Lesions of female breast are much more common than lesions of male breast.

These lesions present as palpable, sometimes painful, nodules or masses.

Most of these lesions are benign.

Breast cancer is 2nd most common cause of cancer deaths in women, following carcinoma of the lung.

The clinical significance of the benign conditions:
1- possible clinical confusion with malignancy
2- association of certain variants with breast carcinoma.
Breast diseases

- No disease: 30%
- Fibrocytic changes: 40%
- Miscellaneous benign: 13%
- Fibroadenoma: 10%
- Cancer: 7%

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Fibrocystic changes

- are the most common cause of breast "lumps"
- a variety of changes that range from innocuous to others associated with an increased risk of breast carcinoma.
- Result from *exaggeration and distortion of the cyclic breast changes that occur normally in the menstrual cycle*.
- HRT and OCPs do **not** increase the incidence of these alterations; (OCPs may *decrease* the risk).
- Previously called *fibrocystic disease* (misleading to physicians) ➔ the term *fibrocystic changes* is preferred.
- arise during reproductive period of life but may persist after menopause
- are so common (at autopsy in 60% to 80% of women)
Fibrocystic changes

1- **Non-proliferative fibrocystic change:**

- the most common type
- = increase in fibrous stroma associated with dilation of ducts and formation of cysts of various sizes.

**Morphology**

- **Grossly:** multifocal and bilateral; cysts (1 cm to 5 cm); brown to blue (blue dome cysts) and filled with serous, turbid fluid; microcalcifications in mammograms.

- **Histologically:** cuboidal to columnar epithelium; commonly large polygonal cells with abundant granular, eosinophilic cytoplasm (called **apocrine metaplasia**); this is almost always benign
2-Proliferative Changes (Epithelial Hyperplasia)

- a range of proliferative lesions within the ductules, the terminal ducts, and sometimes the lobules of the breast.
- May be mild and orderly → carry little risk of cancer; or
- atypical hyperplasias → carry a greater risk

Morphology
- Macroscopic: not distinctive from non-proliferative
- Histologically: increased number of layers in ducts (epithelial proliferation); can be mild, moderate, or severe.
- Atypical hyperplasia ➔ When the hyperplastic cells become monomorphic with complex architectural patterns.
- Atypical ductal or lobular hyperplasia is associated with an increased risk of invasive carcinoma.

Clinical findings in hyperplasia
- Alone does not often produce a breast mass.
- Microcalcifications on mammography
- Nodularity
- Serous nipple discharge (Occasionally)
Classic Epithelial hyperplasia. The lumen is filled with a heterogeneous population of cells of different morphologies. Irregular slit-like fenestrations are prominent at the periphery.
Fibrocystic changes & relation with cancer:

1- Minimal or no increased risk ➔ fibrosis, cysts (microscopic or macroscopic), apocrine metaplasia, mild hyperplasia
2- Slightly increased risk (1.5-2 times ➔ moderate to florid hyperplasia (without atypia)
3- Significantly increased risk (5 times) ➔ atypical hyperplasia (ductular or lobular); (seen in 15% of biopsies).

- Proliferative lesions may be multifocal, and the risk of subsequent carcinoma extends to both breasts.
- A family history of breast cancer may increase the risk in all categories (e.g., to ~10-fold with atypical hyperplasia).
INFLAMMATIONS

- cause pain and tenderness in the involved areas
- not associated with increased risk of cancer.

**Acute bacterial mastitis:**
- Caused by bacteria which access the breast tissue through the ducts
- inspissation of secretions; fissures in the nipples
- usually develop during the early weeks of nursing

**Morphology:**
- *Staph. infections* $\rightarrow$ abscesses + (fever+ leukocytosis).
- *Strep. infections* $\rightarrow$ spread throughout the entire breast, causing pain, marked swelling, and breast tenderness.

**Treatment:** antibiotics + drainage of abscesses
Mammary duct ectasia

- Also called (periductal or plasma cell mastitis)
- **nonbacterial** chronic inflammation of the breast associated with inspissation of breast secretions in the main excretory ducts.
- Ductal dilation with ductal rupture leads to reactive changes in the surrounding breast substance.
- women in 40s and 50s who have borne children.

**Morphology**
- Affects the major excretory ducts of the nipple; dilated ropelike ducts with thick secretions.
- **Histologically.** the ducts are filled by granular debris and macrophages; prominence of a lymphocytic and plasma cell infiltration.
- **Clinical significance:** confusion with cancer ➔ it leads to induration of the breast substance and to retraction of the skin or nipple, mimicking the changes caused by some carcinomas.
- **No increased risk of malignancy.**
Traumatic fat necrosis

- significant only because it produces a mass.
- Most pts report a history of trauma to the breast.

**Morphology:**
- early stage → tender, and sharply localized lesion
- Late stage → ill-defined indurations (scar); may cause skin retraction

**Microscopically:**
- a central focus of necrotic fat cells surrounded by neutrophils and lipid-filled macrophages, which is later enclosed by fibrous tissue and mononuclear leukocytes.
TUMORS OF THE BREAST
Fibroadenoma

- The most common benign neoplasm of the female breast.
- An absolute or relative increase in estrogen activity is thought to contribute to its development.
- May appear with fibrocystic changes.
- The peak incidence is in the third decade of life.
- A discrete, solitary, freely movable nodule, (1 to 10 cm).
- Rarely, they are multiple or may exceed 10 cm in diameter (giant fibroadenoma).
- Usually easily "shelled out" surgically.
- May enlarge late in the menstrual cycle and during pregnancy.
- After menopause they usu. regress and calcify.
- Cytogenetic studies ➔ stromal cells are monoclonal and so represent the neoplastic element of these tumors (the neoplastic stromal cells secrete growth factors that induce proliferation of epithelial cells).
- Fibroadenomas almost never become malignant.

Morphology:
- Grossly ➔ firm, with a uniform tan-white color on cut section.
- Histologically ➔ loose fibroblastic stroma containing ductlike, epithelium-lined spaces of various forms and sizes.
Phyllodes Tumor

- much less common than fibroadenomas
- arise from the periductal stroma and **not** from preexisting fibroadenomas.
- most grow to **large**, possibly massive size, distending the breast.
- exhibit leaflike clefts and slits ➔ they have been designated phyllodes (Greek for "leaflike")
- Most are benign and tend to remain localized and cured by excision.
- The most worrying change is: the appearance of increased stromal **cellularity** with **anaplasia** and high **mitotic activity**, accompanied by rapid increase in size, usually with **invasion** of adjacent breast tissue = malignant phyllodes.
- Malignant lesions may recur
- 15% of cases ➔ metastasize to distant sites.
Carcinoma of the Breast

- the most common cancer in females
- a major cause of death, ranking second only to lung cancer as a cause of cancer death in women.
- The data make clear that despite advances in diagnosis and treatment, almost 1/4 of affected women will die of the disease.
- The lifetime risk is **one in eight** for women in USA.
- 75% of women with breast cancer are **older than age 50**.
- Only 5% are younger than the age of 40.
### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>241,740</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,470</td>
<td>109,690</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>73,420</td>
<td>70,040</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>55,600</td>
<td>47,130</td>
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<tr>
<td>Melanoma of skin</td>
<td>44,250</td>
<td>43,210</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,250</td>
<td>32,000</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>38,160</td>
<td>31,970</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>28,540</td>
<td>24,520</td>
</tr>
<tr>
<td>Leukemia</td>
<td>26,830</td>
<td>22,280</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,090</td>
<td>21,830</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>848,170</strong></td>
<td><strong>790,740</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>87,750</td>
<td>72,590</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,170</td>
<td>39,510</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,470</td>
<td>25,220</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,850</td>
<td>18,540</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>13,980</td>
<td>15,500</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,500</td>
<td>10,040</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,040</td>
<td>8,620</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,510</td>
<td>8,010</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,320</td>
<td>6,570</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,650</td>
<td>5,980</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>301,820</strong></td>
<td><strong>275,370</strong></td>
</tr>
</tbody>
</table>
Pathogenesis

(1) Genetic Changes
- Most likely, multiple acquired genetic alterations are involved in the sequential transformation of a normal epithelial cell into a cancerous cell.
- In addition to well-established familial syndromes, they are also implicated in the genesis of sporadic breast cancer: e.g. overexpression of the \( \text{HER2/NEU} \) proto-oncogene (30% of cases) → a member of the epidermal growth factor receptor family; associated with a poor prognosis.

(2) Hormonal Influences
- increased exposure to estrogen → e.g. long duration of reproductive life, nulliparity, and late age at birth of first child
- Estrogens stimulate the production of growth factors by normal breast epithelial cells and by cancer cells

(3) Environmental Variables
<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well-Established Influences</strong></td>
<td></td>
</tr>
<tr>
<td>Geographic factors</td>
<td>Varies in different areas</td>
</tr>
<tr>
<td>Age</td>
<td>Increases after age 30yr</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>First-degree relative with breast cancer</td>
<td>3.0-1.2</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>3.1</td>
</tr>
<tr>
<td>Premenopausal and bilateral</td>
<td>9.0-8.5</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1.5</td>
</tr>
<tr>
<td>Postmenopausal and bilateral</td>
<td>5.4-4.0</td>
</tr>
<tr>
<td><strong>Menstrual history</strong></td>
<td></td>
</tr>
<tr>
<td>Age at menarche &lt;12yr</td>
<td>1.3</td>
</tr>
<tr>
<td>Age at menopause &gt;55yr</td>
<td>2.0-1.5</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td></td>
</tr>
<tr>
<td>First live birth from ages 25 to 29yr</td>
<td>1.5</td>
</tr>
<tr>
<td>First live birth after age 30yr</td>
<td>1.9</td>
</tr>
<tr>
<td>First live birth after age 35yr</td>
<td>3.0-2.0</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Benign breast disease</strong></td>
<td></td>
</tr>
<tr>
<td>Proliferative disease without atypia</td>
<td>1.6</td>
</tr>
<tr>
<td>Proliferative disease with atypical hyperplasia</td>
<td>2.0&lt;</td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>12.0-6.9</td>
</tr>
<tr>
<td><strong>Less Well-Established Influences</strong></td>
<td></td>
</tr>
<tr>
<td>Exogenous estrogens</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>High-fat diet</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
</tr>
</tbody>
</table>
Major Risk Factors

- **Age:** the risk steadily increases throughout life
- **Genetics and Family History:**
  - 5% to 10% of breast cancers are related to specific inherited mutations. Especially if: before menopause; bilateral cancer; associated cancers (e.g., ovarian cancer); significant family history (i.e., multiple relatives affected before menopause); or belong to certain ethnic groups.
  - 50% of women with **hereditary** breast cancer have mutations in gene **BRCA1**; 30% have mutations in **BRCA2**.
  - other genetic diseases may be associated with breast cancer (e.g. Li-Fraumeni syndrome (caused by germ-line mutations in **p53**); etc)
- **Prolonged exposure to exogenous estrogens postmenopausally (HRT)**
- **Ionizing radiation, in early life years.**
  - note: The low doses of radiation associated with mammographic screening have little, if any, effect on the incidence of breast cancer
  - **Oral contraceptives** (?) ; the newer formulations of balanced low doses of combined estrogens and progestins seem to be safe → OCPs do not increase the risk of breast cancer even in women who have taken the pill for a long time and in women with a family history of breast cancer.