REVIEW OF LITERATURE
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HISTORICAL ASPECTS -

Diseases of the breast attracted medical interest as long as 3000 BC. The earliest description of tumours of breast and probably of tumours in any form was credited to Egyptian physician, Imhotep in 3000 B.C. and recorded in Edwin Smith Surgical Papyrus under case No. 39, "Bulging Tumour of Breast". These includes tumours that were "HARD" & "COOL" to touch as well as abscesses and inflammation that were warm. It is probable that malignant tumours of the female breast were the first human cancers discovered and differentiated from other non-malignant diseases (Sabiston, 1991).

In the second century and for the next 1000 years, medical thinking was dominated by Galen (A.D. 130 - 203). Galen attributed cancer to an excess of black bile and, like Hippocrates earlier, to a systemic imbalance of the cardinal humours. He thought that the most common cancers arose in the female breast. Galen recommended complete excision of tumours of the breast "so as not to leave a single root....". He linked cancer to the crab, with its central body and radiating growth and dilated veins (Sabiston, 1991).

DEVELOPMENT OF BREAST -

In utero, the milk line appears bilaterally at the fifth week of gestation and differentiates into individual
globular structures at about 7 to 8 weeks. Epithelial buds can be seen at 10 - 12 weeks of gestation, and ducts grow progressively during the second and third trimesters. At birth, simple ducts, branched ducts, and a few lobular units may be seen, but there is considerable individual variation in their relative proportions (Anbazhagen et al, 1991).

The breast is a modified skin sweat gland that develops into a complex functional conical projection between the subcutaneous tissue of the chest and the greater pectoral muscle in the females but remains as a rudimentary organ in the male. It develops as an epidermal thickening. First solid, then cords eventually develops lumina. Progressive growth and branching of mammary ducts occur at different ages under the influence of ovarian hormones and hormones of pregnancy.

ANATOMY AND NORMAL HISTOLOGY OF BREAST -

(Fig No-1)

The resting mammary gland consists of about 15-25 ill-defined lobes, each approximately pyramidal in shape and having its apex at the areola. Each lobe is subdivided into lobules, the functional units of the mammary parenchyma. The glandular tissue of each lobe terminates in a single collecting duct that forms a subareolar dilatation known as the lactiferous sinus, before emerging at the nipple.

Within the mammary tissue the ducts ramify as straight, symmetrically dividing tubular structures. Along the length of these ducts arise lobular units consisting of
FIG. - 1: ANATOMY OF THE BREAST AND MAJOR LESIONS AT EACH SITE WITHIN THE VARIOUS UNITS.
a central terminal duct and outer alveolar ducts (ductules), all embedded in a loose connective tissue stroma. The lumen of both the ducts and the lobular units are lined by a continuous single layer of cuboidal to low columnar epithelium surrounded by a basket-weave array of myo-epithelial cell process. Scattered neuroendocrine cells are also present (Russolati et al, 1985). Immuno-histochemistry identifies estrogen receptors in a small minority of epithelial cells, but not in stromal cells (Petersen et al, 1987).

Breast development reaches a maximum by about 20 years of age and displays considerable individual variation at both the gross & microscopic levels (Rudland et al, 1991).

ENDOCRINE (HORMONAL) INFLUENCE ON THE DEVELOPMENT OF THE BREAST AT PUBERTY, PREGNANCY AND MENOPAUSE :-

According to Michael Baum (1981) under the influence of follicular stimulating hormone (FSH) & lutenizing hormone (LH) of pituitary, follicles are induced within the ovaries and as they mature they produce oestrogens, the most important of which is 17-B- estradiol. Under the influence of these oestrogens, mammary growth occurs, rudimentary ducts enlarge & branch to produce mature glandular tissue. With ovulation in ovary corpus luteum is formed producing Progesteron, which produces maturation of the glandular tissue. Disturbance of cyclic changes of hormones causes benign mammary disease known as Fibroadenosis or fibrocystic disease.
During pregnancy the placenta synthesis hormones like prolactin and growth hormones from pituitary which influence the development of breast. Thus glandular tissue within the breast, the ducts and the lobules proliferate enormously in size and number and the breast is fully primed for the production of milk but is inhibited as a result of the placental hormone gonadotropin. Following delivery, this inhibition is removed and suckling - further stimulates the pituitary to secrete the oxytocin hormone which acts on the myoepithelial cells, allowing the glandular structure to empty of milk. Prolactin continues to stimulate the glandular cells to synthesize the milk protein and oxytocin promotes the emptying of the glands so that they do not become engorged.

During menopause when ovarian function rapidly ceases the fall in the level of circulating oestrogens and progesterones leads to involution and atrophy of glandular tissue in most cases which is replaced by the fat.

INFLAMMATORY DISEASES (LESIONS) OF THE BREAST:

The inflammatory lesions of the breast are common and of diverse origin. Although these lesions are considered to be of clinical significance mainly because of the potential for confusing with cancer, sometimes inadequately treated abscess, can result in significant morbidity and even disfigurement (Anderson, 1996).

This includes only a relatively few forms of acute and chronic disease. Out of these, the most important were
non-specific acute mastitis virtually confined to the lactating period. Breast abscess includes under the heading of acute mastitis, the other forms of mastitis consists of Granulomatous mastitis, either tubercular or may be non-tubercular, syphilis (a rare condition) in the form of chancer on the nipple or areola and mammary duct ectasia or plasma cell mastitis, an entity of obscure etiology (Robbins, 1994).

**ACUTE MASTITIS**

Boyd (1947) reported that acute inflammation of the breast were uncommon condition. Practically confined to the first few weeks of lactation and caused by pyogenic organisms takes entry to breast through blood stream, most common were staphylococcus aureus, rarely streptococcus, inflammation takes place through milk ducts or cracks in the nipple, suppuration occurs and abscess may be formed. Usually the disease is unilateral.

Pre-existing duct ectasia is believed to be the underlying cause of many infections (Scholefield et al, 1987; Bunderd et al, 1985). The neonatal infants may frequently show milk secretion caused by transplacental passage of the mother's hormones. This so-called "witches milk" is not an evidence of inflammation (Symmer's, 1974).

**CHRONIC MASTITIS**

May develop insidiously without an obvious acute stage or as sequale of the inadequately treated acute
infection of the breast following subsequent proliferation of bacteria & obstruction to major ducts. Grossly, lump is encapsulated and quite soft. Microscopically, there is fibrosis, abundance of free lipid & foamy macrophages together with a mixed inflammatory cell infiltrate.

Leudrum (1945) reported that lobular hyperplasia was the analogue of chronic mastitis and commonest of all mammary lesions, among the commoner were chronic mastitis, chronic cystic mastitis, chronic interstitial mastitis or fibroadenosis, diffuse fibroadenoma, cystadenoma papilliform, involution cyst, abnormal involution cystic disease of the breast. But W.H.O. (1968) classified cystic disease as benign mammary dysplasia.

**CHRONIC CYSTIC MASTITIS**

Cutler (1961) histologically defined chronic cystic mastitis as cystic desquamated epithelial hyperplasia which end in the formation of cysts. Symmers (1974) reported this common condition has many names including cystic or fibrocystic disease, chronic cystic or interstitial mastitis, fibroadenosis or mammary dysplasia. Histologically there is formation of multiple cyst with varying size which are fairly distributed and separated from one another by mature fibrous tissue. Microscopically, the cyst may be lined by a simple cuboidal or flattened epithelium & proliferation of the epithelial lining and apocrine metaplasia and interstitial accumulation of lymphocytes and other cells.
Minkowitz et al (1973) observed that dilated ducts are lined by single layer of flattened epithelium filled with lipoid laden cells. Sloane (1985) has reported that multi-layered proliferating epithelial lining of cyst exhibit apocrine metaplasia and stroma lost its myxomatous appearance, infiltrated by dense lymphocytes, plasma cells and macrophages (Robbins, 1989). Ultrastructurally, Ahmed (1975) has reported the presence of prominent blood vessels around cyst which is normally avascular. Robbins (1989) said that in smaller cysts the epithelium were more cuboidal to columnar and occasionally multi-layered in focal areas. In larger cysts it may be flattened or totally atrophic.

Frantz et al (1951) examined the breast of 225 autopsies with no history of breast disease and reported cysts in 53% and in 19% the cysts were macroscopic.

Haagensen (1956) reported its incidence 1 in 20 cases during a study of 10 year period. Symmers (1974) reported cystic hyperplasia at necropsy in 50% - 90% or more in different studies.

**PLASMA CELL MASTITIS**

It is the disease of older women. Boyd (1947) reported this rare condition was an acute or subacute inflammation begins with sudden pain in breast, tenderness and diffuse swelling alongwith axillary lymphnode enlargement. Soon, inflammation subsides, leaving the adherent skin and
firm lymphnodes. It is associated with clinical sign of malignancy, but not with lactation, history of difficult nursing is often present. It is caused by stasis and inspissation of breast secretion with rupture of the dilated mammary ducts. Grossly, resembles the carcinoma. Microscopically, it is an endogenous granuloma and was called split-milk mastitis or stale-milk mastitis. There is infiltration of lymphocytes and plasma cells and some macrophages.

Adair (1933) & Cromer (1941) reported that the uncommon entity known as plasma cell mastitis (Pseudotuberculosis) was characterised by the absence of caseation, and tubercle bacilli and predominant feature is plasma cell granuloma formation. Tice (1948) called this plasma cell mastitis as mammary duct ectasia (Comedomastitis).

Cromer & Dockerty (1941) reported 24 cases seen in Mayo Clinic over a period of 30 years. Symmers (1960) reported that plasma cells are sometimes very conspicuous in the advanced lesions of mammary duct ectasia for this reason, "plasma cell mastitis" is not to be thought of as an entity or as invariably manifestation of mammary duct ectasia, histologically it revealed the dilated duct, wall is thickened due to fibrosis and epithelial lining showed no proliferative tendency but atrophy, sometimes it is seen as single layer and these are heavily infiltrated by plasma cells, lymphocytes & some macrophages. Haagensen (1986) claimed that plasma cell
mastitis is a later stage of mammary duct ectasia & chronic lobular mastitis.

**TUBERCULAR MASTITIS**

Mammary tuberculosis usually results from haematogenous infection, may be a primary or secondary. Tuberculosis rarely involves the breast and its incidence has declined considerably in recent years. Ikard and Parkins (1977) found tuberculosis in 0.025% of cases of surgically treated as breast disease in Nash Ville, Tennessee in the United States in 20 years period upto 1977. A higher incidence, however, could be expected in the economically less well developed parts of the world. There were two main pathological forms of the disease; the more usual nodular form and less common sclerosing type (Ikard and Parkins, 1977; Mckeown and Wilkinson, 1952).

Initially, tuberculosis in breast presents as palpable hard mass resembling carcinoma. Subsequently caseation occurs with the formation of large cavities and sinuses opening on the surface.

Microscopically, it shows central caseous necrosis surrounded by epitheloid cell, histocytes, giant cells, macrophages & lymphocytes, and fibrosis. Stroma also shows inflammatory cell reaction.

**FAT NECROSIS**

It is also known as traumatic fat necrosis but a history of trauma can not always be obtained; focal ischaemia has also been suggested as cause (Sloane, 1985).
The gross appearance mimics hard, stellate appearance of invasive carcinoma, but typically, there is chalky streaking and often a central translucent region of necrotic fat. Microscopic appearance is quite variable and depends on the size of the lesion and the time elapsed since the originating trauma. Initially, there is infarct like necrosis of fat with an acute inflammatory cell reaction, latter replaced by mono-nuclear inflammatory cells including foamy macrophages and eventually there is fibrosis and focal calcification. The surrounding ducts may display reactive epithelial hyperplasia or intraductal carcinoma. Fat necrosis is a self-limited lesion and will heal with scarring.

**CHRONIC NON-SPECIFIC GRANULOMATOUS MASTITIS**

It is an uncommon and curious condition of unknown etiology. All cases described by Kessler and Wolloh (1972) and Fletcher et al (1982) occurred within 6 years of pregnancy.

Histologically, discrete non-caseating granuloma composed of epitheloid histiocytes, giant cells, eosinophils and neutrophils confined to breast lobule, damage to ductular epithelium and neutrophils within the lumina.

Fletcher et al (1982) suggested that the finding of polymorphs in some of the ductular lumina indicate a primary damage by some unknown agents, to the epithelium resulting in leakage of contents and subsequent granulomatous response in surrounding stroma.
GALACTOCOELE -

It is a simple milk retention cyst which is rounded, well circumscribed, and easily movable within the breast. It usually occurs after the cessation of lactation or when feeding frequency has been curtailed significantly. Haagensen (1986) states that it may occur upto 6 to 10 months after breast feeding has stopped. The pathogenesis is not well known, but it is thought that inspissated milk within a large lactiferous duct is responsible. The lesion is usually located in the central portion of the breast or under the nipple (Gabiston, 1991).

Histologically, it revealed cystic dilatation of ducts which were lined by double layer of epithelial and myoepithelial cells. The epithelial cells may exhibit active secretion and an abundance of cytoplasmic organelles (Ironsde & Guthrie, 1985).

CLASSIFICATION OF BREAST TUMOURS AND TUMOUR-LIKE LESIONS -

The histomorphological classification for routine reporting have been many and most of these did not help in deciding the mode of treatment or prognosis and even consistancy in reporting from one Pathologist to another. Breast lesions have been classified by various workers on the basis of their nature, inflammatory and non-inflammatory, which divided into benign or malignant, gross macrocyst or microcyst, scirrhous, colloid, medullary, microscopic and
histologic criteria and histogenesis (duct lobule, acini) or activity (infiltrating, non-infiltrating). First time breast tumours were classified by Poote and Steward in 1950 which was as below:

1. **POOTE AND STEWART CLASSIFICATION (1950)**:
   (based on behaviour of the tumour)

i) **Benign Tumors**
   1. Papilloma
   2. Fibroadenoma
   3. Lipoma
   4. Angioma
   5. Granular cell myoblastoma
   6. Dermatomyoma of the muscle of areolar area
   7. Dermatofibrosarcoma Protuberance - the type of inherent recurring fibrous tissue tumour
   8. Osteoma or chondroma

ii) **Malignant tumors**
   1. Paget's disease of nipple
   2. Carcinoma of mammary duct -
      a) Non-infiltrating -
      i) Papillary carcinoma
      ii) Comedo carcinoma
   b) Infiltrating -
      i) Papillary carcinoma
      ii) Comedo carcinoma
   c) Carcinoma with fibrosis (Scirrhous carcinoma)
   d) Medullary carcinoma with lymphoid infiltration
      e) Colloid carcinoma

3. Carcinoma of lobule -
   i) Non-infiltrating
   ii) Infiltrating

4. Relative rare carcinoma -
   a) So-called "sweat gland" carcinoma
   b) Intracystic carcinoma
   c) Adenoid cystic carcinoma
   d) Squamous cell carcinoma
   e) Carcinoma with esesous & cartilagenous metaplasia

5. Malignant cystosarcoma phyllodes
6. Liposarcoma  
7. Angiosarcoma  
8. Lymphosarcoma –  
   a) Follicular lymphosarcoma  
   b) Diffuse lymphosarcoma  
   c) Reticulum cell sarcoma  
9. Miscellaneous sarcoma  
10. Combined forms of the above

2. **WORKING CLASSIFICATION (KUZMA, 1957)**:
   (MODIFIED BY FOOTE AND STEWART) –

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
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<tbody>
<tr>
<td>1. Epithelial</td>
<td>1. Mammary ducts –</td>
</tr>
<tr>
<td>- Papillomas</td>
<td>a) Non-infiltrating tumours</td>
</tr>
<tr>
<td>2. Mixed epithelial and mesodermal</td>
<td>i) Papillary carcinoma</td>
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<tr>
<td>a) Fibroadenoma</td>
<td>ii) Comedocarcinoma or duct carcinoma</td>
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<tr>
<td>i) Intracanalicular</td>
<td>b) Infiltrating tumours (Adenocarcinoma)</td>
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<td>ii) Pericanalicular</td>
<td>i) Paget’s disease</td>
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<tr>
<td>iii) Adenoma</td>
<td>ii) Papillary carcinoma</td>
</tr>
<tr>
<td>3. Mesodermal-breast tumours only by geography &amp; in no way distinct in mammary gland (viz. Lipoma, Angioma, fibroma &amp; myoma)</td>
<td>iii) Comedo-carcinoma</td>
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<td>iv) Adenocarcinoma with productive fibrosis (scirrhous simplex)</td>
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<td></td>
<td>v) Medullary carcinoma</td>
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<td>vi) Mucinous carcinoma</td>
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2. Mammary lobules –
   a) Non-infiltrating-in-situ,  
   b) Infiltrating lobular adenocarcinoma.  

3. Epithelial or mesodermal origin such as tumours of skin, skin appendages and supporting tissues of breast, same as found elsewhere in body - dermoid cyst, sweat gland tumours, basal or squamous cell carcinoma of skin, liposarcoma etc.
The Armed Forces Institute of Pathology (AFIP) (McDivitt, 1968) classified breast carcinoma according to morphological studies which is based upon anatomic or structural units present in female breast.

3. **AFIP Classification (McDivitt, 1968)**

1) Tumours arising from duct epithelium:
   i) Papillary carcinoma
   ii) Comedo carcinoma type

2) Infiltrating duct carcinomas (NOS)

3) Medullary carcinoma

4) Tubular carcinoma

5) Mucinous or colloid carcinoma

6) Infiltrating papillary carcinoma

7) Lobular carcinoma - a) Non-invasive (in situ carcinoma)
   b) Invasive

Two entities represent special manifestation of mammary carcinoma, kept separately:

a) Paget's disease of breast

b) Inflammatory breast cancer

None of these classifications have served useful purpose. Due to the difficulty in the interpreting findings of different Labs, W.H.O. (1968) presented a meaningful classification after a Panel of World Pathologists and again revised this classification in 1982, which aims at promoting uniformity in recording and reporting diagnosis in order to facilitate international and other comparisons (Azzopardi et al., 1982). Both these classifications (W.H.O., 1968 & 1982) have been discussed under the heading Material and Methods.
INDIVIDUAL LESIONS OF BREAST -

ADENOSIS AND SCLEROSING ADENOSIS:

Ewing\(^5\) (1940) first described it as fibrosis or sclerosing adenomatosis. It displays enlargement of one or more lobular unit because of a great increase in the number of alveolar ducts, along with an increase in the density of intralobular fibrous tissue. Its peak incidence reported between 25-35 years of age.

Although most lesions are grossly inapparent, some may appear as stellate lesions measuring up to 1.0 cm in diameter. Microscopically, the alveolar ducts are elongated and are organised into concentrically swirling groups, some times with a dilated central terminal duct. The normal double cell layer is preserved but the lumen is attenuated and may contain microcalcifications. Perineural invasion has been reported (Taylor et al, 1967).

In some cases, the lumen is dilated and called as "Blunt duct adenosis" or "microglandular adenosis" (Page et al, 1987). Its incidence were reported to be 2% of all breast lesions. Haagensen (1986) reported 33 cases in the period of 1936-1972.

Foote & Stewart (1946) from 1936-1972 recognised an early cellular and late sclerotic phase of the proliferating process and reported 12.5% of all benign breast biopsy.
Ahmed (1975) confirmed the benign nature ultrastructurally. Eusebi and Azzopardi (1976) found vascular invasion in 10% cases of sclerosing adenosis of all benign breast biopsies. Hutter et al (1986) reported that it is associated with slightly increased risk (1.5 to 2 times) of developing carcinoma of breast.

**FIBROCYSTIC DISEASE**

Fibrocystic change is a complex of lesions that includes fibrosis, epithelial proliferation and cyst formation. Haagensen (1971) reported 10% of adult women in United States have symptomatic fibrocystic disease. Symmers (1974) reported 73% of fibrocystic disease out of 715 cases of benign lesions of breast.

Fibrocystic disease is a group of heterogenous lesions, the presence of epithelial hyperplasia is the most important risk factor for subsequent malignancy (Dupont et al, 1993). Fibrocystic changes increases progressively in women through the child-bearing years, reach a peak during perimenopausal period and regress after menopause (Bartow et al, 1987; Eruster, 1981). The relative incidence of these changes differs among population groups.

Risk factors - includes early menarche, nulliparity or low parity and late age at birth of first child, oral contraceptives earned a reputation for having a protective effect on the development of fibrocystic changes, but more recent studies suggest that the current formulations, with
relatively low progestogen concentration, have no effect (Mc Gonigle, et al, 1991).

The fibrocystic complex will be separated into its three major components:

A. CYSTIC DISEASE

Cysts are the most common and constant feature of the fibrocystic complex to become clinically apparent (Symmers, 1978; Haagensen, 1986). The human breast cysts are the result of ovarian dysfunction. A variety of bioactive substances are secreted into cyst fluid, including polypeptide hormones and both the male & female sex steroid hormones. Some investigators have attempted to relate these to the development of both proliferative changes and mammary cancer (Greenblatt et al, 1987). By themselves, cysts have little or no malignant significance (Page et al, 1978; Dupont et al, 1993).

Cysts commonly develops in terminal ducts & lobules, its mechanism of formation not known. These cysts vary in size from 100 to 200 um, evenly distributed, separated by abundant mature fibrous tissue stromas, and lined by flattened or cuboidal epithelium (Symmers, 1978) and may contain eosinophilic granular material. Multiple cysts are lined by apocrine cells & sharing nuclear atypia, but it is of no premalignant significance.

The largest cysts are associated with atrophy of the remaining lobular elements, whereas small cysts typically develop as multiple dilatation within same lobule.
B. FIBROSIS (Fibrosclerosis, fibrous disease):

In adult women, mammary fibrous tissue increases progressively until menopause and regresses thereafter. The fibrosis and cyst formation is a normal process. Fibrous nodules occur in a younger age group than the other fibrocystic lesions, and are the sole abnormality in approximately 5% of benign breast biopsy specimens (Rivera-Pomar et al, 1980).

C. EPITHELIAL PROLIFERATIVE CHANGES:

Most epithelial proliferation probably begin in the terminal ducts and manifest themselves as hyperplastic changes of extralobular duct (ductal hyperplasia) and intralobular ductules (lobular hyperplasia) (WHO, 1982).

i) DUCTAL HYPERPLASIA - It characterised by an intraductal proliferation of epithelial cells leading to partial or total obliteration of the lumen.

The proliferating cells form varying degrees of solid masses, gland-like structures or papillary fronds. It is diffuse or multifocal and called as papillomatosis or epithelosis. Small size and uniformity of cells & nuclei, lack of mitosis, presence of myoepithelial layer and of apocrine cells favour the diagnosis of a benign condition.

When atypia is pronounced, the term atypical ductal hyperplasia is used. In the most atypical form, a distinction from intraductal carcinoma may be impossible.
ii) **LOBULAR HYPERPLASIA** - It is of two types: (a) that resulting from an increase in the number of ductules, i.e. adenosis, and (b) that resulting from a proliferation of epithelial cells within intralobular ducts (Papillomatosis, epitheliosis).

The atypical lobular hyperplasia, means the lesions which are quantitatively and qualitatively insufficient to support a diagnosis of lobular carcinoma in situ. The persistence of luminal spaces, lack of marked ductular distension and the persistence of a readily recognizable myoepithelial cell layer help to distinguish atypical lobular hyperplasia from lobular carcinoma in situ (W.H.O., 1982).

**DUCT ECTASIA**

The lesion was first reported by Haagensen (1956). Frantz et al (1957) reported an incidence of 24% in an autopsy study of supposedly normal female breast, which increased up to 46% in older patients over 60 years of age.

Mammary duct ectasia is important because it is common, and confused clinically and macroscopically with carcinoma. The condition occurs most frequently in fifth, sixth or seventh decades.

Patients usually present with pain, blood stained discharge from the nipple and sometimes may present with retraction of nipple due to contraction of the fibrous tissue leads to the shortening of the ducts. Grossly -
disease starts with dilatation of the lactiferous ducts deep to the nipple and areola, producing a mass usually located in the subareolar region. Microscopically - the ducts are distended, the duct wall becomes thickened by fibrosis and periductal stroma is infiltrated by inflammatory cells. The epithelial lining get atrophied and seen as flattened epithelium. Glands contain amorphous pink material. The fatty contents escape into the breast tissue resembling with granulomatous reaction.

Mammary duct ectasia has no special tendency to be associated with carcinoma of breast, indeed, the absence of epithelial hyperplasia is an indication of its benign nature (Symmers, 1978).

**Gynaecomastia**

William (1963) reported 40% out of 447 autopsy cases. Liechty et al (1967) observed 20% (7 out of 40 patients) of men with mammary carcinoma. Haagensen (1971) classified into peripheral hypertrophy occurring in youth and quiescent hypertrophy found in old age.

The histological changes in gynaecomastia have been divided into active, inactive and intermediate phase by Anderson and Gram (1982) & Bannayan & Hajdu (1972).

Gynaecomastia refers to expansion of the subareolar breast bud in men and peaks at three distinct stages: birth, puberty and older adulthood (Braunstein, 1993). In many cases, the cause appears to be a change in the ratio of oestrogens and androgens.
In the pubertal male, the condition is often unilateral and typically occurs between the ages of twelve to fifteen years. By contrast, senescent gynaecomastia is usually bilateral, although there may be asymmetry, and the condition is commonly idiopathic. Other causes are therapeutic drugs, hypogonadism, cirrhosis, malnutrition and endocrinologically active neoplasms (Braunstein, 1993).

Microscopically, proliferation involves both the ductal epithelium and surrounding stroma. The ducts divide and increase in length, but the formation of lobular unit is very rare. The surrounding fibrous stroma is oedematous and concentrically arranged around the ducts, this accounts for most of the increase in volume of the involved breast tissue. The ducts often display papillary intraluminal hyperplasia of the lining epithelium.

**FIBROADENOMA**

Fibroadenoma is a commonest slow growing estrogen induced benign tumour occurring in young females. The benign nature of fibroepithelial tumour of the breast was recognised more than hundred years ago by Sir Astley Cooper, who called them "chronic mammary tumours" (Sabiston, 1991).

Fibroadenomas occur more frequently and more likely to be multiple in blacks and during pregnancy. Frantz et al (1951) reported its incidence approximately 9%. Boyd (1955) reported this tumour as 15% of all neoplasms of the breast.
Haagensen (1971) reported that fibroadenoma was the third most common solid tumour of the breast in American females. Multiple fibroadenoma with variable frequency of 1.4% to 19.9% has been reported by various workers (Willis, 1953; Ellis, 1984 and Haagensen, 1986). Haagensen (1971) divided on the basis of their microscopic structure into adenofibroma and cystosarcoma phyllodes.

W.H.O. Classification (1968) classified them into pericanalicular and intracanalicular and cellular intra-

Canalicular fibroadenoma (Cystosarcoma phyllodes), Brodie's tumour or giant fibroadenoma on the basis of their behaviour, but in W.H.O. Classification (1982) the distinction between intra-canalicular and pericanalicular type, is not considered to be significant and constitutes fibroadenoma into mixed connective tissue and epithelial tumour on the basis of histological appearance.

The possibility that malignant changes might occasionally originate (less than 1%) within fibroadenoma was raised by reports such as that of Harrington & Miller (1940); Willis (1953), most are carcinoma in situ and mostly are lobular type (Carter et al, 1989). Regressive changes are common after 30 years of age, and in post-menopausal women they may be found incidentally as hyalinised nodules with atrophic epithelium (Kern et al, 1973).

Grossly - Fibroadenomas are sharply circumscribed, well-encapsulated, solid mass with smooth borders, sometimes may be lobulated. The size is variable ranging from 1.00 mm to
more than 10 cm. in diameters. The latter is referred to as "Giant fibroadenoma". Cut surface is lobulated with slit-like spaces and ranges from firm to hard in consistancy. Microscopically - there is a balanced proliferation of ducts and stroma. Myxoid stroma predominates in younger patients, but fibrous stroma is more common in older patient. In some lesions, the stroma is more cellular near the ducts, and mitosis are also common at the stroma - epithelial interface, suggestive of an epithelial - stromal interaction (Sawhney et al, 1992). The ductal epithelium is typically double layered but may display papillary intraductal hyperplasia. It is appear to arise from lobules. Atypical ductal and lobular hyperplasia may occur.

More than 100 invasive and non-invasive carcinoma have been reported in pre-existing fibroadenomas since 1985 (Page and Anderson, 1987), approximately 50% of these are lobular carcinoma in situ, 35% were infiltrating carcinomas, and 15% were intraductal carcinoma.

**JUVENILE FIBROADENOMA**

It is an uncommon variant of fibroadenoma that occurs as a large, rapidly growing, highly cellular mass in adolescent females (Ashikari, Farrow and O'Hara, 1971). Grossly - cut section shows yellow-tan and homogenous surface, rather than lobulated of usual fibroadenoma. Microscopically, the stroma is more cellular and display more mitosis. There is a greater tendency towards papillary intraductal hyperplasia,
and lobules are typically present (Ashikari et al., 1971; Pike et al., 1985). It is typically solitary and unilateral lesion and do not recur after excision.

**Phyllodes Tumour (Cystosarcoma Phyllodes):**

The term "cystosarcoma phyllodes" was first described by German pioneer, student Johannes Muller (1938) because of the branching projections of the tumour tissue into cystic cavities within the tumour. There was no objection to the nomenclature except for the malignancy which "sarcomas" attached to the lesion. W.H.O. (1968) classified the condition as "Hypercellular intracanalicular fibroadenoma", which is mainly depend on the behaviour of tumour, but revised classification of W.H.O. in 1982 put it separately into mixed connective tissue and epithelial tumour and characterized by a greater connective tissue cellularity.

The incidence of phyllodes tumour has been reported to vary from 2 - 15% of all the benign lesions of the breast (Treves, 1964; Aurora & Gupta, 1967; Chandra et al., 1969). Haagensen (1971) observed 2% to 3% of fibroadenomas-like lesions seen in the breast clinic at Columbia Presbyterian Hospital, New York.

Treves and Sunderland (1951), Lester & Stout (1954), stressed that giant fibroadenomas of breast was potentially malignant and should be considered malignant until proved otherwise. The incidence of malignancy and metastasis has been found to vary from 0.5% to 10% (Haagensen, 1971;

Phyllodes Tumour, like the fibroadenoma, is a combined proliferation of ductal epithelium and stroma, but phyllodes tumour may display behaviour that ranges from locally aggressive to the frankly malignant. The peak incidence is in fifth decade, with a population range extending from adolescents to the very elderly. Men are affected in less than 1% of cases. Grossly, presents as a larger mass than fibroadenoma & has a history of rapid growth. Mass is firm and may separate into leaflike structures (Greek, Phyllon, leaf, eidos 'form') (Anderson, 1996). Cut surface of the low-grade tumour is quite variegated, in contrast to the more homogenous appearance of fibroadenomas. Microscopically, the epithelial element of phyllodes tumour resembles that of the fibroadenoma, and may infrequently display atypical hyperplasia or in situ carcinoma (Grimes, 1992). Connective tissue stroma is considerably more cellular (≤ 3 mitosis/high power field) (Kirby et al, 1994). In malignant cases, the stroma tends to overwhelm the epithelium, and in some cases there may be a gradient of transformation from a lower to a higher grade. Other stromal elements, such as fat or cartilage, may occasionally co-exist.

Although malignant tumours tend to be larger and more infiltrative, the prognosis is most consistently related to the histologic characteristics of the stromal element -
cellularity, nuclear atypia, mitotic activity, necrosis and the presence of focal histologic transformation.

The lymphnode metastasis is rare, if occur, almost exclusively by the blood-borne route and includes only the stromal component. It appears that only about 20% of cases are histologically malignant, and less than half of these ever metastasize.

HAMARTOMA -

This is an uncommon lesion, presented as a discrete mass lesion occurs in middle aged females. Grossly, a well-demarcated mass or of a sharply demarcated region of fibrocystic change, depending on the amount of epithelium and the cellularity of the intervening stroma. Although size usually less than 5 cm. in diameter, but lesions upto 17 cm. in diameter and weighing upto 1400 gms have been reported (Jones et al, 1991). Histologically, the lesion contain lobular breast tissue with or without fibrocystic changes, along with varying amount of adipose tissue, smooth muscles and cartilage are less frequent. The lesions with abundant adipose tissue have been termed as adenolipoma.

BENIGN EPITHELIAL NEOPLASM

1. INTRADUCTAL PAPILLOMA -

Duct papilloma is not a very common type of breast tumour. Kremer and Rush (1973) found an incidence of 21% on a group of patients over 70 years of age. Ultrastructural studies (Ahmed, 1980) have confirmed the benign appearance of the cells.
Papillomas are the benign, largely intraductal lesion which presented with nipple discharge and as palpable mass. Patient's age ranges between 25 to 35 years. Most papillomas develops as solitary lesions, but about 20% to 25% are multiple and appears on peripheral site. On Gross appearance size measuring 0.5 to 2.0 cm in diameter and occupy a single dilated duct. Microscopically, it is characterized by presence of papillary intraductal proliferation of epithelial fronds that contain fibrovascular core along with fibroplasia.

These lesions also display minimal cellular pleomorphism, little hyperchromasia, low mitotic activity, foci of apocrine metaplasia, little, if any, necrosis, and lack of cribriform pattern. These criteria are helpful in distinguishing papillomas from intraductal carcinoma (Papillary type), found in older women.

Papillomas are associated with increased risk of mammary carcinoma specially in cases of multiple papillomas (Murad et al, 1981; Haagensen, 1986).

2. ADENOMA -

An uncommon, well demarcated, benign tumour composed of glandular element and scant stroma and classified as either tubular or lactating adenomas. Patients are almost in their child-bearing years, but it does not have any relationship with the use of oral contraceptives, (Hertel et al, 1976).

a) Tubular Adenoma - An adenoma composed of regular tubules resembling the ductules of a resting (non-secretory) lobule or resting breast.
b) **Lactating adenoma** - An adenoma composed of tubuloacinar structure with pronounced secretory changes as seen in pregnancy and lactation (O'Hara and Page, 1985).

Both type of adenoma produce distinct masses within breast, though lactating adenoma is less well circumscribed. Both types are composed of closely packed terminal ducts with little surrounding stroma. Myoepithelial cells are present external to the ductal lining epithelium.

It is confused clinically with mammary Paget's disease because of the frequent presence of erosion of the surface epithelium. Microscopically, there is prominent ductal and intraductal proliferation, along with a densely fibrous stroma. This proliferation may be complex and papillary, but the presence of Epithelial and Myo-epithelial cells confirms the benign nature of the process.

**Other Benign Soft Tissue Tumours**: Most frequently encountered benign stromal neoplasms are lipoma and haemangioma.

**Lipoma** - Kleinschmidt (1931) and Cholnoky (1939) reported "lipoma" of breast as 2% - 3% of all benign tumours of breast. Haagensen (1971) reported a total of 186 cases of lipoma of breast during 1927-1968, mentioned another variety of lipoma in 23 cases named adenolipoma in which fat was intermingled with epithelial lobules.

**Haemangiomas** - are most frequently encountered as incidental lesions. They most commonly occur in the perilebular tissues.
and are almost always smaller than 2 cm. in diameter (Jozefczyk et al, 1985), and may not produce a palpable mass. Some shows atypical features, like prominence or budding of the endothelial lining cells, but the absence of necrosis and destructive invasion should point to a benign diagnosis.

The term "Tumour" is defined as "An abnormal mass of tissue, the growth of which exceeds and unco-ordinated with that of the normal tissue and persists in the same excessive manner after cessation of the stimuli which evoked the change" (R.A. Willis, 1952).

**CARCINOMA BREAST**

The earliest description of cancer of breast and probably cancer in any form is credited to Egyptian Physician, Imhotep in 3000 B.C.

**INCIDENCE AND EPIDEMIOLOGY**

Breast cancer is the second most common cancer among women in the world, in developed countries, it is the most common (Parkins et al, 1992). By the year 2000, it is estimated that breast cancer will account for 500,000 deaths annually (Pisani et al, 1993).

For reasons not yet known, incidence of carcinoma breast is very low in Japan than other oriental countries.

Mormon, Seventh-Day Adventist, Alaskan, American Indian and Eskimo, Mexican-American, Japanese and Filipino women living in Hawaii have a lower per capita incidence of breast cancer than other Americans; Hindu and Jewish women
have a higher than average incidence. Women living in less industrialized nations tend to have lower rates of breast cancer than those living in industrialized countries but Japan is an exception (Kirby et al, 1994).

Breast carcinoma causes some 20% of cancer deaths among females and has been called "the foremost cancer" in women (Shingelton, 1987).

Reddy & Reddy (1958) reported 20.8% and 13.4% incidence of breast cancer from Madras and Andhra Pradesh. Paymaster and Sanghvi (1964) found that almost one half of all cancers in Hindu women occur in the cervix while the breast is affected only 14%, this proportion is reversed in Parsi women in whom the breast is seat of cancer in 50% and the cancer cervix is only 9%.

The percentage of carcinoma of the breast in India is almost half that observed in the United States (W.H.O.1960) but it was higher than that in Japan (Segi et al, 1957). Wahi et al (1958) reported the incidence of carcinoma of breast as 4% of all malignant neoplasms, and compared the incidence with those of Bombay, London, New York, which were 7.4%, 16% and 16.2% respectively. Haagensen (1986) reported 20.1% per 1,00,000 women in Bombay, India. Sharma et al (1994) reported incidence of cancer female breast in Rajasthan 19.4%, surpassing cancer cervix 18.2%.

Age specific incidence rates rise rapidly with increasing age, but breast cancer differ from other common
cancers as the rate of increase declines after age of 50 years, around the age of menopause (Pike et al, 1993). Breast cancer is exceedingly rare under the age of 20 years & in women less than 30 years of age, it constitutes less than 2.0% of the total cases (Haagensen, 1986). Thereafter, the incidence rises to an annual frequency of greater than 300 cases per 1,00,000 in the eighth decade of life.

AETIOLOGY

Various authors (Pathologists) has given their views about the aetiological factors in predisposition of breast cancer, which are given below -

1. GENETIC FACTORS -

Henderson et al and Lynch et al (1991) have documented the importance of heredity and genetic predisposition for breast cancer. Definitions suggested by Lynch et al are as follows:

(a) **SPORADIC BREAST CANCER (SBC)**:

A breast cancer patient with no family history of cancer of the breast through two generations involving siblings, offspring, parents, aunts and uncles, and both sets of grand-parents.

(b) **FAMILIAL BREAST CANCER (FBC)**:

A breast cancer patient with a family history including one or more first or second degree relatives with breast cancer that does not fit the hereditary breast cancer definition.
(c) **HEREDITARY BREAST CANCER (HBC):**

A breast cancer patient with a positive family history of breast cancer and, sometimes, related cancer (e.g. ovarian, colonic) with high incidence and a distribution in the pedigree. And also show increase incidence of bilateral breast cancer and other multiple primary cancers. Lynch and associates documented 225 consecutive breast cancer patients, updated with 103 new patients, 68% of the 328 probands studied were sporadic, 23% were familial, and 9% were hereditary. This may represent a considerable under-estimation of the frequency of hereditary breast cancer.

The risk for developing hereditary breast cancer is determined by Pedigree, appears to be independent of age at first pregnancy, and is enhanced when a biopsy confirm atypical hyperplasia.

2. **FAMILY HISTORY** —

A family history of breast cancer increases the likelihood of breast cancer development. This may be attributable to genetic and environmental similarities among family members. Early age at onset of breast cancer is the strongest indicator of genetic susceptibility (Slattery et al, 1993).

Overall, only 10% - 15% of breast cancer is attributable to family history and about half of this is attributable to dominantly inherited susceptibility genes (Weber et al, 1993).
Breast cancer is rare in men and family history of the disease is a risk factor. The recently discovered "BRCA 2 gene" on chromosome 13q is thought to account for some families with increased risk of breast cancer, including male breast cancer.

3. HORMONAL FACTOR -

Hormones probably various endogenous and exogenous hormones act at more than one stage in the development of breast cancer. In the human breast, malignancy probably arise largely from basal cells of the ductal epithelium. Hormones of the ovarian-pituitary axis undoubtedly play an etiological role, these are most likely exert their carcinogenic effect by increasing or decreasing rates of proliferation, atrophy, or differentiation of stem or intermediate cells. About 55% of tumours of the breast in non-pregnant females are hormone dependent and in pregnant subject, the frequency reaches 90%, although this may be an age effect (Cale, 1957).

In women, breast cancer does not occur before puberty. Risk of breast cancer increases as the age at menarche decreases, and as the age at menopause increases, so that the longer a woman has normal ovarian function the greater her risk. Furthermore, premenopausal oophorectomy, without exogenous estrogen replacement therapy reduces risk, and the degree of protection is inversely related to the age at which the ovaries are removed, child-bearing also alters risk; parous women are at lower risk than nulliparous women.
Pregnancy accompanies initially by proliferation, but is then followed by marked differentiation of mammary epithelial cells and there is some evidence that risk of breast cancer following radiation is initially enhanced and then reduced by a first pregnancy (Shore et al, 1980). If the first pregnancy interrupted during the first trimester, the risk of breast cancer may be increased (Pike et al, 1981), and this could be due to the initial cell proliferation not being followed by differentiation.

These concepts have been developed and incorporated into an elegant mathematical model for the genesis of breast cancer by Moolgavkar et al (1980).

The hormones most likely involved in these pathogenic cellular changes are estrogens and progesterone, but androgens and prolactin may also play a role. Estrogens cause proliferation of human breast tissue, and therefore expected to increase risk of breast cancer by stimulating the growth of stem and intermediate cells. Progesterone, which is largely produced during the luteal phase of menstrual cycle, causes alveolar cell growth in the estrogen primed breast, but also differentiation, so it is unclear whether its net effect would be to increase or decrease the risk of breast cancer. Androgens depress mammary cell growth, and would be expected to be protective against breast cancer. Prolactin acts on the estrogen-primed breast to stimulate and maintain lactation, and since it is associated with the functioning of differentiated cells, rather than the stimulation of cell growth, it would be expected to decrease risk.
4. DIBARY INFLUENCES

The committee on Diet, Nutrition & Cancer of the National Academy of Sciences concluded that a causal relationship exists between dietary mammalian fat and the incidence of breast cancer. Fried, high-fat foods can increase the risk of developing breast cancer approximately two-fold.

A study conducted by the National Cancer Institute noted that dietary fat intake in breast cancer patients was contributory. Compared with controls, the highest quartile for beef or pork consumption increased the relative risk for cancer 2.7-fold over that of the lowest quartile.

5. ESTROGEN RECEPTORS AND BREAST CANCER

The two stage model hypothesis of Moolgavkar et al (1980) and also from the estrogen window hypothesis of Korenman (1980), both theories emphasize the role of a long exposure of the mammary gland to estrogen as a factor in carcinogenesis promotion. As during various phase cells multiply from 10 cells to $10^7$ cells so may form nodules. At the post-menopausal period the long anovulatory cycles are seen (Sherman, 1975). In pre-menopausal breast cancer patient studied by Grattarola in 1964, only 181 had ovulatory cycles, secretory endometrium, without any luteal stimulation, glandular hyperplasia and adenomatous hyperplasia were observed in 19%, 10%, 33% respectively. A continuous unopposed estrogen stimulation of mammary tissue in approximately 82% of these patients was related to development of breast cancer.
As with the first estrogen window, benign breast diseases like fibroadenoma are frequently observed, and during second estrogen window, the perimenopausal period the true fibrocystic disease is accompanied by high risk of breast cancer (Kuttenn et al, 1983 and Mauvais-Jarvis, 1981).

In 1967, Jensen proposed that the in-vitro technique might be extended to human tumor tissue sample to predict the response to adrenalectomy. By this time, "estrogen receptor" had been discovered in tumors and appeared to be responsible for the specific uptake of estrogen by these tissues. Direct studies of the presence and role of receptor in mammary tumors followed and raised the possibility of using the presence of the receptors to predict hormonal dependency.

According to Mc Guire, Pearson and Segaloff (1975) estrogen receptor value in primary tumor ranges from zero to almost 1000 fmol/mg of cytosol protein. The wide range of values may be due to a combination of various factors.

Leclercq et al (1971) originally reported that approximately 70% of primary mammary carcinoma were ER positive and of these 50-60% respond to hormonal therapy, depending upon site of biopsy, as normal breast tissue in females does not have estrogen receptors, method employed, its sensitivity and definition of receptor positivity.

A primary carcinoma in women over 60 years of age at the time of diagnosis was more likely to be ER positive than patient younger than 40 years. Between 40-60 years age
appears to be an approximately equal likelihood of ER positivity or negativity (Rosen et al, 1975).

Most of the studies indicated a higher incidence and concentration of ER positivity in post-menopausal women compared to pre-menopausal and menopausal women. Johansen and associate (1970) observed no correlation between menstrual status and number of ER in breast cancer tissue. Reason given for higher value in post-menopausal women are — (1) low level of endogenous estrogen in plasma of post-menopausal patient, (2) Possibly the higher level of circulating progesterone limits ER synthesis in pre-menopausal patients (Rosen et al, 1975), (3) Other factors yet unknown may be involved. Other factors could be length of reproductive life, parity, age at first child birth, obesity, oral contraceptives, exogenous estrogen, EGF, oncogens and diet etc.

6. PREGNANCY AND RISK OF BREAST CANCER

Hormonal stimulation of dormant malignant cells to accelerated growth during pregnancy, rather than hormonal induction of breast cancers seems most likely to cause the increased incidence of breast cancer in other primigravid women (Mac Mohan, 1973). Increasing age at first pregnancy was "positively associated" with stromal infiltration by linear strands of tumour cells, areas of intraductal carcinoma and areas of lobular carcinoma in situ, these histologic breast cancer characteristics were also found more frequently in nulliparous than in parous women, an increase in breast cancer with declining breast feeding.
7. LACTATION AND RISK OF BREAST CANCER -

Recently, a beneficial effect of lactation has been reported at the time of premenopausal life but not for postmenopausal age; the breast cancer rate in premenopausal women was decreased by two-thirds (Anderson, 1971). Breast cancer is extremely rare in Canadian Eskimos females (1.3 per 1,000,000 population/year as compared to 72.5 per 1,000,000 in the United States). Eskimo women breast feed their infants for three or more years and some lactate continuously from the age of 17 to 50 years; however, genetic, racial, dietary and environmental factors may also account for the reduced breast cancer incidence in Eskimos (Schoefer, 1969).

Lactation has been connected with a more severe course of co-existing breast cancer. Fulminating, inflammatory or acute carcinoma of the breast is more often observed during pregnancy and lactation. "Lactation cancer" and the prognosis of continued life is "only about one year" has been considered as a "high grade malignancy" with 80% to 91% of patients having axillary metastasis, "the death risk is somewhat higher than for the other cases" (Westbay, 1946).

8. RADIATION AND BREAST CANCER RISK -

Ionizing radiation is the only known risk factor for breast cancer that most likely acts by causing DNA damage of the basal cells of ductal epithelium in human breast (Thomas, 1984).
Atomic bomb survivors from Nagasaki and Hiroshima, women treated with high-dose irradiation for acute post-partum mastitis, and women who have received multiple chest fluoroscopic examination for treatment of pulmonary tuberculosis have a higher incidence of breast cancer. Risk from multiple exposures to relatively low dosage is similar to the risk of one large dose of similar irradiation yield. Risk of breast cancer is reduced after irradiation treatment for cancer of the cervix and related to reduction of estrogen level.

9. OBESITY -

The majority of studies suggests that breast cancer risk directly correlates with relative weight, obese women experience a 1.5 to 2.0-fold increased risk. This relative risk increase is restricted to post-menopausal individuals (Kirby et al, 1994).

10. MISCELLANEOUS FACTORS -

(a) Socio-Demographic Factors - Unlike most other groups of common cancers, breast cancer incidence is higher among women of upper rather than lower social class, it is more common in Jewish rather than non-Jewish women, and the lowest rates in the U.S.A. occur in groups with prescribed life styles, e.g. Mormons (Lyon et al, 1994) and Seventh Day Adventists (Mills et al, 1989). Rates are lowest in the U.S.A. among women of Asian ancestry and highest among white women, except below age 40 years when African-American rates are the highest (Miller et al, 1993).
(b) **Exercise** - Physical activity in adolescence and young adult life has been shown to reduce the risk of breast cancer in premenopausal and postmenopausal women. Risk reductions may be hormonally mediated, since physical activity delays the onset of menarche and decreases the number of ovulatory menstrual cycle (Freidenreich et al, 1995).

(c) **Alcohol** - Consumption of 15 gm or more of alcohol (2 to 3 drinks per day) increases risk by about 50% relative to non-drinkers (Longnecker, M.P., 1994).

Increase in plasma oestrone and oestradiol induced by alcohol may be responsible for this increase (Reichman et al, 1993).

(d) **Smoking** - Cigarette smoking has been reported both to increase and decrease risk of breast cancer. The decrease has been suggested to be due to the reduced serum and urinary oestrogens found in smokers (Michnovics et al, 1988). Studies showing an increased risk attribute this effect to the numerous carcinogens in cigarette smoke, the effect of which may be enhanced among women who are genetically predisposed to the slow acetylators of aromatic amines (Ambrose et al, 1995).

11. **BIOLOGICAL FACTORS** -

Women in whom more than 75% of the breast has nodular densities on mammography are at increased risk (OZA and Boyd, 1993). However, the age of the woman is important in risk determination because normal breasts of premenopausal women have more extensive nodular densities than the breasts of postmenopausal women (Swann et al, 1988).
MALIGNANT EPITHELIAL TUMOURS OF BREAST -

The W.H.O. histological classification (1982) is based primarily on histological appearances rather than on histogenesis. Most carcinomas of the breast contain combinations of the growth patterns. If a component is a minor one only, the tumour should be classified by the predominant pattern. Extensive mixtures, however, require multiple diagnoses. Histological grading of breast carcinomas has proved to be useful in evaluating prognosis.

1. NON-INVASIVE CARCINOMA -

It accounts for about 10% of all breast cancer, though the incidence may vary from one clinical setting to another.

I. INTRADUCTAL CARCINOMA -

Sandison (1962) found a total of 195 intraductal carcinoma constituting about 3% of all breast carcinoma. Page et al (1982) reviewed 11,760 biopsies and found 28 cases of intraductal carcinomas. These are believed to arise from transformed cells located in terminal ducts (Page et al, 1987; Harris et al, 1992). The two major categories currently recognised are referred to as "Ductal carcinoma in situ" (DCIS) and "Lobular carcinoma in situ" (LCIS). DCIS is further sub-divided into comedo, cribriform, micropapillary, solid and papillary sub-types. Recent studies have shown that, relative to the other sub-types of DCIS, Comedo DCIS is associated with many aggressive biologic and clinical features.
(A) **DUCTAL CARCINOMA IN SITU**

(i) **COMEDO TYPE** – It accounts for 3% to 5% of all breast carcinomas and 35% to 50% of solitary non-invasive carcinomas (Page et al, 1987; Silverstein et al, 1991, and Bellamy et al, 1993). The natural history of DCIS is poorly understood because it was treated by total mastectomy resulting in 96% to 100% long term survival (Harris et al, 1992). Further studies of Alpers et al (1985) have shown that these tumours appear in 10% cases in form of invasive carcinoma.

Recent studies of comedo DCIS treated by lumpectomy report local recurrence rate of 7% to 20% with half the recurrences being invasive (Lagios et al, 1989; Solin et al, 1991). This clinical aggressiveness is consistent with the aggressive biological features associated with comedo DCIS, including absence of hormone receptors (Poller et al, 1993), a high proliferation rate (Meyer J.S., 1986) and an aneuploid DNA content (Aasmundstad et al, 1990).

**Gross Examination** –

Most of the cases presents as well circumscribed palpable masses measuring 2–3 cm. in diameter but upto 5 cm. in diameter is an usual finding. Cut section characteristically exudes cheesy, "comedo-like", necrotic debris from distended ducts.

**Microscopic Examination** –

Shows non-invasive tumour cells distending the ducts ten times of their normal diameter. Few may show a solid
growth pattern, most show prominent central necrosis, with viable cells being present only at the periphery in solid or perforated arrangements. Cytologic and nuclear features, includes large, irregularly shaped cells with abundant cytoplasm. Nuclei are large, pleomorphic, contain dark condensed chromatin, prominent nucleoli, and numerous atypical mitotic figures.

The major problem in differential diagnosis involves distinguishing cancerization of lobules from micro-invasive carcinoma. This problem can be minimized by adoption of the conservative strategy of requiring the invasive cells to extend beyond the specialized intralobular connective tissue.

(ii) NON-COMEDO TYPE - Accounts for 5% to 8% of all breast carcinomas and 50% to 70% of solitary non-invasive carcinomas (Patchesky et al, 1989; Schwartz et al, 1992). It is less aggressive lesion than comedo DCIS, with lower short-term recurrence rates (less than 5%) after local excision and strong associations with favourable biologic features such as presence of hormone receptors (Poller et al, 1993), low proliferation rates and diploid DNA content (Aasmundstad & Haugen, 1990).

The majority of non-comedo DCIS are non-palpable and are initially associated with small micro-calcifications seen on mammograms (Schwartz et al, 1992), although few are incidentally found in breasts on which biopsies are done for other reasons.
Various sub-types of non-comedo Ductal Carcinoma in situ are as follows:

a) **CRIBRIFORM NON-COMEDO TYPE** - Microscopically, it is composed of cells forming evenly spaced, uniform, rounded microacini in moderately distended ducts. Extension of the tumour to the lobule is rare. Central necrosis of cells within ducts may be present and is occasionally prominent. Cytologic and nuclear features are of low grade, includes uniform, small, round cells with distinct surface membranes and scant-to-moderate amount of cytoplasm. Nuclei are typically small to intermediate in size and round to oval in shape and contain relatively homogenous chromatin and small nucleoli. Mitotic figures are rare.

b) **MICROPAPILLARY NON-COMEDO TYPE** - It is characterized by small papillary projections of cells without fibrovascular cores. The micropapillary are similar in length and smooth in outline and have slightly bulbous tips. Cytological features are same as that of cribriform subtype.

c) **SOLID NON-COMEDO TYPE** - Characterized by uniform cells with the same cytologic features but which distend ducts as a solid proliferation without forming discernible acini or micropapillae.

d) **NON-INVASIVE PAPILLARY CARCINOMA** - is rarer than the other forms of non-comedo DCIS. Grossly, presents as 1 to 3 cm palpable mass with an "intra-cystic" appearance (Carter et al, 1983). Microscopically, composed of elongated branching
papillae with fibrovascular core lined by columnar cells showing variable degree of atypia. Papillae may fuse, forming solid or cribriform cellular arrangements.

II. LOBULAR CARCINOMA IN SITU -

It accounts for 1% to 3% of all breast carcinomas and 10% to 30% of solitary non-invasive carcinomas. It is a non-palpable microscopic lesion nearly always encountered as an incidental finding in the breasts of premenopausal women (Haagensen et al, 1986). The risk of developing invasive carcinoma in a breast with previously excised LCIS increases about 1% per year, a rate that translates to a greater than ten-fold relative risk and a 20% absolute risk after 20 years (Haagensen et al, 1978; Rosen et al, 1978 and Page et al, 1991).

This risk is bilateral, and most invasive cancers that develop are ductal rather than lobular, indicating that LCIS may be a marker for the development of invasive breast cancer rather than a precursor. Microscopically, LCIS is usually multicentric and characterized by lobular units in which all acini are filled and distended by loosely cohesive cells with generally low-grade cytologic and nuclear features.

The cells are small, rounded or polygonal and have distinct cell membranes and moderate amounts of relatively clear cytoplasm. They may have prominent cytoplasmic vacuoles imparting a signet-ring appearance. Nuclei are typically round or oval and contain homogenous dark chromatin and small or inconspicuous nucleoli. Mitotic figures are rare. LCIS has
a tendency to spread beneath the epithelium of proximal large ducts in a pagetoid fashion.

2. **INVASIVE CARCINOMA BREAST**

These are account for about 90% of all breast carcinomas. These characteristics are quite heterogenous in the majority of invasive carcinomas.

a) **INVASIVE DUCTAL CARCINOMA NOT OTHERWISE SPECIFIED (IDC-NOS)** —
It is a heterogenous group of lesions, the majority of invasive breast carcinoma fall in this category which includes all those lesions that lack specific features. The National Surgical Adjuvant Breast Project (NSABP) 1975, reported its incidence about 52.6%. It is biologically and clinically more aggressive than the special types of invasive carcinoma. These are characterized by a relative absence of the histologic features that define the special types of invasive carcinoma.

Recent studies shows that it account for about 60% of all breast carcinomas and 70% of invasive carcinomas, though its relative incidence varies with clinical stage. Typical mammograms show an irregular density with internal microcalcifications, which are nearly always interpreted as either consistent with or highly suspicious of cancer.

Macrosopically, IDC-NOS is usually whitish grey approximately 2-3 cm in size, firm in consistancy having gritty texture. Shapes vary from those with an irregular stellate outline, reflecting on infiltrative growth front
microscopically, to those with a lobulated or circumscribed contour, reflecting a blunt pushing growth front microscopically.

IDC-NOS has no typical features microscopically. Some lesions may be solid and highly cellular, whereas others may be solid but pauci-cellular and accompanied by a prominent desmoplastic stroma. Acinus or tubule formation may dominate, or be combined with solid tumour.

The cytologic and nuclear features of IDC-NOS are also heterogenous. Cells may be small, intermediate, or large; they may be round, pleomorphic, or intermediate in shape. The amount of cytoplasm is highly variable. Nuclear features (including size, shape, chromatin and nucleoli) may show mild, moderate or severe atypia. The number of mitotic figure is highly variable and their confirmation may be normal or atypical.

W.H.O. (1968) classified IDC-NOS as infiltrating carcinoma, contain a large range of malignant epithelial growths, from well differentiated adenocarcinoma to completely un-differentiated carcinoma for prognostic point of view, carcinoma were graded into four grades according to the criteria given by Bloom and Richardson (1957) i.e. Tubule formation, hyperchromatism and mitosis, irregularity of size, shape and staining of nucleus. This tumour has been referred to as carcinoma of no special type, infiltrating carcinoma with productive fibrosis, scirrhous carcinoma, infiltrating carcinoma and carcinoma simplex and on the basis of diffuse fibrous stroma or growth pattern carcinoma sub-divided as stellate or circumscribed type.
Recently, new grading system of infiltrating ductal carcinoma is given by Elston & Ellis (1991), a modification of Bloom-Richardson (1987).

The numerical scores are assigned to each of three major histologic features: the percentage of tubule formation, the degree of nuclear pleomorphism, and the number of mitoses per 10 high-power field, based on a thorough microscopic evaluation of entire lesion. The score for each feature are then added to determine the histologic grade, which is directly related to differentiation.

**HISTOLOGIC GRADING OF BREAST CARCINOMA (ELASTON MODIFICATION):**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Feature score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PERCENT TUBULE FORMATION</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 75</td>
<td>1</td>
</tr>
<tr>
<td>10 - 75</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>3</td>
</tr>
<tr>
<td><strong>NUCLEAR PLEOMORPHISM</strong></td>
<td></td>
</tr>
<tr>
<td>Mild (small and uniform)</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>Severe (Pronounced variation)</td>
<td>3</td>
</tr>
<tr>
<td><strong>MITOTIC COUNTS PER 10 HIGH-POWER FIELDS (HPFS)</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 9 mitoses/10 HPFs</td>
<td>1</td>
</tr>
<tr>
<td>10 - 19 mitoses/10 HPFs</td>
<td>2</td>
</tr>
<tr>
<td>≥ 20 mitoses/10 HPFs</td>
<td>3</td>
</tr>
</tbody>
</table>

**TOTAL SCORE**

<table>
<thead>
<tr>
<th>Grade</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 - 5</td>
<td>I (Well Differentiated)</td>
</tr>
<tr>
<td>6 - 7</td>
<td>II (Moderately Differentiated)</td>
</tr>
<tr>
<td>8 - 9</td>
<td>III (Poorly Differentiated)</td>
</tr>
</tbody>
</table>

The percentage of tubule formation is based on assessment of the entire tumour. However, nuclear pleomorphism is assessed in the worst area, and mitotic counts at the leading edge of tumour growth.
Using this grading system in a prospective study involving more than 1800 patients with invasive breast cancer, median 10-year survivals of 90%, 60% and 40% were associated with grade I, grade II and grade III lesions, respectively.

The major problem in the differential diagnosis of IDC-NOS involves distinguishing it from special types of invasive carcinoma. In general, if less than 75% of a lesion shows the features of a special subtype, it should be diagnosed as IDC-NOS because its prognosis is likely to be worse than that for the special type. Classical lobular carcinoma rarely presents a problem, though its variants may be confused with IDC-NOS.

b) Invasive ductal carcinoma with a predominant intraductal component - The term was used in W.H.O. Classification (Azzopardi et al, 1982) to describe carcinoma which are overwhelmingly intraductal and contain only small foci of stromal invasion.

c) Infiltrating Lobular Carcinoma (ILC) - It includes both the classical and the variant subtypes, accounts for about 15% of all invasive breast cancer (Anderson et al, 1991; and Simpson and Page, 1992). Classical ILC is the most common (75% of cases) and studies of this sub-type have reported 7 to 10 year survivals of 80% to 90% for all stages (Anderson et al, 1991 and Poen et al, 1992).

The prognosis of ILC variants is similar to that of IDC-NOS (Dixon et al, 1985), but their recognition remains
important because all sub-types of ILC are associated with
significant rates of concurrent (10% to 15%) or subsequent
(20% to 35%) contralateral invasive breast cancer (Wheeler
and Enterline, 1976; Dixon et al, 1983). Patients may
present with a palpable mass or a diffuse lesion that is not
detectable by palpation or mammography.

Macrosopically, some lesions are discrete, firm and
stellate, whereas others appear as an ill-defined thickening
identifiable as cancer only under the microscope.

Microscopically, classical ILC is characterised by
uniform, small, round, poorly cohesive cells with low-grade
nuclear features growing in short, straight, single-file
arrangements ("Indian file"), or swirling around vessels,
ducts, and lobules ("targetoid" pattern). Signet - ring cells
may be common. LCIS is present in 80% to 90% of classical ILC
(Dixon et al, 1982).

Variants of ILC include solid, alveolar, mixed and
pleomorphic subtypes. The cytologic features of the solid,
alveolar, and mixed variants are the same as in classical ILC,
and they are distinguished by their growth patterns.

The solid variant grows in sheet-like cellular
arrangements. The alveolar variant is characterized by small,
crowded, solid nests of cells. The mixed variant shows
combinations of classical, solid and alveolar patterns.
Pleomorphic ILC has a diffuse growth pattern and is
distinguished by its high-grade nuclear atypia. LCIS is
present in less than 50% of ILC variant.
d) MUCINOUS CARCINOMA (Gelatinous or Mucoid Carcinoma) -

Mucinous carcinoma is also known as colloid carcinoma, has typical and variant sub-types collectively account for only 2% to 3% of all breast carcinomas (Page et al, 1991). The variants are three times more common than the typical subtypes (Anderson et al, 1991) and are common in older women (Rosen et al, 1985). Typical mucinous carcinoma has a very good prognosis, with survival in the range of 85% to 90% at 10 years, compared with only 70% to 80% for the variant subtypes (Morris and Taylor, 1965 and Silverbeag et al, 1971). Recurrences after mastectomy are relatively rare, and 50% of these occur after 10 years of disease-free survival.

Mucinous carcinoma present as soft palpable masses with vague, non-specific, findings on mammograms. Grossly, it's well circumscribed, size measuring 2 cm to 3 cm in diameter, glistening tan colour, and soft gelatinous texture.

Microscopically, composed of small islands of malignant cells suspended in large amounts of extracellular epithelial mucinous material (Page et al, 1987).

The tumour border is blunt rather than infiltrative. As in situ component is rare, cell groups may be solid or perforated by acinar spaces. Cytological and nuclear features are of a low-grade to intermediate-grade tumour. For a lesion to be diagnosed as typical mucinous carcinoma, these combined features should constitute more than 90% of the tumour. In the variant subtype they account for only 75% to 90% of the lesion.
If less than 75% of the tumour contains these features, it should be categorized as IDC-NOS.

e) **MEDULLARY CARCINOMA (ENCEPHALOID CARCINOMA)**

Haagensen (1971) called it as "Circumscribed Carcinoma". It constitutes about 7% of all breast cancer. This includes both the typical and the variant subtypes which are equally frequent (Rapin et al., 1988). Typical medullary carcinoma has a better prognosis than IDC-NOS with reports of 10 year survival of 80% to 90% (Margolis and Silverberg, 1988; Fisher et al., 1990). The "National Surgical Adjuvant Breast Project" (1975) reported its incidence 6.2% of all invasive breast cancer.

Medullary carcinoma, usually presents as a palpable, mobile, circumscribed mass ranging from 2 cm to 3 cm in greatest dimension, though lesions larger than 5.0 cm may be encountered. Gross pathologic features reflect the clinical presentation. Lesions are well circumscribed, lobulated, tan-white, relatively soft and homogenous in consistency.

Microscopic features of typical medullary carcinoma include a blunt or pushing leading edge, solid-syncytial groups of cells with high-grade nuclei, scanty loose stroma, and a prominent interstitial lymphocytic infiltrate. These features must be well developed and compose more than 90% of the lesion. Bizarre tumour giant cells and foci of squamous metaplasia are occasionally encountered. There may be a minor in situ component that is usually solid or of the comedo type. Medullary carcinoma variant has these same features, constitute only 75% to 90% of
the lesion. Lesion with similar features in less than 75% of
the tumour should be diagnosed as IDC-NOS, because they will
generally have the poorer prognosis associated with this type.

f) PAPILLARY CARCINOMA -

The incidence of papillary carcinoma has been reported
by various authors, ranging between 0.3% - 3% (Hart, 1927;
Krans and Neubecker, 1962; Haagensen, 1971; The National
Surgical Adjuvant Breast Project, 1975), generally present in
seventh decade.

The typical papillary cancer is small in size measuring
less than 2 cm to 3 cm in diameter. Morphologically, these
cancers are well circumscribed; papillary differentiation in
the form of papillae with well-defined fibrovascular stalks
and multilayered epithelium may harbour moderately pleomorphic
cells (Kirby et al, 1994).

Mc Divitt and Stewart and Berg (1968) have reported
slow growth rate and low incidence of mitoses while Kraus and
Neubecker (1962) found its behaviour similar to that of breast
carcinoma in general. Although, Axillary metastases occur in
upto one-third of patients, papillary carcinoma represents a
more indolent, slowly progressive disease than the common
adenocarcinoma.

g) TUBULAR CARCINOMA -

One of the least malignant and also infrequent type
of carcinoma of the breast was first well described in 1968,
and named tubular carcinoma by Mc Divitt, Stewart and Berg.
Recently, it has been described as highly differentiated, infiltrating carcinoma composed of uniform cells arranged in well developed tubules, accounts for 1.4% of all breast cancers (Sloane, 1985). Mc Divitt, Boyce and Gersell (1982) defined tubular carcinoma in which at least 75% of the tissue exhibit the classical appearance with no more than 25%, resembling infiltrative ductal carcinoma.

The National Surgical Adjuvant Breast Project (1975) reported 1.2% of all mammary neoplasia. The small size of tumour, the single layer of cells lining the tubules, the cytologically benign appearance and the presence of apocrine snouts should serve to distinguish tubular carcinoma from the more well-differentiated form of infiltrative duct carcinoma (Sloane, 1985).

Tubular carcinoma including typical and variant subtypes, accounts for about 5% of all breast cancer, though the incidence varies with the clinical setting and is higher among lesions detected by mammography. The typical subtype has the best prognosis of all the special types of invasive breast carcinoma with reports of 5-year survival of 95% to 100% (Mc Divitt, 1982). Concurrent or subsequent contralateral invasive breast cancer may be present in upto 20% of patients with tubular carcinoma (Cooper et al, 1978).

Tubular carcinoma may present as a hard, palpable mass with an average diameter of 1.0 cm, majority of tumours are detected by mammography. They typically have a firm, white, stellate appearance on gross examination.
Microscopically, composed of small glands or tubules with round, oval, or angular ("tear-drop") shapes. Glands are uniformly distributed in a centrally dense fibrous stroma with prominent elastosis. The stroma is less dense near the periphery where isolated glands may invade adjacent adipose tissue. A single layer of cuboidal or columnar cells with low-grade cytologic and nuclear feature line the malignant glands. Cribriform or micropapillary DCIS may be present in up to 65% of tubular carcinomas.

h) **ADENOID CYSTIC CARCINOMA (CYLINDROMA)** -

Several pseudonyms have been used to describe this lesion such as adenocystic basal cell carcinoma (Stein & Geschiekter, 1934), cribriform carcinoma (WHO, 1968) and cylindroma (Haagensen, 1971). It is a rare type of carcinoma. Various workers reported its incidence from 1% to less than 1% of all malignant tumours of the breast (Geschiekter, 1945; Foote and Stewart, 1946; Ackerman, 1956; The National Surgical Adjuvant Breast Project, 1975). Anthony and James (1975) found three cases only out of 2686 breast carcinomas.

The tumour is usually apparently well localised and is characterised by a honey-combed structure formed by epithelial spaces filled with an epithelial mucin and lined by uniform epithelial cells (Koss et al, 1970). There may be a vague resemblance to carcinoid tumours but argyrophilia is not seen and neither is the argentaffin reaction positive (Peters and Wolff, 1982).
The tumours grow slowly and metastasis is rare. Local recurrence may be seen if local excision is the treatment chosen by the surgeon (Lusted, 1970; Peter & Wolff, 1982).

i) **SECRETORY (JUVENILE) CARCINOMA**

Recently, described by W.H.O. (1982) this is the most common type of breast carcinoma in children and adolescence although it also occurs in adults. It is rare tumour and there are probably less than 40 documented cases (Sloane, 1985). The lesion is less than 2.5 cm in diameter and not circumscribed. Histologically characterised by numerous tubular spaces filled with PAS-positive eosinophilic secretion giving a follicular appearance.

j) **APOCRINE CARCINOMA**

Also known as Oncocytic or sweat gland carcinoma, in its pure form it is very rare and accounts for under 1% of carcinomas (Azzopardi, 1979). Histologically, the cells have copious variably granular eosinophilic cytoplasm with large rounded nuclei with prominent nucleoli. Eosinophilic inclusions seen in benign apocrine metaplasia may be present and sparse PAS-positive intracytoplasmic granules can usually be demonstrated. Foci of apocrine tumour cells may be seen in other types of mammary carcinoma.

**OTHER RARE TYPES OF BREAST CARCINOMA**

Several exceptionally rare types of invasive carcinomas collectively accounts for less than 1% of all breast cancer.
Metaplastic carcinomas are in this group and include squamous cell carcinoma and pseudosarcomatous (Wargotz and Norris, 1989; 1990). Because focal squamous metaplasia is frequent in the common types of breast carcinoma, lesions diagnosed as squamous carcinoma must show unequivocal squamous differentiation throughout.

Pseudosarcomatous lesions must be composed of at least 20% metaplastic elements, which most commonly are fibrous, chondroid, or osseous. They have very poor prognosis.

Also includes among the rare malignant epithelial lesions as signet-ring cell carcinoma, carcinoid tumour, clear cell carcinoma, secretory carcinoma. Signet-ring cell carcinoma must contain more than 20% signet-ring cells to qualify for this diagnosis, it has a diffuse ILC-like growth pattern, has very poor prognosis.

Lesions with light microscopic, ultrastructural, and biochemical features of carcinoid tumours occur in the breast, but it is controversial whether they represent true neuroendocrine neoplasms. Malignant salivary gland like tumours includes muco-epidermoid and adenocystic carcinomas, with the latter being more common.

**Unusual presentation of breast carcinoma:**

Two unusual presentations of otherwise common breast cancer are Paget's disease of the nipple (Ashikari et al., 1970) and inflammatory carcinoma (Jaiyesimi et al, 1992).
A) **PAGET'S DISEASE OF THE NIPPLE**

This condition was first described by Valpeau (1856). In 1874, Sir James Paget observed that an eczematoid lesion of the nipple at times preceded carcinoma of the breast. Drier (1889) first identified the Paget's cells. Various workers reported 0.3% to 3% incidence of all mammary carcinoma (Dockerty & Harrington, 1951; Reddy and Reddy, 1958; The National Surgical Adjuvant Breast Project, 1975). About 2% of breast carcinomas were associated with Paget's disease (Fisher et al, 1975 a), associated with a greater frequency of multicentric carcinoma (Fisher et al, 1975 b).

Paget's disease almost invariably associated with an underlying breast carcinoma of either the intraduct or infiltrating type, occasionally there was an associated lobular in situ carcinoma. It presents as an encrusted, scaly, hyperemic, and enlarged tumour that occupies the surface of the nipple-areola complex. Patients presents with breast tenderness, itching, burning and intermittent haemorrhage. Intraductal adenocarcinomas often involve the epidermis of the nipple and areola by intra-epithelial dissemination. Physical findings in the nipple-areola complex precede the identification of a palpable mass in the subareolar area. One-quarter to one-third of patients have axillary node metastasis at diagnosis. In general, this breast cancer has a better prognosis than the majority of lesions because the nipple-areola changes promote early consultation, biopsy and diagnosis.
Microscopically, Paget's disease presents as an intra-epithelial tumour composed of small groups of or single clear cells with large vesicular or prominent nuclei. The intraductal lesion is often multifocal; ducts throughout the entire breast may be dilated as a result of obstruction of central collecting ducts at the ampulla of the nipple. Pathognomonic of the entity is the presence of very large, pale, vacuolated cells (Paget's cells) in the rete pegs of the epithelium.

This lesion may be confused with superficial melanoma. The diagnosis is differentiated by demonstration of S-100 protein or melanoma-specific antigen immunoreactivity in malignant melanoma. The immunohistochemistry, specifically demonstrate carcinoembryonic antigen (CEA) within Paget's cells, which does not found in melanoma.

The origin (histogenesis) of the Paget's cell remains controversial and two hypotheses are considered -

i) Epidermotrophism of underlying tumour cells, and

ii) Intra-epithelial carcinomatous metaplasia.

The presence of typical Paget cells and associated findings are diagnostic of the entity even in the absence of subareolar mass (Kirby et al, 1994).

B) INFLAMMATORY CARCINOMA OF BREAST -

It is characterised clinically by prominent skin oedema, redness and warmth a visible eryseploid margins and induration of the underlying breast. Biopsies of the involved
skin revealed undifferentiated cancer cells in the subdermal lymphatics causing an obstructive lymphangitis. Inflammatory cells are rarely present. Prognosis of inflammatory breast cancer is poor even in apparently localized lesions because of invasion of dermal blood vessels and embolisation of the dermal lymphatics.

OTHER SOFT TISSUE TUMOURS -

SARCOMA OF BREAST - These constituting less than 1% of breast malignancies, the full histologic continuum of sarcomas occurs in the breast.

Angiosarcoma - It is the most common, with the remainder being made up mainly of fibrous neoplasms. Because these tumours appear to be derived from the extralobular connective tissue and are usually not responsive to hormonal therapy. Mammary Angiosarcomas develops primarily in women with child-bearing age and may even be diagnosed during pregnancy. Rosen et al (1988), rarely reported in men. These are histologically separated into low-grade and high-grade varieties, though even the former may metastasize in a minority of patients. Peripheral regions of a high-grade tumour may display a low-grade histologic features. High grade tumours are associated with poor prognosis (approximately 15%, 5-year survival).

Primary mammmary angiosarcoma should not be confused with postmastectomy angiosarcoma which develops in the arm or axilla of patients with chronic lymph edema and often occurs 10-20 years after the original axillary lymphnode dissection (Rosen et al, 1988 a).
Fibrous Neoplasms - range morphologically from fibromatosis to fibrosarcoma and malignant fibrous histiocytoma. These tumours are grossly and histologically identical to their counterparts in other tissue and display the same tendency for recurrence and metastasis (Jones et al, 1992).

Fibromatosis - may be mistaken for mammary carcinoma in patients with skin or nipple retraction.

Fibrosarcoma and fibrous histiocytoma - have been separated into low-grade and high-grade varieties on the basis of mitotic activity and nuclear atypia. Only high-grade lesions tended to metastasize, though recurrence occurred in over half of the cases with low-grade tumour.

METASTASIS OF BREAST CARCINOMA -

Approximately 30% of breast cancer patients have metastatic implants in regional axillary lymph nodes when they are first diagnosed, and another 10% have distant metastatic disease. The clinical assessment of lymphnode status is extremely inaccurate and error rates up to 30% have been reported in studies comparing clinical to histopathologic evaluation (Fisher, 1984). There may be a significant error in the routine histopathologic evaluation of nodes for metastatic disease, recent studies have shown that more extensive serial sectioning or immuno-staining with antibodies to epithelial components detect micrometastases in up to 10% of patient originally diagnosed as having negative nodes (International (Ludwig) Breast Cancer Study Group, 1990). Large studies have shown a 10% reduction in 5-year survival associated with such occult micrometastatic tumour.
Distant metastatic disease is the first sign in about 50% of women with previously excised breast cancer who relapse (Lee, 1988). Nearly all patients dying of breast cancer have widely disseminated metastatic disease, with lung, liver and bone being the favoured sites (Hagemeister et al, 1980).

CANCER METASTATIC TO THE BREAST -

Nearly every type of cancer has metastasized to the breast at one time or another, though collectively it is quite rare. When it occurs, it is usually late in the clinical course of widely disseminated disease (Nielsen et al, 1981). Non-Hodgkin's lymphomas, myeloid leukemias and systemic myeloma are among the most frequent tumours that metastasize to the breast. Lymphomas may also be primary in the breast but are exceedingly rare (Less than 0.1% of all breast cancer) (Mambo et al, 1977).

Lung carcinomas and malignant melanoma are the most common solid cancer that metastasize to the breast (Mc Crea et al, 1983).

CARCINOMA MALE BREAST -

Breast cancer occurring in the mammary gland of males comprising less than 1% of the incidence in women (Donegan et al, 1973 and Haagensen, 1986). The incidence appears to be highest among North Americans and the British male, constitutes 0.4% to 1.5% of all male cancers. An increased incidence also occurs in Jewish and black males. The incidence peaks between sixty and sixynine years of age, the tumour is rarely seen in young males (Kirby et al, 1994). Bilateral breast cancer in a male has been reported (Brodie & King, 1974).
Gynaecomastia precedes approximately one-fifth of these malignancies. Male breast cancer has been associated with Klinefelter syndrome (47-XXY), estrogen therapy, high endogenous estrogen level related to testicular feminizing syndromes, irradiation and trauma. Male breast cancer very often contains steroid hormone receptors, 84% of tumours arising in male mammary glands contain estrogen receptors (Gupta et al, 1980).

The breast tumours in male involves the pectoralis major muscle more commonly, probably because the breast tissue is scant. Delay in diagnosis also must have a role in the more advanced presentation of male breast cancer (Yap et al, 1979).

Patient presents with breast mass, nipple retraction, discharge, skin fixation, ulceration and pain in breast involved.

Histologically, tumours of the male breast are mostly infiltrating ductal carcinomas, similar in appearance to their counterparts in women. Lobular carcinoma both invasive and non-invasive, are rarely seen in men. Regional lymphnode metastases is very early as compared to females breast cancer.

The presence of nodal metastases appears to have at least the same prognosis in men as in women.