



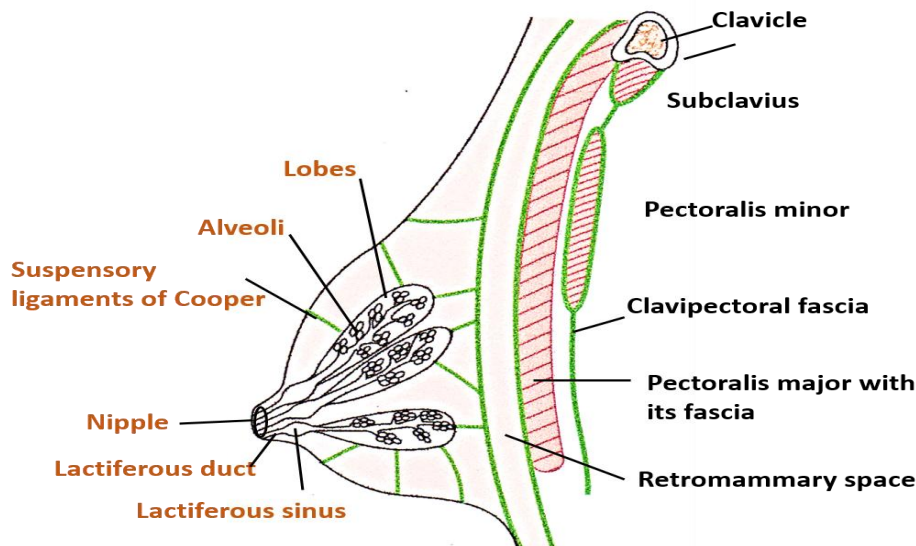
BREAST PATHOLOGY

ANATOMY & HISTOLOGY

The size and structure of the breast vary with the age, sex, hormonal status and heredity of the individual. The areola is the circular pigmented area that contains sebaceous glands. In its center, the elevated nipple is covered by wrinkled skin lined by stratified squamous epithelium. It contains 15-20 lactiferous ducts (lined by two-layered cuboidal cell mucosa) which branch successively distally, leading eventually into the terminal ducts. Before puberty, this complex system ends blindly but at menarche, it proliferates distally giving rise to 30- epithelium lined ductules or acini. Each terminal duct and its ductules compose the terminal duct lobular unit. The ductules are covered by cuboidal and myoepithelial lining cells. In addition to ramifying ducts, the female breast consists of connective and adipose tissue, although few alveoli may develop and involute concomitantly with the menstrual cycle. In the male breast, there are only rudimentary ducts surrounded by connective tissue

The female breast is in the unique position of being a gland which is non-functioning except during lactation. However, its extreme sensitivity to hormonal influences disposes it to a number of pathological conditions.

Structure of Mammary Gland and its Deep Relations

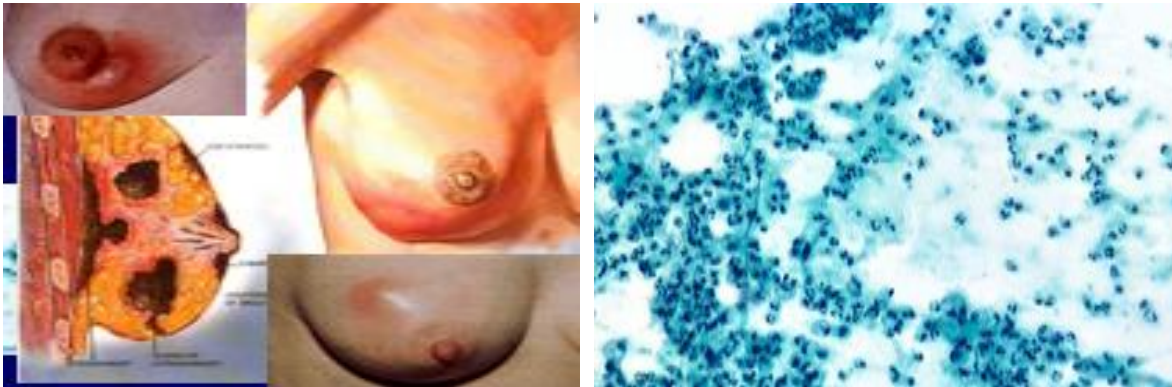


PATHOLOGICAL CLASSIFICATION OF BREAST DISEASES

Inflammatory and related lesions:

- **Acute Infections (Pyogenic Mastitis and Breast Abscess)**

Mastitis, a local or generalized inflammation of the breast, is precipitated by lactation, trauma or infection through the ducts or nipple abrasions. It is usually caused by *Staph. Aureus* which may invade the breast tissue and progress to the formation of single or multiple abscesses; where by the localized collection of pus causes conspicuous tenderness. Less commonly, *Strept. Pyogenes* may cause cellulites. If extensive necrosis occurs the destroyed breast substance will be replaced by fibrous scar which may cause retraction of the overlying skin or nipple, stony hardness and axillary lymphadenopathy; changes mimicking a malignant neoplasm. Chronic inflammation if neglected may lead to fistula formation.



- **Chronic Infections and Granulomatous inflammations**

Granulomas are caused by different infectious agents:

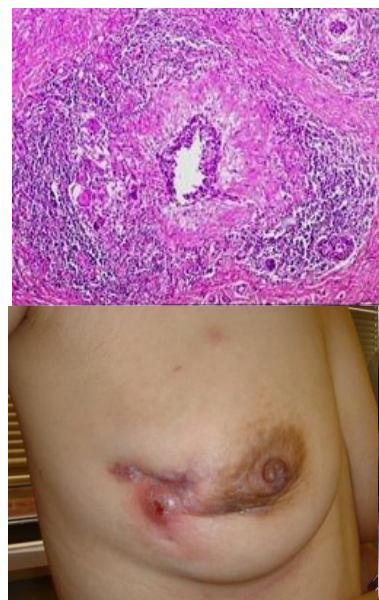
Tuberculomas involving the breast have been described. Although it is relatively rare, but it usually arises from hematogenous, lymphatic or direct spread. It presents as a single caseating lesion which sometimes discharges through the skin.

Sarcoidosis: reveals similar picture without caseation or acid-fast bacilli.

Fungal infection: Coccidioidomycosis and actinomycosis are associated with necrotizing granulomas. These are diagnosed by special stains such as PAS or tissue culture.

Idiopathic Granulomatous mastitis:

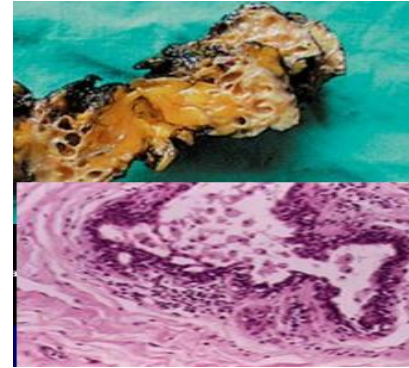
This rare condition is seen mainly in young women, usually after pregnancy. Patients present with firm tender mass. It may be complicated by overlying skin ulcerations and multiple draining sinuses.



- **Non-Infective inflammatory lesions:**

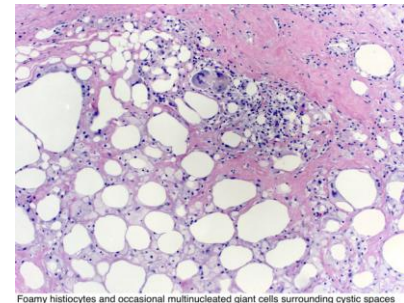
- 1. Mammary Duct Ectasia**

This disorder tends to affect perimenopausal women usually in the fifth decade of life. Patients are often multiparous and have lactated, but may have had trouble in nursing due to inverted nipples. It begins with dilatation of the terminal collecting ducts beneath the nipple and areola where they become distended with cellular debris and lipid containing material. This may be followed by marked periductal and interstitial chronic granulomatous inflammatory reaction and fibrosis, sometimes associated with a large number of plasma cells (*plasma cell mastitis*). It could rarely be palpable as a “bag of worms”. Fibrosis may cause skin retraction which may be mistaken for carcinoma. It is often symptomless but there may be nipple discharge. Hyper-prolactinemia is suggested to play a role in its pathogenesis. Duct ectasia could result in a firm mass with adjacent skin dimpling and nipple retraction.



- 2. Traumatic Fat Necrosis**

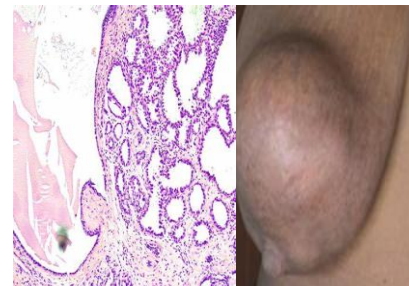
It often follows trauma and presents clinically as a firm hard mass within the fatty tissue of an obese pendulous breast and is sometimes associated with skin retraction. It consists of a central focus of liquefactive fat necrosis, surrounded by lipid-laden macrophages and numerous neutrophilic inflammatory infiltrations. This is followed by fibroblastic proliferation, foreign-body giant cell infiltration and ending into scar tissue (which together with the calcification accounts for the hardness of the lump). Extensive fibrous reaction may further cause nipple retraction and fixation thus simulating malignancy.



Foamy histiocytes and occasional multinucleated giant cells surrounding cystic spaces

- 3. Galactocele**

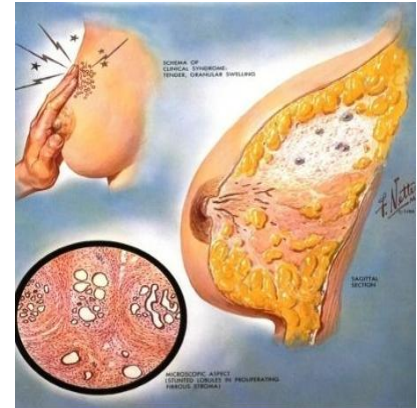
This is a cystic dilatation of a duct occurring during lactation and presenting as a tender mass. It results from obstruction of the lactiferous duct, distention by milk and desquamated epithelial cells. Secondary obstruction may convert these single and multiple cysts into foci of acute mastitis or abscesses, or may induce granulomatous reaction. The aspirated material is usually yellowish-white, creamy fluid, sometimes curd-like or blood-tinged containing histiocytes, and foamy ductal cells within a background of abundant protein and lipid deposits.



- 4. Fibrocystic Changes or Cystic Mastopathy**

This is a pleomorphic disorder in which variable morphological patterns are encountered in different patients, different areas within the same lesion and even in different microscopical fields within the same slide.

It develops in females between puberty and menopause and is considered the commonest cause for a lump in the breast. Patients usually present with ill defined tender thickness of the breast tissue, palpable lumps or physiological nodularity which may vary during the period of the menstrual cycle. It has been postulated that those changes are related to imbalance between estrogens and progestins (with excessive estrogenic stimulation).



Fibrocystic Changes are of clinical significance:

- Some variants may clinically mimic carcinoma.
- They may coexist with carcinoma.
- They may predispose to the development of carcinoma.

It is possible to distinguish 3 dominant patterns of morphological changes:

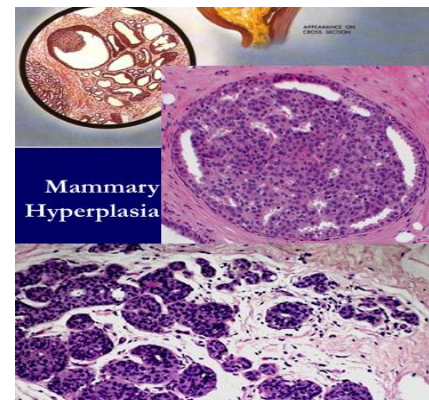
a) Cystic Formation and Fibrosis (Simple Fibrocystic Changes)

This is the most common type of alteration characterized by an increase in fibrous stroma associated with ductal dilatation and formation of cysts of various sizes, probably due to obstruction. Unopened cysts are brown to blue in colour due to the contained semitranslucent turbid fluid. Sometimes haemorrhage or rupture leads to secondary inflammation. Cysts are lined by columnar, cuboidal or flattened epithelium that may be atrophic in larger ones. The epithelium may consist of large polygonal cells with abundant granular eosinophilic cytoplasm and small hyperchromatic nuclei (*apocrine metaplasia*), which is virtually always benign. In general, the breast should be palpated again after cystic aspiration and any residual mass should be reaspirated.



b) Epithelial Hyperplasia (Epitheliosis)

Hyperplasia affecting mammary ducts and ductules is the histological variant that increases the risk of subsequent development of malignancy; especially if it is associated with atypia. It may take three main forms: solid, cribriform or papillary. The degree of hyperplasia can be mild, moderate, or severe. In some instances the hyperplastic cells show complex architectural patterns and approaching morphologically those of ductal carcinoma in situ, such hyperplasia is called *atypical*.



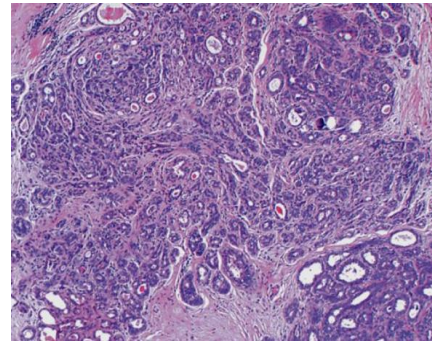
Atypical lobular hyperplasia describes hyperplasias that cytologically resemble lobular carcinoma in situ, but the cells do not fill or distend more than 50% of the acini within a lobule. *Atypical lobular hyperplasia is associated with an increased risk of invasive carcinoma. In general, epithelial hyperplasia does not often produce a clinically discrete breast mass.*

Microscopically, proliferation causes increase in the layers of the ductal epithelium, sometimes encroaching to completely fill the duct lumen obliterating it (*solid*) or forming fenestrations with gland-like spaces (*cribriform*). Papillary epithelial projections may grow into the lumen (ductal or florid *papillomatosis*). The presence of ductal papillomatosis or moderate to severe atypia increases the risk of malignancy. Atypical ductal or lobular hyperplasia may show various degrees of cellular or architectural atypias that should be differentiated from carcinoma in situ.

c) *Adenosis and Sclerosing Adenosis*

Adenosis: Refers to enlargement of the lobules and/or formation of new lobules, It could be a physiological process which occurs during pregnancy and reproductive life; however, it tends to be accentuated in fibrocystic changes.

Sclerosing Adenosis: Is a significant variant of fibrocystic changes because its clinical and morphologic features may be deceptively similar to those of carcinoma. Grossly, the lesion has a hard, rubbery consistency, and thus simulates that of breast cancer. Microscopically, this variant is characterized histologically by intralobular fibrosis and proliferation of small ductules or acini which yield small glandular masses or cellular cords within a fibrous stroma. Well-defined glands may be closely aggregated and backed to each other (*adenosis*). Stromal overgrowth may distort and compress the glands creating solid cords. Cells from sclerosing adenosis form clusters of up to 30 cells with some nuclear piling and minimal anisonucleosis. Sclerosing adenosis is associated with only a minimally increased risk of progression to carcinoma.



Relationship of the various patterns of Fibrocystic Changes to Carcinoma:

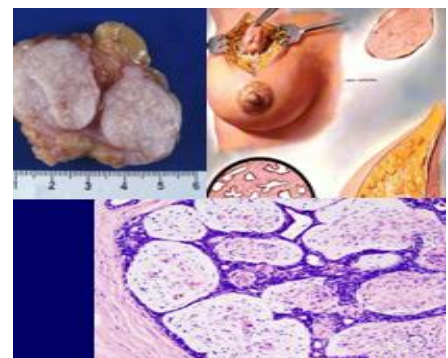
- **Minimal or no increased risk** of breast carcinoma: Fibrosis, Cystic changes, Apocrine Metaplasia, mild Hyperplasia and Fibroadenomatosis.
- **Slightly increased risk** (1.5-2 times): Moderate to florid hyperplasia (without atypia), Ductal Papillomatosis and Sclerosing Adenosis.
- **Significantly increased risk** (5 times): Atypical Hyperplasia (ductular or lobular).

A family history of breast cancer may increase the risk in all categories specifically if there is atypical hyperplasia.

Benign Tumors:

• **Fibroadenoma**

This is the most common benign tumor of the female breast. It is a new growth composed of both fibrous and glandular tissue occurring commonly in young women (before the age of 30), and probably caused by hormonal imbalance. Areas resembling fibroadenoma sometimes occur in Fibrocystic Changes (*Fibroadenomatosis*).



Clinically, palpation reveals a dominant discrete, well-circumscribed elastic round or oval firm mass which resists penetration by the aspiration needle but proves to be mobile when penetrated. Usually small (2-4 cm) but may reach 7 cm with a uniform tan-white color on cut section. They are usually encapsulated affecting one breast, and rarely multiple in both breasts. Microscopically, there are two varieties: the **"Intracanalicular"** type which encroaches into and obliterates the ducts with broad, polypoidal branches of loose connective tissue lined by cuboidal ductal cells. The **"Pericanalicular"** type encircles the ducts, with dense, concentric mesenchyme. The clinical and cytological presentation of both types is identical. Rarely insitu lobular or ductal carcinoma arise in fibroadenoma.

- **Adenomas**

These are variants of fibroadenoma with glandular rather than stromal proliferation. It is a homogenous sharply demarcated epithelial tumour that is composed either of tubules (**Tubular Adenoma**) or dilated alveoli containing secretory foamy material (**Lactationg Adenoma**). Microscopically, the small rounded acini lined by cuboidal or (during pregnancy) secretory columnar cells are tightly packed with little intervening stroma. Because of the lack of mesenchyme and the presence of eosinophilic macronucleoli, the lesion may resemble well-differentiated adenocarcinoma.

Adenoma of the Nipple

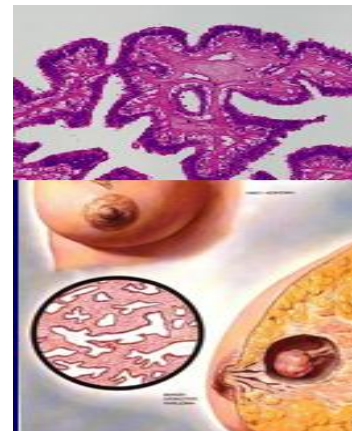
This is a benign epithelial tumor arising in one of the ducts of the nipple. It demonstrates intraductal proliferation which may be papillary, solid or tubular. Occasionally the lesion may extend through the overlying skin and thus mistaken clinically as malignant.

- **Intraductal Papilloma**

The main secretory ducts are the most common sites of this neoplasm, which is often associated with hemorrhagic discharge from the nipple. It is often solitary and present clinically as a result of:

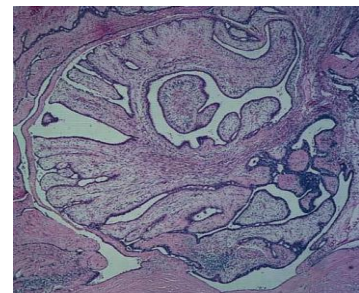
- Appearance of serous or bloody nipple discharge.
- Presence of small subareolar tumour.
- Rarely nipple retraction.

According to WHO definition, duct papilloma is a regular papillary overgrowth without mitosis or hyperchromatism". Histologically, it is composed of multiple papillae, each having a connective tissue axis covered by cuboidal or cylindrical epithelium with myoepithelial cells.



- **Phyllodes Tumour (Cystosarcoma Phyllodes)**

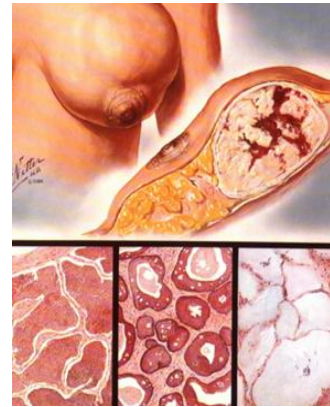
Infrequently fibroadenoma may grow rapidly often to 10 cm. or more in diameter (**Giant Fibroadenoma**). Most are benign but few are malignant (**Cystosarcoma**). On palpation, these are usually large circumscribed, mobile and some may become lobulated and cystic. Grossly, they exhibit leaf-like



clefts or finger-like projections (*phylloides*). They may distort the breast producing pressure necrosis and skin retraction and ulceration. Histologically, these lesions tend to have a more cellular myxoid stroma than do the usual fibroadenoma. Features suggesting its aggressive nature include lack of encapsulation, large dimensions, remarkable nuclear anaplasia, and abnormal mitosis.

Malignant Mammary Lesions (Breast Cancer):

Breast cancer is the most common type of malignancy among the Iraqi population in general; forming approximately one third of the registered female cancers.. Worldwide, most of the data point to three sets of influences that may be important in increasing the risk for breast cancer: genetic predisposition, hormonal imbalance and environmental factors.



Risk factors for Breast Cancer:

1) Genetic Predisposition and Family History:

Up to 10% of breast cancers are related to specific inherited mutations. Women are more likely to carry a susceptibility gene if they have:

- a. Premenopausal breast cancer
- b. Bilateral breast cancer
- c. Other associated cancers (e.g., ovarian cancer)
- d. A significant family history (i.e., multiple relatives affected before menopause).

About 50% of women with hereditary breast cancer have mutations in gene BRCA1, and an additional 30% have mutations in BRCA2. Both BRCA 1 and 2 seem to be involved in DNA repair and act as tumor suppressor genes. Cancer arises when both alleles are inactive (defective); one due to a germ-line mutation and the second by a subsequent somatic mutation. It is possible that other mechanisms, such as methylation of regulatory regions, act to inactivate the genes in sporadic (nonhereditary) cancer.

Over expression of the HER2/NEU proto-oncogene has been found to be amplified in up to 30% of invasive breast cancers. Mutations of the well-known tumor suppressor genes RB and p53 may also be present.

2) Reproductive Factors and Ovarian Activity:

i- Age at Menarche and Menopause (length of reproductive life)

It has been noted that women who had menarche before twelve years of age and women who develop natural menopause at age 55 or older are at increased risk.

ii- Pregnancy

It is well-known that breast cancer is more frequently encountered in nulliparus than in multiparus women. Several studies reported that the risk is inversely proportional to the number of children born.

iii- Lactation

Through its inhibitory activity on ovarian function, lactation has been thought to lower

the risk of breast cancer. Nevertheless, other studies indicated that breast cancer has no relationship with lactation.

iv- Oophorectomy

It has been reported that bilateral oophorectomy before the age of 44 years may protect against breast cancer.

All the above mentioned factors imply increased risk with increased exposure to estrogen peaks during the menstrual cycle.

3) Exogenous Hormones:

Several trials and reports have indicated that women using contraceptive pills or hormone replacement therapy for a long term might be at increased risk.

4) Effect of Age:

Breast cancer has been reported in various age groups, but it is more often seen in patients over 40 years; as the risk increases with age. The risk also increases regularly with the increase of age at first childbirth.

5) Geographical Influence:

Breast cancer rates are 5 or 6 times higher in Western Europe and North America than in Japan and other Asian and African populations; probably attributable to environmental, nutritional or life style factors .

6) History of Fibrocystic Changes:

Patients who exhibited a remarkable degree of ductal hyperplasia (florid papillomatosis) had a slightly increased risk (1.5-2 times) of developing subsequent breast cancer. This risk was increased significantly (5 times) when atypical hyperplasia was observed .

7) Multiple Primary Cancers:

Carcinoma of the contralateral breast increases the risk. Similarly, it is reported that women with endometrial cancer have a breast carcinoma risk of 1-2 times more than the general population. Breast cancers displaying a familial association with ovarian and colonic cancers have been also reported.

8) Diet and Nutrition:

It has been proposed that breast cancer is a disease of high socioeconomic status with good quality food:

i- Fat Consumption

Epidemiological evidence supported by experimental data strongly suggests that dietary fats play a vital role in breast cancer pathogenesis. This association may include the hypothesis that intestinal flora produce estrogens from ingested fat.

ii- Protein Consumption

It has been concluded that women whose diets contained high levels of animal proteins (Including meat, dairy products, bovine milk, high-fat cheese and butter) showed significantly increased risk.

iii- Effect of Caloric, Vitamin Intake and Alcohol Consumption

Caloric restriction inhibited the development of tumors of the mammary glands and other organs in mice and rats. The protective roles of vitamins A, C and E have been also suggested. Recent studies demonstrated that the risk is increased with alcohol intake in patients who consumed more than three pints per day.

9) Obesity:

Obesity seems to be associated with an increased breast cancer risk since it has been reported that these women have increased peripheral conversion of Androstenedione to Estrone; the latter is considered a carcinogenic agent. Obese patients were also found to have greater chance of early recurrence and shorter survival than do non-obese patients.

10) Ionizing radiations:

Studies reported that female survivors of atomic bomb explosions in Japan as well as patients exposed to high dose of 90 R or more developed breast cancer at a rate 2-4 times more than that for non-exposed individuals. That was specifically obvious when exposure targeted adolescent females (immature breasts).

11) Viruses:

Although still debatable, yet three animal models exist for the viral induction of breast cancer, namely Mouse Mammary Tumor Virus (MMTV), Mazon Pfizer Monkey Virus (MPMV), and Rat Mammary Tumor Virus (R-35 Virus. It has been demonstrated that a filterable agent transmitted through the mother's milk caused breast cancer in suckling mice. This MMTV was later identified as retrovirus.

WHO Pathological Classification of Breast Tumor Types

I.

Epithelial Tumors:

A. Benign

1. Intraductal papilloma
2. Adenoma of the nipple
3. Adenoma
 - a. Tubular
 - b. Lactating

B. Malignant

1. Non-invasive

- a. Intraductal carcinoma
- b. Lobular carcinoma in situ

2. Invasive

- a. Invasive ductal carcinoma
- b. Invasive ductal carcinoma with a predominant intraductal component
- c. Invasive lobular carcinoma
- d. Mucinous carcinoma
- e. Medullary carcinoma
- f. Papillary carcinoma
- g. Tubular carcinoma
- h. Adenoid cystic carcinoma
- i. Secretory (juvenile) carcinoma
- j. Apocrine carcinoma
- k. Carcinoma with metaplasia
 - i. Squamous type
 - ii. Spindle-cell type
 - iii. Cartilaginous and osseous type
 - iv. Mixed type

3. Paget's disease of the nipple

II. Mixed Connective Tissue and Epithelial Tumors:

- A. Fibroadenoma
- B. Phyllodes tumor (cystosarcoma phyllodes)
- C. Carcinosarcoma

III. Miscellaneous Tumors :

- A. Soft tissue tumors
- B. Skin tumors
- C. Tumors of Haemopoietic and Lymph tissues

IV. Unclassified Tumors

V. Mammary Dysplasia / Fibrocystic Change

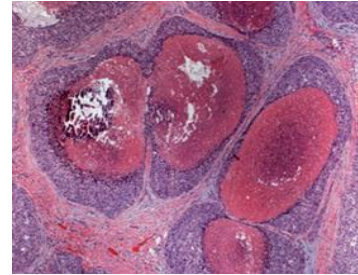
VI. Tumor-like Lesions :

- A. Duct ectasia
- B. Inflammatory pseudotumors
- C. Hamartoma
- D. Gynecomastia

Non-Invasive Carcinomas:

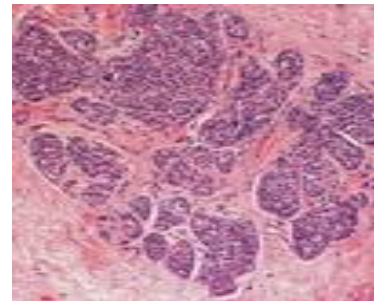
▪ *Intraductal Carcinoma*

Carcinoma limited to the ducts (Ductal Carcinoma in situ DCIS) is reported in different age groups with increasing frequency, mainly attributable to the benefits of screening mammography. It begins with an atypical ductal proliferation which completely fills and plugs the ducts with neoplastic proliferation. When the breast is sectioned, cord-like ducts are observed filled with necrotic, cheesy tumor cells which can be extruded upon slight pressure (*comedocarcinoma*). The growth may be (*cribroform*) indicating the presence of duct-like structure within the primary dilated ducts, or there may be a predominant (*papillary*) pattern.



• *In Situ Lobular Carcinoma*

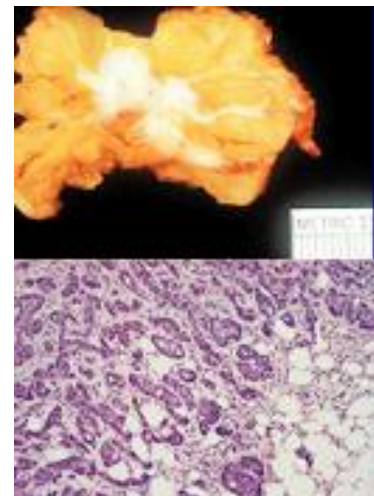
It is generally a non-palpable lesion diagnosed by mammography which may be located adjacent to fibrocystic changes or occurs concomitantly with infiltrative lobular carcinoma. Histologically, the terminal ducts and/or acini are distended by relatively uniform cells obliterating the lumens). Intracellular mucin vacuoles (signet ring cells) are common.



Invasive Carcinomas:

• *Invasive Duct Carcinoma – NOS (Not Otherwise Specified)*

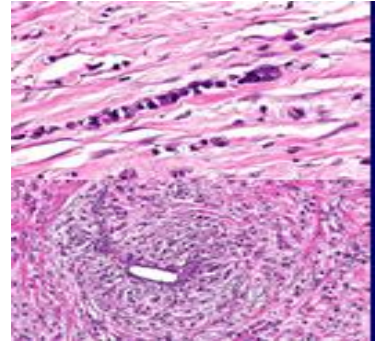
This is the most common type exhibiting marked increase in dense fibrous stroma or desmoplastic response giving the tumor a hard consistency (*Scirrhus*). This type of cancer is usually associated with DCIS. The tumor margins are usually irregular. On palpation, it manifests as stony hard nodules, which may have infiltrative attachments to the chest wall and skin resulting in dimpling and nipple retraction. Histologically, there are anaplastic duct cells arranged in glands, cords or solid nests. Because of the remarkable fibrosis, aspirates may yield only few cancer cells. Therefore a tissue biopsy may be recommended to confirm the cytological diagnosis.



• *Lobular Carcinoma*

It arises from the terminal ductules of the breast lobule. This type tends to be bilateral and multicentric. Histologically, the classical type is characterized by small uniform strands of infiltrating tumor cells often one cell in width (*Indian-file*) dispersed through a fibrous matrix. Neoplastic cells could be arranged in concentric rings around normal ducts

(*targetoid*). Occasionally they surround cancerous or normal-appearing acini or ducts, creating a so-called bull's-eye pattern.. Because of the considerable amount of fibrosis, cells may be difficult to aspirate and thus the few aspirated isolated monomorphic cells may yield a false negative cytology report. In general, these cells exhibit a high nucleocytoplasmic ratio with small cytoplasmic vacuoles containing a central condensation of mucus.



- ***Mucinous (Colloid Carcinoma)***

Tends to occur in older patients and often produces large masses which give the tumor its soft consistency on palpation. Histologically, there are large lakes of lightly staining amorphous mucin within which floats in small islands of isolated neoplastic cells, sometimes forming glands or cohesive cell clusters exhibiting slight nuclear abnormalities. A positive mucicarmine stain can confirm the diagnosis.

- ***Medullary Carcinoma***

This defined by WHO as a well-circumscribed carcinoma composed of poorly differentiated cells with scanty stroma and prominent lymphoid infiltration. These tumors present with fleshy masses more yielding on palpation. A lymphoid component at the periphery and within the tumor is often present (which gives it its special significance and better prognosis). Histologically, this carcinoma is characterized by solid syncytium-like sheets of large cells with vesicular pleomorphic nuclei containing prominent nucleoli and frequent mitosis.

- ***Papillary Carcinoma***

Is described by WHO as a rare carcinoma in which invasive pattern is predominantly in the form of papillary structures. It may be adjacent to the nipple causing bloody or serosanguinous discharge. Histologically, it could be distinguished from intraductal papilloma mainly by the absence of double cell layer and myoepithelium, scanty stroma, necrosis and invasion. Severe cytological atypia, abnormal mitotic figures, and absence of apocrine metaplasia also favors a malignant process. It is recommended that all papillary lesions should be surgically excised and examined histologically since differentiation between both entities on the bases of cytology alone may be very difficult.

- ***Tubular Carcinoma***

These tumors occur as small, firm, discrete masses. The WHO describes it as well-differentiated carcinoma whose cells are arranged in regular well defined tubules typically lined by one epithelial layer and accompanied by abundant fibrous stroma. Cytologically, there are minor nuclear abnormalities.

- ***Apocrine Carcinoma***

The tumour is composed predominantly of cells with apocrine type epithelium, i.e., large cells with eosinophilic granular cytoplasm . The differentiation of benign from malignant is sometimes difficult. However, cancer cells often show variability in their nuclear size and prominent nucleoli and as a rule, they are usually dispersed whereas benign apocrine cells often form cohesive sheets.

- **Adenoid Cystic Carcinoma**

Uncommon tumours, having characteristic cribriform pattern and are of the type seen more typically in the salivary gland. Cells are usually small, basaloid, with scanty cytoplasm and minimal anisonucleosis. Cell clusters containing mucoid cores are characteristics.

- **Paget's Disease of the Nipple**

It is a specialized form of ductal carcinoma arising in the main secretory ducts and extend to involve the skin of the nipple and areola, which exhibit eczematous changes.. Ductal carcinoma with or without invasion frequently antedates the skin changes. The histological landmark is the involvement of the epidermis by (*Paget's Cells*). These are large oval, polyhedral, pale-staining cells with clear cytoplasm, hyperchromatic nuclei and perinuclear halos. These are usually observed in exfoliative specimens.



- **Secretory (Juvenile) Carcinoma**

Defined by WHO as a carcinoma which is composed of pale-staining cells showing prominent secretory activity of the type seen in pregnancy and lactation. This tumor is more frequently seen in young girls.

- **Inflammatory Carcinoma**

This is defined clinically by an enlarged, swollen, erythematous breast, usually without a palpable mass. The underlying carcinoma is generally poorly differentiated and diffusely invades the breast parenchyma. The blockage of numerous dermal lymphatic spaces by carcinoma results in the clinical appearance. True inflammation is minimal or absent. Most of these tumors have distant metastases, and the prognosis is poor.



Features Common to All Invasive Cancers:

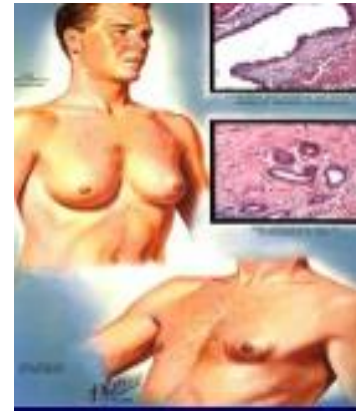
In all forms of breast cancer , discussed above, progression of the disease leads to certain local morphologic features. These include a tendency to become adherent to the pectoral muscles or deep fascia of the chest wall, with consequent fixation of the lesion, as well as adherence to the overlying skin, with retraction or dimpling of the skin or nipple. The latter is an important sign, because it may be the first indication of a lesion, observed by the woman herself during self-examination. Involvement of the lymphatic pathways may cause localized lymphedema. In these cases the skin becomes thickened around the exaggerated hair follicles, a change known as *peau d'orange* (orange peel).



The Male Breast:

▪ Gynecomastia

It is an endocrine related enlargement of the male breast that occurs most frequently in adolescents and elderly; mainly in response to excessive estrogenic stimulation. Generalized hypertrophy is usual, but there may be a discrete tumour adjacent to the nipple. Microscopically, there is ductal hyperplasia and dilatation with loose stromal proliferation and an inflammatory infiltrate. Because of the cellularity, anisonucleosis and nucleoli, caution should be experienced in diagnosing these lesions cytologically.



▪ Carcinoma

This is often rare; occurring at advanced age, with a frequency ratio to female breast cancer approximating 1:100. Because of the scanty amount of breast tissue, male mammary carcinoma tends to infiltrate rapidly and ulcerate through the skin with prominent axillary nodal involvement.

GRADING of Mammary Ductal Carcinoma

The prognosis of Breast Cancer depends on the degree of anaplasia (tumour differentiation). Different systems of grading have been successfully applied for better evaluation of cancer evolution. In general, the classification of Scarff, Bloom and Richardson (SBR) is the most currently used and recommended by the WHO. It comprises the description of three characters:

A. Tubular Differentiation; B. Nuclear Pleomorphis; and C. Mitotic Activity

Accordingly, mammary carcinoma could be classified histopathologically into **Grade I** which carries a favorable prognosis; **Grade II** corresponding to moderate prognosis, and **Grade III** indicating bad prognosis.

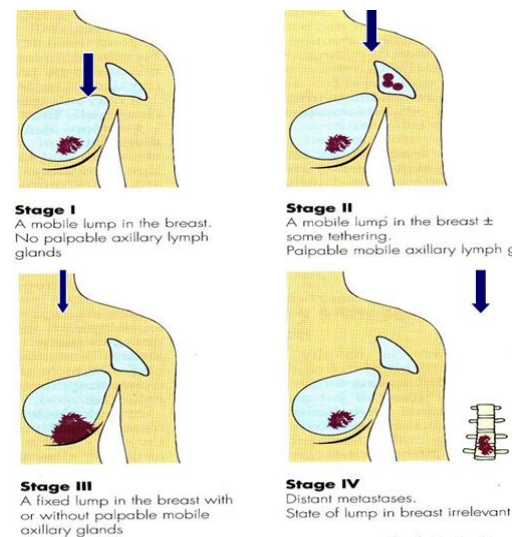
STAGING of Mammary Carcinoma

According to the Committee of the Clinical Staging of the International Union Against Cancer (UICC), the recommended Staging System was adopted in 1989 by the American Joint Committee on Cancer (AJCC).

The classification depends upon the **size of the primary tumor (T)**, **extent of regional lymph node metastases (N)** and **distant metastases (M)**.

The designation **TNM** has been chosen for clinical staging and **pTNM** refers to pathological staging.

Clinical staging is important for precise individualized treatment planning and estimation of prognosis.



However clinical staging is less accurate than the pathological since there is a tendency to overestimate the size of the primary tumor and inaccurately assess the axillary lymph nodes for the presence of metastatic carcinoma.

| | | Stage | Primary tumour (T)* | Regional lymph node status (L) | Distant metastasis (M) |
|----------------------|--|--------------|---------------------------|--------------------------------------|------------------------------|
| T- Tumour | | 0 | Tis | N0 | M0 |
| T1 | Tumour \leq 2 cm | I | T1 | N0 | M0 |
| T2 | Tumour \geq 2 cm but \geq 5 cm | | T0 | N1 | M0 |
| T3 | Tumour \geq 5 cm | IIA | T1 | N1 | M0 |
| T4 | Tumour of any size with direct extension to chest wall or skin | | T2 | N0 | M0 |
| N- Lymph node | | IIB | T2 | N1 | M0 |
| N0 | No cancer in regional node | | T3 | N0 | M0 |
| N1 | Regional movable metastasis | III A | T0 | N2 | M0 |
| N2 | Non-movable regional metastases | | T1 | N2 | M0 |
| N3 | Cancer in the internal mammary lymph nodes | | T2 | N2 | M0 |
| M- Metastasis | | | T3 | N1/N2 | M0 |
| M0 | No distant metastases | III B | T4 | Any N | M0 |
| M1 | Distant metastases | III C | Any T | N3 | M0 |
| | | IV | Any T | Any N | M1 |

Criteria for staging breast tumours according to the UICC ICD-10 TNM classification.

*Size measurements are for the tumour's greatest dimension.

PROGNOSTIC FACTORS

Prognosis – the prediction of the duration, course and outcome of the disease in a patient is an essential part of medical practice. In breast cancer patients, prognosis of individual cases depends on several factors that include:

- **Age:** Higher mortality rates due to breast cancer are usually recorded before 35 and after 70 years of age.
- **Pregnancy:** There is a general agreement that breast cancer manifesting during pregnancy and lactation is associated with a poor prognosis; whereas it has been shown that pregnancy two years following treated breast cancer is not unfavorable.
- **Early Diagnosis:** The relative 5 and 10 years survival rates for asymptomatic breast

cancer detected in large screening projects were 88% and 79% respectively. This is attributable to the fact that most of these tumors were small, devoid of axillary metastasis and a high percentage was of microscopically favorable types.

- **Tumor Stage** which depends upon:

The Size of the Tumor: Tumors measuring less than 2cm. are often associated with favorable prognosis, compared to larger tumors.

Lymph Node Involvement: This is one of the most important prognostic parameters. With no histological nodal involvement, the 5-year survival rate is about 80%, falling to 21% in the presence of four or more nodes.

- **Histological Grade:** The 10-year survival rate for patients with Grade I tumors is around 80%, dropping to 45% in Grade III.
- **Histological Type:** Morphological variants of invasive ductal carcinoma with a more favorable prognosis are tubular, cribriform, pure mucinous, medullary, papillary, adenoid cystic and juvenile carcinomas. There is no significant prognostic difference detected between ordinary invasive ductal and invasive lobular carcinoma .
- **Other microscopical findings** such as:
 - **Type of Tumor Margins:** Tumors with pushing margins have better prognosis than those with infiltrative margins.
 - **Stromal Reactions:** While necrosis is associated with increased incidence of lymph node metastases, the absence of necrosis within the tumor and the presence of elastosis are claimed to be associated with better prognosis.
- **Presence or Absence of invasion:**

The importance of this valuable prognostic denominator is demonstrated by the fact that in situ cancer is 100% curable with mastectomy. Nipple involvement is found to be associated with a higher incidence of axillary metastases. The presence of tumor emboli in lymphatics or blood vessels increases the risk of tumor recurrence.

- **The Proliferative Rate and Presence of Aneuploidy:**

The fraction of cells scattered outside the modal peaks of DNA histograms correlates with poor behavior. Euploid mammary carcinoma have a significantly better prognosis than aneuploid carcinomas.

- **The Presence or Absence of Hormone Receptors:**

The number of Estrogen and Progesterone Receptors in breast cancer is found proportional to the degree of cellular differentiation. Patients having hormone receptor positive carcinomas carry a better prognosis.

- **Presence of Growth factors or Amplified Oncogenes:**

Experimental evidence links Epidermal Growth Factor (EGF) Receptors with carcinogenesis. Similarly, certain oncogenes e.g. C erb or HER2 oncogenes are correlated with aggressive behavior.