 5:** highly suggestive of malignancy >95% chance of malignancy; appropriate action needs to be taken.
- **BI-RADS 6:** a case of a proven malignancy by a biopsy; here the image is taken as follow up for treatment or to look for a different focus of metastasis. After chemotherapy or radiotherapy; the patient remains a BI-RADS 6. However, after surgical removal of a lesion, the patient returns to BI-RADS 1.

Nipple discharge

Definitions

- **Lactation:** normal milk production in breastfeeding women.
- **Galactorrhea:** milk production in non-breastfeeding women or men. (Galactorrhea in men is associated with **hypogonadism** and **gynecomastia**.)
 - Discharge varies in color (clear, white, yellowish, or greenish).
 - Expressed from either or both breasts.
- **Non-milky nipple discharge:** production and secretion of fluids other than milk.

Etiology

- **Galactorrhea**
 - Endocrine-related: **hyperprolactinemia** (may be related to endocrine disorders or medication), **primary hypothyroidism**.
 - Chronic nipple stimulation (e.g., piercings, tight clothing, etc.)
- **Non-milky nipple discharge**
 - Benign causes: intraductal papilloma (52–57% of cases), mammary duct ectasia, fibrocystic changes, breast abscess.
 - Malignancy: 5–15% of cases (mostly ductal carcinoma in situ).

Diagnostics

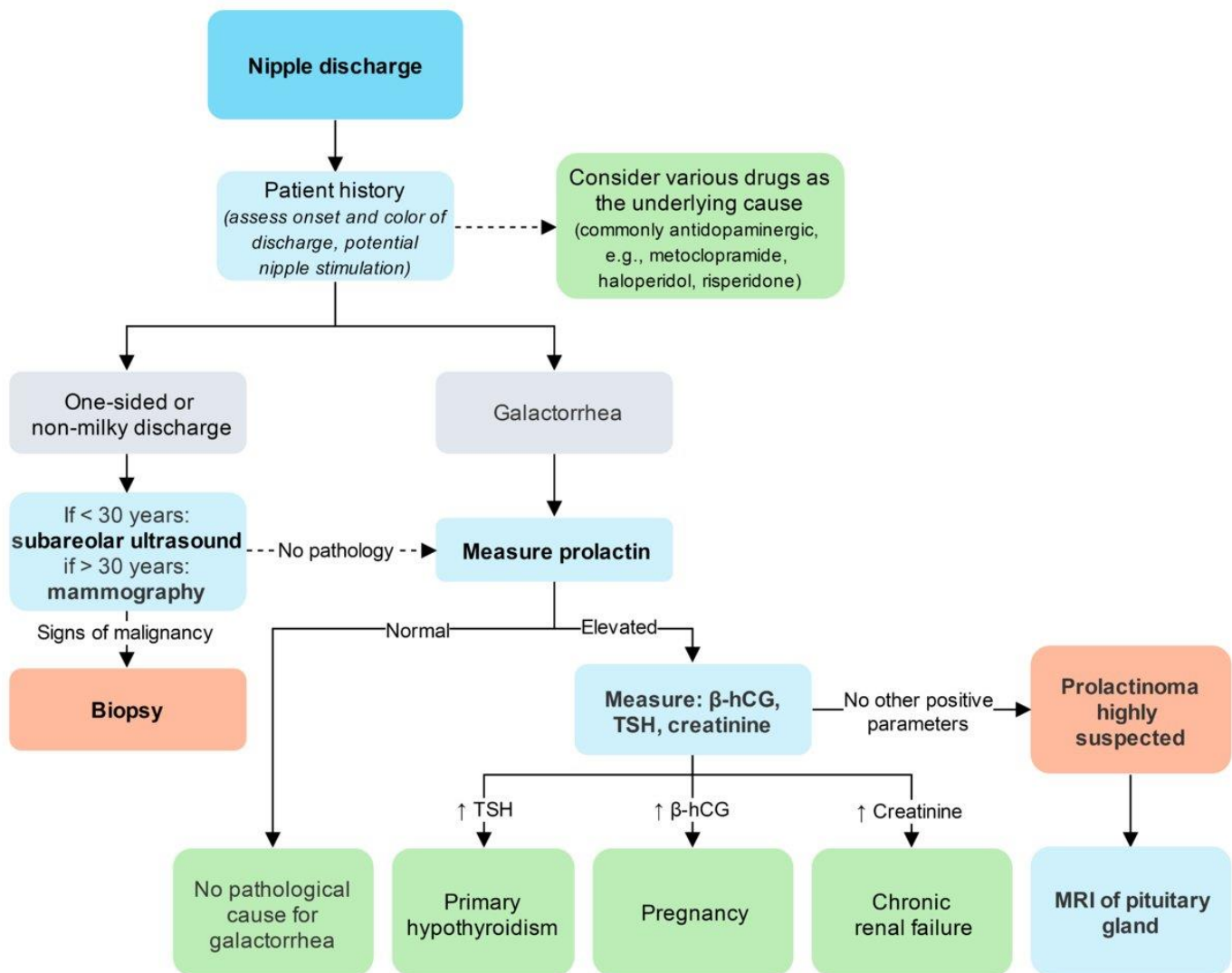
- Patient history (Findings, such as the onset of the discharge, its color, and potential nipple stimulation, are very important).
- Galactorrhea
 - hCG to exclude pregnancy.
 - Prolactin level (Patients with normoprolactinemic galactorrhea generally do not require further testing).
 - TSH level (Primary hypothyroidism → ↑ thyroid-releasing hormone → ↑ prolactin+ ↑ TSH).
- One-sided and/or non-milky discharge
 - Mammogram (in woman > 30 years).
 - Subareolar ultrasound (in woman < 30 years).

Signs that suggest malignancy

- Spontaneous, unilateral, uniductal, and bloody, or guaiac-positive discharge (The guaiac test allows detection of hidden blood from a fluid sample. It is usually employed to detect hidden blood in stool samples.)
- Presence of a breast mass or abnormalities in imaging
- Age > 40 years

Note: Biopsy is **mandatory** if **malignant disease** is suspected.

Diagnostic approach to nipple discharge



Treatment

Galactorrhea

1. In the case of hyperprolactinemia:

- **Dopamine agonists** (treatment of choice): bromocriptine, cabergoline, quinagolide.
- Treat the underlying cause
 - Transsphenoidal resection of the pituitary adenoma. (in the case of **prolactinomas**).
 - Discontinue or lower the dose of the offending drug. (in case of drug induced hyperprolactinemia, the most important category is **dopamine antagonists**. Dopamine inhibits prolactin secretion, so dopamine antagonists would therefore disrupt the inhibition and lead to increased prolactin secretion.)
 - Treatment of **primary hypothyroidism**.
 - Renal transplant for patients with CRF. (in case of CRF, probably due to decreased prolactin clearance or disordered hypothalamic regulation.)

2. In the case of normoprolactinemic galactorrhea: Reassurance and avoidance of nipple stimulation.

Non-milky nipple discharge

Treatment depends on the underlying disorder and can be found under respective causes (e.g., terminal ductal excision in the case of intraductal papilloma).

Summary

Overview of Benign breast conditions

	Epidemiology	Clinical features	Diagnosis	Treatment
Fibrocystic changes	<ul style="list-style-type: none"> Most common benign lesion of the breast 	<ul style="list-style-type: none"> Tender breast nodules 	<ul style="list-style-type: none"> Ultrasound and/or mammogram 	<ul style="list-style-type: none"> Only required if severe symptoms are present Oral contraceptives, tamoxifen
Mastitis	<ul style="list-style-type: none"> Most common in nursing mothers 	<ul style="list-style-type: none"> Tender, firm, swollen, erythematous breast (generally unilateral) 	<ul style="list-style-type: none"> Clinical 	<ul style="list-style-type: none"> In nursing mothers: frequent emptying of the breast Analgesics and cold compresses Antibiotics (dicloxacillin)
Fat necrosis	<ul style="list-style-type: none"> < 3% of all breast lesions Peak incidence: 50 years Often associated with soft tissue trauma 	<ul style="list-style-type: none"> Irregularly defined and dense peri areolar breast mass Skin retraction, erythema, and ecchymosis 	<ul style="list-style-type: none"> Ultrasound and/or mammogram 	<ul style="list-style-type: none"> Unnecessary
Galactocele	<ul style="list-style-type: none"> Most common benign breast lesion in lactating women Frequently occurs during or after lactation 	<ul style="list-style-type: none"> Painless, firm mass 	<ul style="list-style-type: none"> Mainly clinical diagnosis Fine-needle aspiration Ultrasound or mammogram 	<ul style="list-style-type: none"> Repeated needle aspiration or surgical excision if cysts are symptomatic
Gynecomastia	<ul style="list-style-type: none"> Physiological gynecomastia: common in male and female neonates, male adolescents, and men > 50 years Drug-induced gynecomastia: most common type of pathological gynecomastia 	<ul style="list-style-type: none"> Firm, concentric mass at the nipple areolar complex, which may be tender 	<ul style="list-style-type: none"> Mainly clinical Mammogram (in ambiguous cases) 	<ul style="list-style-type: none"> Only required in persistent cases Medical therapy: testosterone replacement or tamoxifen Surgery (subcutaneous mastectomy) Treatment of the underlying cause

Fibroadenoma	<ul style="list-style-type: none"> • Most common breast mass in women < 35 years 	<ul style="list-style-type: none"> • Solitary, well-defined, non-tender, rubbery, and mobile mass 	<ul style="list-style-type: none"> • Ultrasound • Fine-needle aspiration 	<ul style="list-style-type: none"> • Regular check-ups
Phyllodes tumor	<ul style="list-style-type: none"> • Rare (< 1% of all breast tumors) • Peak incidence: 40–50 years 	<ul style="list-style-type: none"> • Painless, smooth, multinodular lump • Variable growth rate • Generally > 3 cm 	<ul style="list-style-type: none"> • Ultrasound and/or mammogram • Core needle biopsy 	<ul style="list-style-type: none"> • Surgical excision
Intraductal papilloma	<ul style="list-style-type: none"> • Peak incidence <ul style="list-style-type: none"> ○ Solitary lesions: ~ 48 years ○ Multiple lesions: ~ 41 years 	<ul style="list-style-type: none"> • Solitary lesions <ul style="list-style-type: none"> ○ Bloody nipple discharge ○ Palpable breast tumor close to or behind the nipple • Multiple lesions <ul style="list-style-type: none"> ○ Usually asymptomatic 	<ul style="list-style-type: none"> • Core needle biopsy 	<ul style="list-style-type: none"> • Surgical excision
Mammary duct ectasia	<ul style="list-style-type: none"> • Perimenopausal women 	<ul style="list-style-type: none"> • Unilateral greenish or bloody discharge • Nipple inversion • Firm, stable, painful mass under the nipple 	<ul style="list-style-type: none"> • Mammogram and/or ultrasound 	<ul style="list-style-type: none"> • Usually unnecessary • Antibiotic therapy if infected • Surgical excision for persistent lesions

Differential diagnosis of breast conditions

			Breast mass	Nipple discharge	Skin changes	Ultrasound/Mammography	Biopsy
Benign	Nonneoplastic	Fibrocystic breast changes (Most common benign lesion of the breast.)	<ul style="list-style-type: none"> • Premenstrual bilateral breast pain • Tender breast nodules 	<ul style="list-style-type: none"> • Clear or slightly milky 	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Normal appearance or focal regions of thick parenchyma • Clear borders • +/- cysts • +/- dispersed calcifications 	<ul style="list-style-type: none"> • Stromal fibrosis • Cysts • Papillary apocrine changes • Mild epithelial hyperplasia or calcifications
		Gynecomastia	<ul style="list-style-type: none"> • Firm, concentric, sometimes tender mass at the nipple areolar complex 	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Mammogram only required in doubtful or persistent cases) 	<ul style="list-style-type: none"> • Unnecessary
	Inflammatory	Mastitis	<ul style="list-style-type: none"> • Tender, firm, swollen, erythematous breast (generally unilateral) • Flu-like symptoms, malaise, fever, and chills • Possible reactive lymphadenopathy 	<ul style="list-style-type: none"> • Milky • Bloody 	<ul style="list-style-type: none"> • Signs of inflammation (swelling, warmth, erythema) 	<ul style="list-style-type: none"> • Unnecessary 	<ul style="list-style-type: none"> • Unnecessary • Milk sampling + culture only if initial treatment fails
		Fat necrosis	<ul style="list-style-type: none"> • Irregularly defined and dense peri areolar breast mass 		<ul style="list-style-type: none"> • Skin retraction, erythema, and ecchymosis 	<ul style="list-style-type: none"> • Fluid-filled cyst • Course rim calcification 	<ul style="list-style-type: none"> • Foam cells, multinucleated giant cells, hemosiderin deposition, and chronic inflammation

		Breast abscess	<ul style="list-style-type: none"> • Fluctuant mass 				
		Eczema of the breast	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Eczematous rash with poorly defined margins and no infiltration 	<ul style="list-style-type: none"> • Unnecessary 	<ul style="list-style-type: none"> • Only if diagnosis is inconclusive or malignancy is suspected
Neoplastic		Fibroadenoma	<ul style="list-style-type: none"> • Solitary, well-defined, non-tender, rubbery and mobile mass 			<ul style="list-style-type: none"> • Well-defined mass • Possibly popcorn-like calcifications 	<ul style="list-style-type: none"> • Fibrous and glandular tissue
		Phyllodes tumor	<ul style="list-style-type: none"> • Painless, smooth, multinodular lump • Variable growth rate • Generally > 3 cm 			<ul style="list-style-type: none"> • Similar findings to fibroadenoma, but phyllodes tumors tend to be larger and grow faster than fibroadenoma 	<ul style="list-style-type: none"> • Leaf-like architecture with papillary projection of epithelium-lined stroma and varying degrees of atypia and hyperplasia
		Intraductal papilloma	<ul style="list-style-type: none"> • Solitary lesions: palpable breast tumor close to or behind the nipple • Multiple lesions: usually asymptomatic 	<ul style="list-style-type: none"> • Bloody (most common cause) 	<ul style="list-style-type: none"> • None 		<ul style="list-style-type: none"> • Fibrovascular tissues surrounded by epithelial cells within lactiferous ducts
Malignant		Invasive carcinoma (ductal and lobular)	<ul style="list-style-type: none"> • Firm, rigid mass with irregular borders • Asymmetry to the contralateral breast 	<ul style="list-style-type: none"> • Bloody 	<ul style="list-style-type: none"> • Thickening • Retraction • Dimpling 	<ul style="list-style-type: none"> • Focal mass or density with poorly defined margins • Spiculated margins • Clustered microcalcifications 	<ul style="list-style-type: none"> • Ductal: malignant cells in duct, stromal invasion, microcalcifications, fibrosis in surrounding tissue

		<ul style="list-style-type: none"> • Fixation to the skin or chest wall • Axillary adenopathy 				<ul style="list-style-type: none"> • Lobular: malignant cells in lobules; monomorphic cells in a single file pattern ("Indian file" pattern)
	Inflammatory breast cancer	<ul style="list-style-type: none"> • A rapidly growing breast mass • Tenderness, burning sensation • Axillary lymphadenopathy 	<ul style="list-style-type: none"> • Blood-tinged 	<ul style="list-style-type: none"> • Erythematous and edematous (peau d'orange) skin plaques directly above the breast mass 	<ul style="list-style-type: none"> • Focal mass or density with poorly defined margins • Spiculated margins • Clustered microcalcifications 	<ul style="list-style-type: none"> • Dermal lymphatic invasion, angioinvasion
	Paget disease of the breast	<ul style="list-style-type: none"> • Possibly a firm, rigid mass with irregular borders (similar to invasive ductal carcinoma) 	<ul style="list-style-type: none"> • Blood-tinged (when the lesion ulcerates) 	<ul style="list-style-type: none"> • Erythematous, scaly, or vesicular rash affecting the nipple and areola • Pruritus, burning sensation, nipple retraction 	<ul style="list-style-type: none"> • Focal mass or density with poorly defined margins • Spiculated margins • Clustered microcalcifications 	<ul style="list-style-type: none"> • Nipple scrape cytology: large, round cells with prominent nuclei