**TUMORS OF THE BREAST**

**LEC. 1**

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**Fibroadenoma** is the most common benign neoplasm of the female breast. An increase in estrogen activity is thought to contribute to its development, and indeed similar lesions may appear with fibrocystic changes (fibroadenomatoid changes). The peak incidence is in the third decade of life.

***Gross features***

* The tumor is usually solitary, well-defined, and freely movable.
* It is variable size & may reach up to 10 cm in diameter. Larger tumors are referred to as *giant fibroadenoma*.
* It is firm, with a uniform tan-white color on cut section.

***Microscopically***

* There is a loose fibroblastic stroma containing epithelium-lined duct-like spaces of various forms and sizes.
* The duct-like spaces are lined with single or multiple layers of benign epithelial cells having an intact basement membrane.
* In some lesions the ductal spaces are open, and fairly regular (*pericanalicular fibroadenoma*),whereas inothers they are compressed by the proliferation stroma and thus appear as slits or irregular, star-shaped structures (*intracanalicular fibroadenoma*).

Cytogenetic studies reveal that the stromal cells are monoclonal and thus represent the neoplastic element of these tumors. It is possible that the neoplastic stromal cells secrete growth factors that induce proliferation of epithelial cells.

**Phyllodes Tumors**are much less common than fibroadenomas. They are thought to arise from the periductal stroma. Most grow to large, possibly massive size; the patient typically has a history of a rapidly growing palpable breast mass.

***Grossly***, the tumors are lobulated and cystic and on sectioning exhibit leaf-like clefts and slits. The latter feature is responsible for the naming them as phyllodes tumors (Greek for "leaflike"). **Microscopically**, there are expansion and increased cellularity of the stromal component. *The most ominous change is the appearance of anaplasia and high mitotic activity, usually with invasion of adjacent breast tissue* (*malignant phyllodes tumor*). Most of these tumors remain localized and are cured by excision; malignant lesions may recur, but they also tend to remain localized. *Only the most malignant,* *about 15% of cases, metastasize to distant sites.*

**Intraductal Papilloma** is a neoplastic papillary growth within a duct. Most lesions are solitary, found within the principal lactiferous ducts or sinuses, thus present clinically with a serous or bloody nipple discharge and/or a small subareolar nodule and rarely, nipple retraction.

 ***Grossly,*** the tumors are usually solitary and less than 1 cm in diameter.

 ***Microscopically***, they consist of delicate, branching papillary growths within a dilated duct (or cyst). Each papillary projection has a connective tissue core covered by double layer of cells; outer cuboidal epithelial cells that overlies myoepithelial cells. Some cases display multiple papillomas (*intraductal papillomatosis****)****.* The latter sometimes become malignant, whereas the solitary papilloma is virtually benign.

 **Papillary carcinoma is distinguished by: -**

1. The absence of a myoepithelial component.

2. The epithelial cells show either severe cytologic atypia or monotonous ductal morphology.

**BREAST CARCINOMA (BRCA)**

Breast carcinoma in the USA ranks second only to lung cancer as a cause of cancer death in women; in our country it probably ranks first. Despite advances in diagnosis and treatment, almost 25% of women who develop this neoplasm will die of the disease. This has incited an intense study of the possible causes and origins of this form of cancer and of ways to diagnose it early enough to permit cure. 75% of women with breast cancer are older than age 50; only 5% are younger than the age of 40.

***Epidemiology and Risk Factors***

A large number of risk factors have been identified that modify the likelihood of developing BRCA. These risk factors are divided into well-established and less well-established groups.

*1. Geographic Variations*: the risk for BRCA is significantly higher in North America and northern Europe than in Asia and Africa. For example, the incidence and mortality rates are five times higher in the United States than in Japan. These differences seem to be environmental rather than genetic in origin, because migrants from low-incidence to high-incidence areas tend to acquire the rates of their adoptive countries, and vice versa. *Diet, reproductive patterns, and nursing habits* are thought to be involved.

*2. Age*: BRCA is uncommon in women younger than age 30. Thereafter, the risk steadily increases throughout life reaching a plateau after menopause.

*3. Genetics and Family History*: up to 10% of BRCA are related to specific inherited mutations. Women are more likely to carry a BRCA susceptibility gene if they have: -

a. BRCA before menopause.

b. Bilateral cancer.

c. Other associated cancers (e.g., ovarian cancer).

d. A significant family history (i.e., multiple relatives affected before menopause).

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

*3. Prolonged exposure to exogenous estrogens*: short-term use of combined estrogen plus progestin as *hormonal replacement therapy* in postmenopausal women is associated with an increased risk of breast cancer.However,a large study concluded that birth control pills do not increase the risk of breast cancer.

*4. Ionizing radiation*: e.g. to the chest increases the risk of breast cancer. Only women irradiated before age 30, during breast development, seem to be affected. For example, 20% to 30% of women irradiated for Hodgkin lymphoma in their teens and 20s develop breast cancer, but the risk for women treated later in life is not elevated.

*5. Other less well-established risk factors,* such as *obesity, alcohol consumption*, and a *diet high in fat*, have been implicated in the development of breast cancer on the basis of population studies. *Obesity is a recognized risk factor in postmenopausal women.*

***Pathogenesis***

The exact cause of breast cancer remains unknown. However, three sets of influences seem to be important:

*1. Genetic changes.*

*2. Hormonal influences.*

*3. Environmental factors****.***

*Genetic Changes*

In addition to those producing the well-established familial BRCA, genetic changes have also been implicated in the genesis of sporadic (nonfamilial) breast cancer. Mutations affecting proto-oncogenes and tumor suppressor genes in breast epithelium contribute to the malignant transformation process. Overexpression of the *HER2/NEU*proto-oncogene has been found to be amplified in up to 30% of invasive breast cancers. This gene is a member of the epidermal growth factor receptor family, and its overexpression is associated with a poor prognosis. Similarly, amplification of *RAS* and *MYC* genes has also been reported in some human breast cancers. Mutations of the well-known tumor suppressor genes *RB* and *p53* may also be present. Multiple acquired genetic alterations seem to be involved in the sequential transformation of a normal epithelial cell into a cancerous cell.

*Hormonal Influences*

Endogenous estrogen excess clearly has a significant role. This is supported by the following observations: -

1. Many of the risk factors mentioned (long duration of reproductive life, nulliparity, and late age at birth of first child) imply increased exposure to estrogen peaks during the menstrual cycle.

2. Functioning ovarian tumors that elaborate estrogens are associated with breast cancer in postmenopausal women.

3. Estrogens stimulate the production of growth factors by normal breast epithelial cells and by cancer cells. It seems that estrogen (and progesterone) receptors normally present in breast epithelium, and often in breast cancer cells, may interact with growth promoters (such as transforming growth factorα) produced by human breast cancer cells, to create an autocrine mechanism of tumor development.

*Environmental factors*are suggested by the variable incidence of breast cancer in genetically identical groups and the geographic differences in prevalence. Other important environmental variables include irradiation and exogenous estrogens, described earlier.

***Pathological features of BRCA***

* About 4% of women with breast cancer have bilateral primary tumors. The locations of the tumors within the breast are:

 *Upper outer quadrant 50%*

 *Central sector (subareolar) 20%*

 *Upper inner 10%*

 *Lower outer 10%*

 *Lower inner 10%*

*Breast cancers are classified into those that have not penetrated the limiting basement membrane (noninvasive) and those that have (invasive). The chief forms of carcinoma of the breast are classified as follows:*

***Non invasive: -***

1. *Ductal carcinoma in situ (DCIS).*
2. *Lobular carcinoma in situ (LCIS).*

***Invasive (infiltrating): -***

1. *Invasive ductal carcinoma ("not otherwise specified" or NOS).*
2. *Invasive lobular carcinoma.*
3. *Medullary carcinoma.*
4. *Colloid carcinoma (mucinous carcinoma).*
5. *Tubular carcinoma.*
6. *Others.*

* Of these, *invasive ductal carcinoma is the most common*. Because it usually has an abundant fibrous stroma, it is also referred to as *scirrhous carcinoma***.** There are two types of noninvasive breast carcinoma: ductal carcinoma in situ (*DCIS) and lobular carcinoma in situ (LCIS)* both usually arise from the terminal duct lobular unit (TDLU). Both are confined by a basement membrane and do not invade into stroma or lymphovascular channels.
* ***DCIS***
	+ Have several of histologic appearances. Architectural patterns are often mixed and include solid, comedo, cribriform, papillary, etc.
	+ Nuclear appearance ranges from bland and monotonous (low nuclear grade) to pleomorphic (high nuclear grade).
	+ The *comedo subtype* is distinctive and is characterized by cells with high-grade nuclei distending spaces with extensive central necrosis. The name derives from the toothpaste-like necrotic tissue that can be extruded from transected ducts with gentle pressure.

DCIS only rarely presents as a palpable or radiologically detectable mass. If detection is delayed, a palpable mass or nipple discharge may develop. The cells in the better differentiated tumors express estrogen and, less often, progesterone receptors. The prognosis for DCIS is excellent, with over 97% long-term survival after simple mastectomy.

* ***Paget disease of the nipple*** is caused by the extension of DCIS up to the lactiferous ducts and into the contiguous skin of the nipple. The clinical appearance is usually of a unilateral crusting exudate over the nipple and areolar skin. In about half of cases, an underlying invasive carcinoma will also be present. Prognosis is based on the underlying carcinoma and is not worsened by the presence of Paget disease.
* In ***LCIS*** the cells are small & monomorphic with bland, round nuclei and occur in loosely cohesive clusters within distended lobular ductules & acini. Intracellular mucin vacuoles (signet ring cells) are common.

LCIS is virtually always an incidental finding, and, unlike DCIS, it does not form masses. *Approximately one-third of women with LCIS will eventually develop invasive carcinoma.* *Unlike DCIS, subsequent invasive carcinomas arise in either breast at significant frequency.* Current treatment requires either close clinical and radiologic follow-up of both breasts or bilateral prophylactic mastectomy.