



Breast Cancers

Lecture 7

430 Pathology Team

Seham AlArfaj

Aliya AlAwaji

Red: Doctors' and important notes.

Green: Team notes.

Breast Carcinoma:

- The most common **malignancy of breast is carcinoma**
- Carcinoma of the breast is the most common cancer in women
- **Incidence is extremely high**, women who lives to age 90 has a one in eight chance to have breast cancer.
- **Breast cancer occurs most frequently in the upper outer quadrant of the breast.**
- **Sites of metastasis include axillary lymph nodes, lung, liver, and bone.**

Breast Cancer:

- Mammographic screening increased dramatically the detection of small invasive cancers
- DCIS (ductal carcinoma in situ) by itself is almost exclusively detected by mammography, so the incidence of DCIS is increased with the use of mammography.
- The number of women with an advanced cancer is markedly decreased
- In 1994, the mortality rate started to decline
- Currently only 20% of the women with breast cancer are expected to die of the disease.

Risk Factors:

1. **Age:** There is a steady increase in the incidence of breast cancer, as women grow older. The age-specific incidence rate is **highest in postmenopausal women. Breast cancer is rare before 25 yrs**, except familial forms, 77% of cases occur in women >50 yrs of age. The average age at diagnosis is 64 years.
2. **Age at Menarche:** The younger a woman's age at menarche, the higher her risk of breast cancer. For each 2 years delay in onset of menstrual activity, the risk is reduced by about 10%. Menarche younger than age 11 has a 20% increased risk to that who have their menarch at 14yrs.
3. **First Live birth: the earlier a woman has her first birth, the lower her lifetime risk for breast cancer.** This is independent of parity. A woman who has her first birth after 30 years has an increased risk. A nulliparous woman has increased risk. **Full term pregnancy** before age 20 years has half the risks of nulliparous, or women who have first birth after age 35.
4. **Breast-Feeding: The longer the women breast-feed, the lower the risk**
5. **First Degree relative** with Breast Cancer. The relative risk of breast cancer in a woman with breast cancer in first-degree relative (mother, sister, or daughter) ranges from 1.5 to 2.5. The risk increases with the number of affected first degree relatives. The majority of cancers occur in women without such history
6. **Breast Biopsy:** atypical hyperplasia increases the risk for breast cancer
7. **Race:** overall incidence of breast cancer is **lower in African American women.**
8. **Estrogen Exposure:** The later a woman's age at menopause, the higher her risk of breast cancer. Women who had their menopause after 55 years have 2 times the risk of those who had their menopause before 45 years postmenopausal hormone replacement slightly increase the risk
9. **Radiation exposure:** Higher rate of breast cancer
10. **Women who have had a breast cancer have a 10-fold increased risk** of developing a second primary breast cancer.
11. **Geographic influence:** Breast cancer is more common in Western industrialized countries than in developing countries. Four to seven times in USA and Europe higher than those in other countries.
12. **Diet: Fat** might increase the risk
13. **Obesity:** may play a role
14. **Exercise:** some studies showed degreased risk
15. **Environmental toxins:** pesticides.

16. **Tobacco: not associated with breast cancer**, but associated with the development of **peri-ductal mastitis, or sub-areolar abscess, lung, urinary bladder, pancreatic and oral cancers**.

The major risk factors for the development of breast cancer are hormonal and genetic (family history). Breast carcinomas can, therefore, be divided into sporadic cases, possibly related to hormonal exposure, and hereditary cases, associated with family history or germ-line mutations

Hereditary Breast Cancer:

- A family history of breast cancer in a first-degree relative is reported in 13% of women with the disease
- *About 25% of familial cancers (or around 3% of all breast cancers) can be attributed to two highly penetrant autosomal-dominant genes: BRCA1 and BRCA2*

Sporadic Breast Cancer:

The major risk factors for sporadic breast cancer are related to hormone exposure: gender, age at menarche and menopause, reproductive history, breast-feeding, and exogenous estrogens. The majority of these cancers occur in postmenopausal women and overexpress estrogen

Breast Carcinoma

Classification:

- Almost all are Adenocarcinoma
- Divided into In situ Carcinoma(non-invasive) and Invasive carcinoma
- Noninvasive carcinoma (Carcinoma in situ): This is epithelial proliferation that is still confined to the TDLU (**terminal duct lobular unit**), has not invaded beyond the basement membrane and is therefore incapable of metastasis.

A. Carcinoma in situ:

There are two subtypes:

1. Ductal carcinoma in situ (DCIS) or intraductal carcinoma **80%**
2. Lobular carcinoma in situ. The incidence in autopsy studies is about **20%**.

1. DCIS:

- DCIS comprises a **heterogeneous group** of noninvasive neoplastic proliferation with risk of development of subsequent invasive carcinoma.
- The tumor distends and distorts the **ducts in the TDLU** so that the terminal ducts enlarge and resemble large ducts.
- DCIS occurs throughout the age range of breast carcinoma with mean age at diagnosis between **50 and 59 years**, similar to the mean age of women with invasive ductal carcinoma.
- **Mammography** is a very sensitive **diagnostic procedure** for detecting DCIS, as a substantial proportion is not palpable. Mammographically detected **microcalcifications** are found in 72 to 98% of DCIS.
- Rapidly increased in the past two decades
- Half of mammographically detected cancers
- Most frequently as a calcifications
- Less frequently as a density or a vaguely **palpable mass or nipple discharge**

Microscopic subtypes:

1. Comedocarcinoma (**due to the presence of comedonecrosis= A type of necrosis occurring with glands in which there is central luminal inflammation with devitalized (dead) cells**).
2. Solid
3. Papillary.
4. Micropapillary.

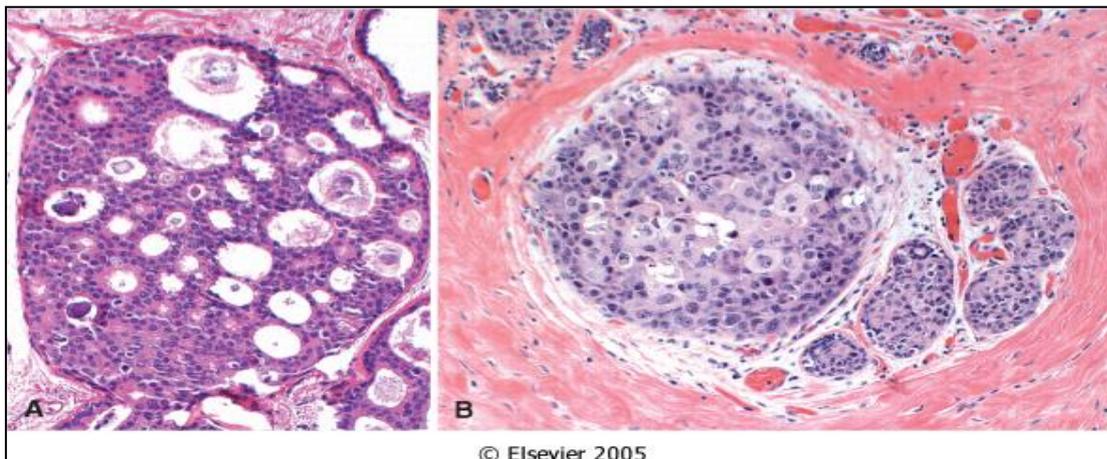
Carcinoma in situ can also be classified into high grade and low grade depending on the nuclear pleomorphism and necrosis. This is important because the risk of many subtypes of the carcinoma in situ to develop into invasive cancer is almost 100% like in cases of comedocarcinoma.

Clinical behavior:

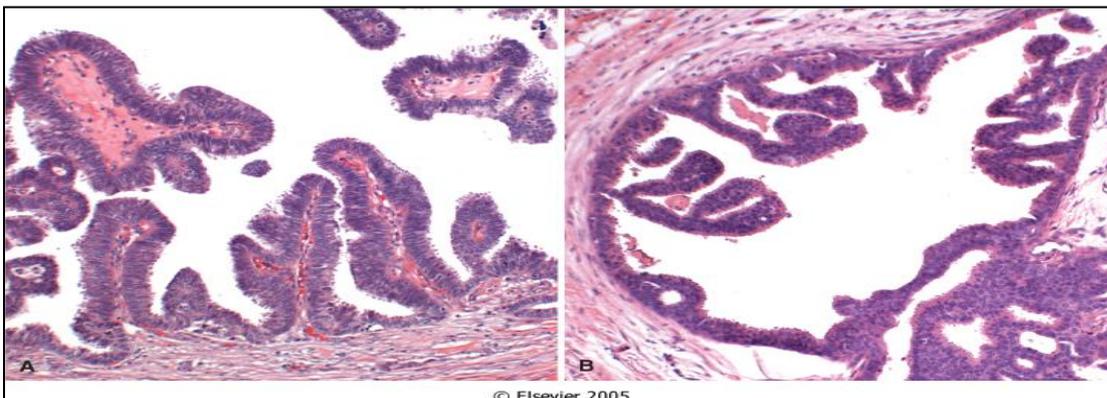
- The two types of DCIS differ markedly in their risk of subsequent invasive carcinoma.
- Comedocarcinoma has essentially a 100% chance of becoming invasive if left untreated.
- Pure cribriform/micropapillary carries only a 30% chance of invasive carcinoma.



Comedo DCIS fills several adjacent ducts (or completely replaced lobules) and is characterized by large central zones of necrosis with calcified debris. This type of DCIS is most frequently detected as radiologic calcifications. Less commonly, the surrounding desmoplastic response results in an ill-defined palpable mass or a mammographic density.



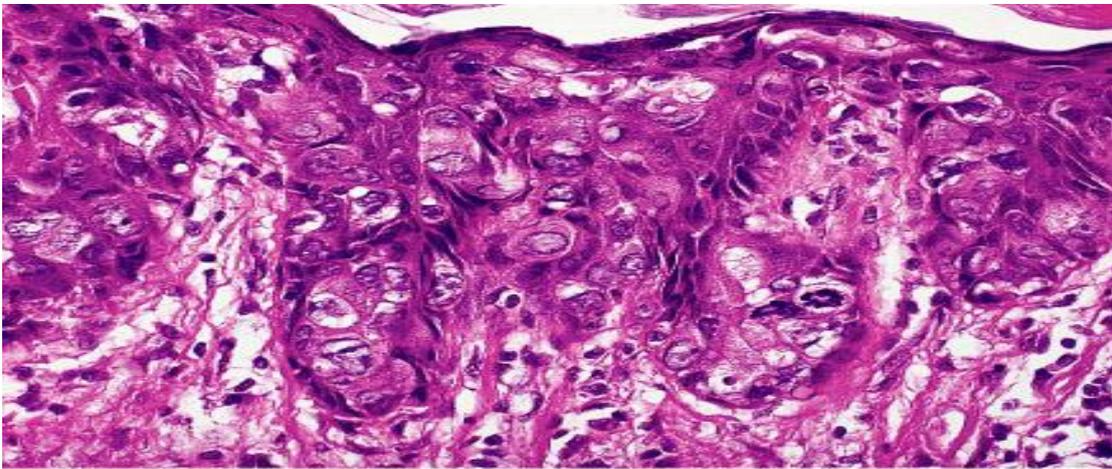
Noncomedo DCIS. A, Cribriform DCIS comprises cells forming round, regular ("cookie cutter") spaces. The lumens are often filled with calcifying secretory material. B, This solid DCIS has almost completely filled and distorted this lobule with only a few remaining luminal cells visible. This type of DCIS is not usually associated with calcifications and may be clinically occult.



Noncomedo DCIS. A, Papillary DCIS. Delicate fibrovascular cores extend into a duct and are lined by a monomorphic population of tall columnar cells. Myoepithelial cells are absent. B, Micropapillary DCIS. The papillae are connected to the duct wall by a narrow base and often have bulbous or complex outgrowths. The papillae are solid and do not have fibrovascular cores.

Paget's Disease:

- Rare **skin manifestation (epidermis) of breast cancer** (1 to 2 %)
- Paget's disease of the nipple presents with an eczematous area of the nipple, which may be subtle or form an obviously eroded (**loss of some or all of the epidermis**), weeping (**sore or rash**) lesion.
- **Pruritus is common**, might be mistaken for Eczema, presents as a unilateral erythematous eruption with a scale crust.
- Malignant cells, referred to as Paget cells and are found scattered in the epidermis.
- The histological hallmark of Paget's disease of the nipple is the infiltration of the epidermis by large ductal neoplastic cells with abundant clear or pale cytoplasm and nuclei with prominent nucleoli. The cells usually stain positively for mucin.
- Paget cells extend from **DCIS (most of the time)** within the ductal system into nipple skin without crossing the basement membrane
- **Palpable mass is present in 50 to 60%** of women with Paget disease indicating an underlying invasive carcinoma.



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2. LCIS -Lobular Carcinoma in Situ:

- Always an incidental finding in a biopsy performed for another reason
- Infrequent (1% to 6%)of all carcinomas
- Bilateral in 20% to 40% of women when both breasts are biopsied
- LCIS is frequently **multicentric** and **bilateral** and subsequent carcinomas occur at equal frequency in both breasts.
- Lobular carcinoma in situ (LCIS) **does not form a palpable mass** and cannot be detected clinically, felt at operation or seen grossly on pathological examination.
- Although LCIS may have **microcalcifications**, these are infrequent and so mammography has not been useful for detecting it.
- The tumor presents as a coincidental finding in breast tissue removed for other reasons. The disease tends to be bilateral and multicentric.
- LCIS shows a proliferation of cells that fill and distend the TDLU.

Clinical behavior:

If LCIS is left **untreated**, about **30% of women develop an invasive cancer** within 20 years of diagnosis. The invasive cancer may be ductal or lobular. **LCIS is therefore a marker of increased cancer in both breasts**



Lobular carcinoma in situ. A monomorphic population of small, rounded, loosely cohesive cells fills and expands the acini of a lobule. The underlying lobular architecture can still be recognized.

B. Invasive Breast Carcinoma:

Classification:

Invasive breast carcinoma is tumor that has extended across the basement membrane. This permits access to lymphatics and vessels and the potential distant metastases and thereby a lethal outcome. There are several different types of invasive carcinoma.

Invasive breast carcinoma is subdivided into:

- 1- NOS (non otherwise specified) Ductal 80%
- 2- Lobular 10%
- 3- tubular 6%
- 4- Mucinous (Colloid) 2%
- 5- Medullary 2%
- 6- Papillary 1%
- 7- Metaplastic Carcinoma 1%

Clinical features of breast cancer:

- **Palpable mass.**
- *By the time a cancer becomes palpable, over half the patients will have axillary lymph node metastases.*
- Larger carcinomas may be fixed to the chest wall or cause dimpling of the skin.
- Lymphatics may become so involved as to block the local area of skin drainage and cause lymphedema and thickening of the skin, a change referred to as *peau d'orange*.
- When the tumor involves the central portion of the breast, retraction of the nipple may develop.
- In older women undergoing mammography, invasive carcinomas most commonly present as a density and are, on average, half the size of a palpable cancer. Fewer than 20% will have nodal metastases.
- Invasive carcinomas presenting as **mammographic calcifications without an associated density** are **very small in size, and metastases are unusual (no lymph node involvement).**
- **Grossly it appears as ill defined mass, firm, hard, white in color, gritty, and calcification.**
- The term "**inflammatory carcinoma**" refers to the clinical presentation of a carcinoma extensively involving **dermal lymphatics (cutaneous lymphoid vessels)**, resulting in an enlarged **erythematous breast**. The diagnosis is made on clinical grounds and does not correlate with a specific histologic type of carcinoma.

1. Invasive Ductal Carcinoma ,NOS:

- It is the commonest type of breast cancer, forming up to 80% of these cancers.
- Most of these tumors excite a pronounced fibroblastic stromal reaction to the invading tumor cells producing a palpable mass with hard consistency (hence scirrhus carcinoma), which is the most common presentation.
- The tumor shows an infiltrative attachment to the surrounding structures and may cause dimpling of the skin (due to traction on suspensory ligaments) or nipple retraction.
- Grossly ,firm ,hard, and have an irregular border
- Cut surface is gritty and shows irregular margins with stellate infiltration and in the center there are small foci of chalky white stroma and occasionally calcifications
- Characteristic grating sound when cut or scraped
- Could be soft and well demarcated
- **Accompanied by varying amounts of DCIS**
- **Histologically:** the tumor cells are larger than normal epithelium, and can assume a variety of patterns such as glandular formation, cords of cells, broad sheets of cells or a mixture of all these, usually within a dense stroma.
- The tumors range from well differentiated, in which there is glandular formation, to poorly differentiated, containing solid sheets of pleomorphic neoplastic cells.
- **Carcinomas associated with a large amount of DCIS require large excisions with wide margins to reduce local recurrences.**

2. Invasive Lobular Carcinoma:

- It is the second most common type of invasive breast cancer forming up to 10% of breast cancers.
- The tumor may occur alone or in combination with ductal carcinoma.
- It tends to be **bilateral** more often than ductal carcinoma and **multicentric**.
- The amount of stromal reaction to the tumor varies from dense desmoplasia to little reaction and therefore the presentation varies from a discrete mass to a subtle, diffuse indurated area.
- **Most are firm to hard with irregular margins**
- Single infiltrating cells ,often one cell width
- No tubules or papillary formation In
- In about 10% of cases, tumors **have mixed features of invasive ductal and lobular carcinomas.**
- **Histologically:** characterized by Indian file where the tumor cells follow each other in one row

3. Medullary Carcinoma:

- Rare.
- This subtype of breast cancer presents as a **well circumscribed mass**.
- **Inflammatory lymphoid tissue infiltrates.**
- May mistaken clinically and radiologically for fibroadenoma
- It does not produce any fibroblastic (desmoplastic) reaction and therefore is soft and fleshy (encephaloid). On section foci of necrosis and hemorrhage are evident.
- **Microscopically:** the tumor is composed of solid sheets of malignant cells and frequent mitoses. There is scant fibrous stroma. Lymphocytes and plasma cells surround the tumor cells.
- **Prognosis: good.**

4. Colloid Carcinoma/ Mucinous carcinoma:

- Tends to occur in **older women**.
- **Mucin production**
- **Prognosis: good.**
- It is **sharply circumscribed**, lacks fibrous stroma and is slow growing.

- Is soft and gelatinous and has a glistening (**shiny**) cut surface.
- It may be in pure mucinous or mixed in which it is associated with other types of invasive breast carcinoma.
- The mucinous tumor is composed of small islands, occasionally forming glands, and isolated tumor cells floating in pools of extracellular mucin

Breast Carcinoma, Major Prognostic Factors:

1. **Invasive or In situ disease:** By definition, in situ carcinoma is confined to the ductal system and cannot metastasize. Breast cancer deaths associated with DCIS are due to the subsequent development of invasive carcinoma or areas of invasion undetected at the time of diagnosis. The great majority of women with adequately treated DCIS will be cured. In contrast, at least half of invasive carcinomas will have metastasized locally or distantly at the time of diagnosis.
2. **Distant metastasis:** Once distant metastases are present, cure is unlikely, although long-term remissions and palliation can be achieved. Favored sites for dissemination are the lungs, bones, liver, adrenals, brain, and meninges.
3. **Lymph node metastasis:** *Axillary lymph node status is the most important prognostic factor for invasive carcinoma in the absence of distant metastases.* The clinical assessment of nodal involvement is very inaccurate; therefore, biopsy is necessary for accurate assessment. With no involvement, the **10-year disease-free survival rate** is close to 70% to 80%; the rate falls to 35% to 40% with one to three positive nodes and 10% to 15% in the presence of more than 10 positive nodes.
4. **Tumor Size:** The size of the carcinoma is the **second most important prognostic factor**. The risk of axillary lymph node metastases does increase with the size of the carcinoma.

Note : all the above parameters are used to stage the tumor. Stage is a combination of size and lymph node status. Tumor size less than 2 cm is associated with a favorable prognosis. The single most important prognostic indicator is the lymph node status. Negative lymph nodes have the best prognosis. Involvement of 1 to 3 lymph nodes has an intermediate prognosis and 4 or more positive nodes have the worse prognosis.

5. **Locally advanced disease:** tumors invading into skin or skeletal muscle are frequently associated with concurrent or subsequent distant disease. With increased awareness of breast cancer detection, such cases have fortunately decreased in frequency and are now rare at initial presentation.
6. **Inflammatory Carcinoma:** Women presenting with the clinical appearance of breast swelling and skin thickening have a particularly poor prognosis with a 3-year survival rate of only 3% to 10%.

Minor Prognostic Factors:

- 1- **Histologic Subtype:** Infiltrating ductal and lobular carcinomas have the worse prognosis, medullary and mucinous have intermediate and tubular and cribriform have the most favorable prognoses
- 2- **Tumor Grade:** This is calculated by the pathologist. Grading separates tumors into three categories according to the amount of well formed tubules, the degree of nuclear pleomorphism, and the mitotic rate. The most commonly used grading system to assess the degree of tumor differentiation (*Bloom Richardson*). There are three grades with grade 1 having better prognosis and grade 3 having poorer prognosis.
- 3- **Estrogen and progesteron receptors:** 50% to 85% of carcinomas express estrogen receptors, such tumors are more common in postmenopausal women, hormone positive cancers have

better prognosis. They respond well to specific chemotherapeutic drugs eg. Tamoxifen. Therefore reporting of ER/PR positivity is important when reporting breast cancer.

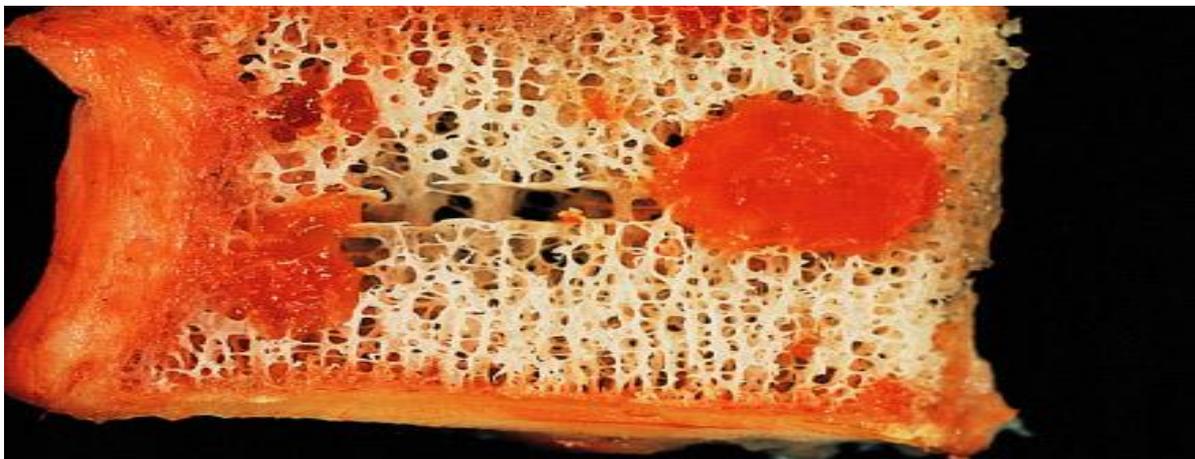
4- HER2/neu. (human epidermal growth factor receptor 2 or *c-erb B2* or *neu*) is a glycoprotein overexpressed in 20% to 30% of breast carcinomas.

- Many studies have shown that overexpression of *HER2/neu* is associated with a poor prognosis.
- In addition, ongoing studies have shown that *HER2/neu*-overexpressing tumors respond very well to hormonal or anthracycline chemotherapy regimens
- eg. Trastuzumab (Herceptin). Therefore evaluation of *HER2/neu* is most important when reporting breast cancer.

5- Lymphovascular invasion: Tumor cells may be seen within vascular spaces (either lymphatics or small capillaries) surrounding tumors. This finding is strongly associated with the presence of lymph node metastases and is a poor prognostic factor in women without lymph node metastases.

6- Proliferative rates: mitotic activity

Metastasis to vertebra:



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Stromal Tumors:

2 basic stromal tumors are:

1. Fibroadenoma
2. Phylloids tumor

Fibroadenoma:

- **The most common benign tumor of the female breast** and is composed of both **epithelial and stromal** tissue derived from the TDLU.
- **The tumor is completely benign.**
- Occur at any age, **most common before age 30**
- Usually present with a palpable mass
- Regression usually occurs after menopause
- The tumor vary in size and presents as a **spherical**, rubbery nodule, which is **sharply circumscribed** from the surrounding breast tissue and so is freely **movable** and can be shelled out.
- It may increase in size during pregnancy and cease to grow after menopause. The tumor is usually solitary but may be **multiple** and involve both breasts. The cut surface is pearl-white

- The tumors may be classified into two types:
 1. **Intracanalicular fibroadenoma:** stroma compresses and distorts glands into slitlike spaces
 2. **Pericanalicular fibroadenoma:** glands retain round shape
- **Treatment:** lumpectomy (only the lump is removed)
- **Histologically:** the tumor is composed of a mixture of ducts and fibrous connective tissue
- Rarely, carcinoma may arise within a fibroadenoma. The predominant type has been lobular carcinoma

Phylloides tumor:

- Phyllodes tumors, like fibroadenomas, arise from intralobular **stroma (major component)**. Although they can occur at **any age**, most present in the sixth decade, 10 to 20 years later than the average presentation of a fibroadenoma
- **It can be benign, borderline or malignant while fibroadenoma is always benign.**
- **It can metastasize to lymph nodes, lungs and bones.**
- **Majority of cases present as huge palpable masses**
- **Microscopically:** cystic spaces containing projections and myxoid contents are characteristic.
- Phyllodes tumors must be **excised with wide margins to avoid the high risk of local recurrences.**
- The majority are low-grade tumors that may recur locally but only rarely metastasize. Rare high-grade lesions behave aggressively, with frequent local recurrences and distant hematogenous metastases in about one third of cases.

Summary

Hereditary Breast Cancer: *can be attributed to BRCA1 and BRCA2*

Sporadic Breast Cancer: *The major risk factors for are related to hormone exposure: gender, age at menarche and menopause, reproductive history, breast-feeding, and exogenous estrogens. The majority of these cancers occurs in postmenopausal women and overexpress estrogen*

Breast Carcinoma: almost all are Adenocarcinoma. Divided into In situ Carcinoma (non-invasive) and Invasive carcinoma.

Type	Comments
Noninvasive	
Ductal carcinoma in situ (DCIS)	<ol style="list-style-type: none"> 1.Nonpalpable 2.Patterns: cribriform (sieve-like), comedo (necrotic center) 3.Commonly contain microcalcifications 4.One third eventually invade
Lobular carcinoma in-situ	<ol style="list-style-type: none"> 1.Nonpalpable; virtually always an incidental finding in a breast biopsy for other reasons 2.Lobules distended with bland neoplastic cells; one third eventually invade 3.Increased incidence of cancer in the opposite breast
Invasive	
Infiltrating ductal carcinoma	<ol style="list-style-type: none"> 1.Stellate-shaped, indurated, gray-white tumor 2.Gritty on cut section 3.Induration caused by reactive fibroplasia (desmoplasia)
Paget's disease of nipple	<ol style="list-style-type: none"> 1.Extension of DCIS into lactiferous ducts and skin of nipple producing a rash with or without nipple retraction 2.Paget's cells
Medullary carcinoma	<ol style="list-style-type: none"> 1.Associated with BRCA1 mutations 2.Bulky, soft tumor with large cells and lymphoid infiltrate
Inflammatory carcinoma	<ol style="list-style-type: none"> 1.Erythematous breast with dimpling like an orange (peau d'orange) 2.Plugs of tumor blocking lumen of dermal lymphatics cause localized lymphedema 3.Very poor prognosis
Invasive lobular carcinoma	<ol style="list-style-type: none"> 1.Neoplastic cells arranged in linear fashion or form concentric circles (bull's-eye appearance)
Colloid (mucinous) carcinoma	<ol style="list-style-type: none"> 1.Usually occurs in elderly women 2.Neoplastic cells are surrounded by extracellular mucin

Questions

1. A 47-year-old woman undergoes routine mammographic screening and has an abnormal mammogram with multiple small areas of increased density, though a single distinctive mass lesion is not detectable either by palpation or by mammography. A fine needle aspiration biopsy of an abnormal density reveals cells suspicious for a malignancy. An excisional breast biopsy yields a diagnosis of lobular carcinoma in situ of the breast. Which of the following is the most likely finding associated with this woman's carcinoma?
- A. This neoplasm will remain localized
 - B. The opposite breast may also be involved.
 - C. A family history of breast cancer is unlikely.
 - D. Paget disease of the nipple probably preceded this lesion
 - E. Estrogen receptor assay of this neoplasm will probably be negative.

Answer: (B). Bilaterality is a frequent characteristic of lobular carcinoma in situ.

2. A 65-year-old woman is found to have a 1-cm mass in the upper outer quadrant of the left breast. The most likely cause is
- A. Fibrocystic disease.
 - B. Acute mastitis.
 - C. Fibroadenoma.
 - D. Carcinoma.
 - E. Paget disease of the breast.

Answer: (D) according to the location of the mass and the age of the patient it is most probably carcinoma.

3. A 50-year-old woman has a lumpectomy following mammographic discovery of a carcinoma of the breast. Which of the following is a well-known characteristic or association of breast cancer?
- A. Low-fat diet
 - B. Positive family history
 - C. Excessive thinness
 - D. Late menarche
 - E. Multiparity

Answer: (B) a positive history of breast cancer in first degree female relatives and a diet high in animal fats are important association of breast cancer.

4. A 20-year-old woman presents with a solitary discrete, freely movable, firm, rubbery, nontender, well-circumscribed breast lesion. On resection biopsy. The most likely diagnosis is:
- A. Fibrocystic disease.
 - B. Fibroadenoma.
 - C. Medullary carcinoma.
 - D. Colloid carcinoma.
 - E. intraductal carcinoma

Answer: (B) fibroadenoma is a benign tumor most often presenting as a single, freely movable lesion.

5. A 57-year-old woman who has not seen a physician in more than 20 years now presents with left breast pain. On examination, the left breast is markedly erythematous, swollen, and warm to touch. There is also significant dimpling of the breast (peau d'orange). In addition, the left nipple is completely retracted. Which of the following is the likely diagnosis?

- A. Mastitis
- B. Invasive ductal carcinoma
- C. Medullary carcinoma
- D. Inflammatory carcinoma
- E. Mucinous carcinoma

Answer: (D) the presentation is of inflammatory carcinoma of the breast, which typically has an extremely poor prognosis.

6. A 27-year-old woman requests a mammogram because both her mother and sister died of metastatic breast cancer before 40 years of age. Which of the following would add to this patient's risk factors for breast cancer?

- A. Multiparity
- B. High-fiber diet
- C. Oral contraceptive use
- D. BRCA-1 mutation
- E. Bilateral fibroadenomas

Answer: (D) both BRCA-1 and BRCA-2 mutations are major risk factors of developing breast cancer.