Sheets Pathology

Number 1

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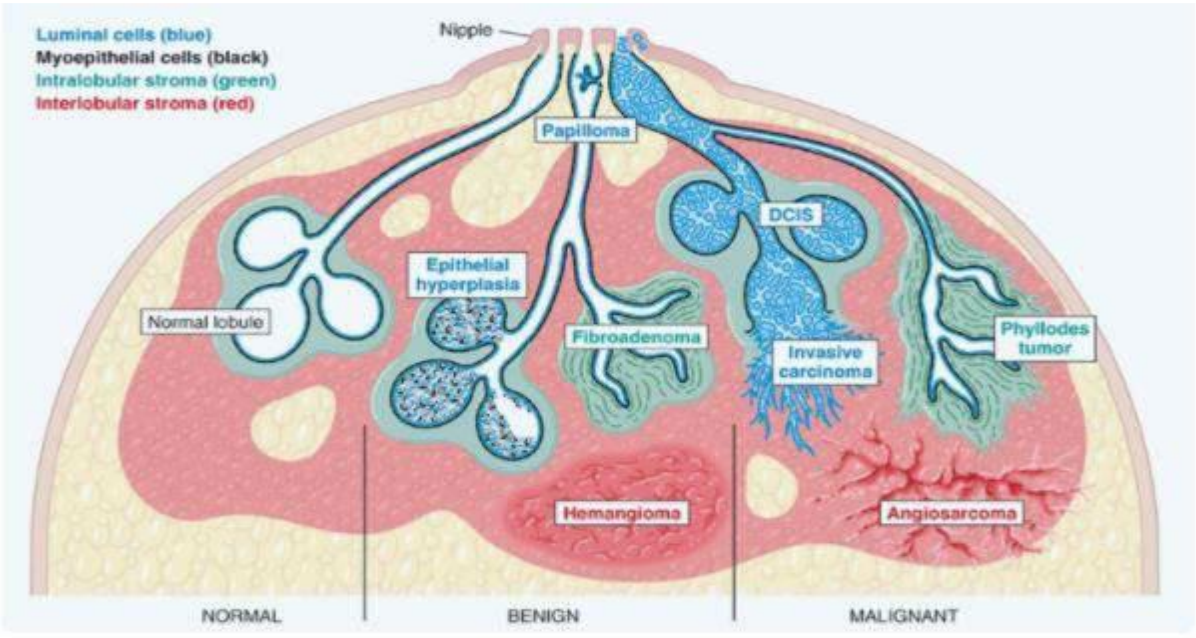
Breast pathology

The basic histological units of the breast are called lobules, which are composed of glandular epithelial cells (luminal cells) resting on basement membrane, which is composed of collagen type IV and laminin mainly.

The cancer which arises from epithelial cells in lobules is called ***ductal carcinoma in situ (DCIS)*** when it's limited by the basement membrane. By the time DCIS invade the basement membrane we call it invasive carcinoma. So when we say mammary carcinoma we mean by that the malignant epithelial cells ***(invasive ductal carcinoma)***

There are other neoplasms of the breast like:

- ***Fibroadenoma*** (benign) which arises from the stroma (mesenchyme) around the individual lobule.
- ***Hemangioma*** (benign tumors from the blood vessels).
- ***Phyillodes tumor*** (similar to fibroadenoma, it arises from stroma and could be benign, borderline or malignant).
- ***Angiosarcoma*** (arises from blood vessels, extremely rare).



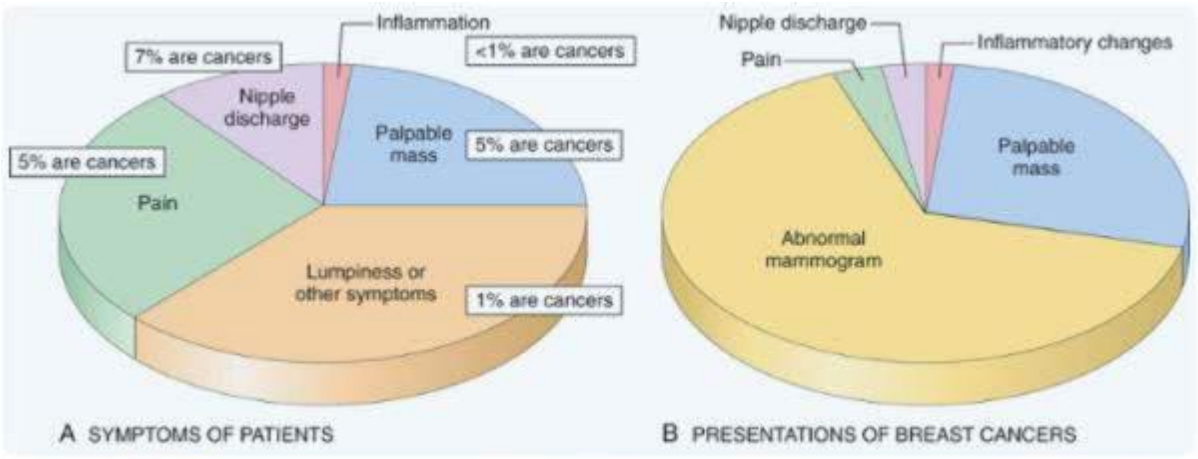
Clinical presentations of breast diseases: (important)

- ***Pain***
  - ✓ Just 5% percent of cases who present with pain have cancer.
- ***Inflammation*** (edema and erythema)
- ***Nipple discharge***
  - ✓ Bloody discharge is more serious than white or milky discharge. Just 7% of cases have cancer.
- ***Lumpiness***
  - ✓ When there is something wrong in the breast contour upon self-examination. Here is the importance of education to detect the cancer early. Just 1% of cases have cancer; so benign diseases are much more common than cancers.
- ***Palpable mass***
  - ✓ It can felt when it reaches 2-3 cm in diameter. Just 5% of cases have cancer. There are other benign diseases which present with a mass like fibroadenoma, fibrocystic diseases etc...
- ***Gynecomastia***
  - ✓ Is the term we use in males, remember that breast cancer can happen in males also and it's a little bit more aggressive. The breast tissue is regressed in males because there are high levels of testosterone and low levels of estrogen, so gynecomastia is a serious issue which can result from cancer or other conditions like drugs.

So we conclude that benign diseases of the breast are much more common than cancers.

On the other hand, most of breast cancer patients will have abnormal mammogram (75%) (We have 2 special imaging techniques for the breast; mammogram and ultrasound), which helped us in detecting cancer earlier which is the key for better survive.

90% of breast cancer will have abnormal mammogram & palpable mass.



General facts

- Likelihood of malignancy increase with age.
  - ✓ The risk of cancer is more in 55 years old woman who has palpable mass than that of 20 years old woman who has the same condition.
- Mammography was introduced in 1980s to detect ***asymptomatic*** breast cancer cases (it did), now smaller (1cm) cancers are found which is good
- Palpable breast cancer is 2-3 cm
  - ✓ Once the patient feels a palpable mass it's too late because it had been through millions of multiplications so our goal is to detect earlier.
- Abnormal mammogram: increase likelihood of cancer with increase in age.
  - ✓ The risk of cancer is more in 70 years old woman who has abnormal mammogram than that of 20 years old woman who has the same condition.

Now we will start talking about benign diseases which are much more common than cancer as we said earlier.

Inflammatory processes

- Infections (mastitis), autoimmune diseases, and foreign body type reactions
- Lactation infections which happen during lactation -breast feeding- (mastitis, staph) they present with pain, redness and systemic signs of inflammation (fever& leukocytosis) which are treated by antibiotics unless there is an abscess. When there is an abscess the treatment is surgical drainage with antibiotics.

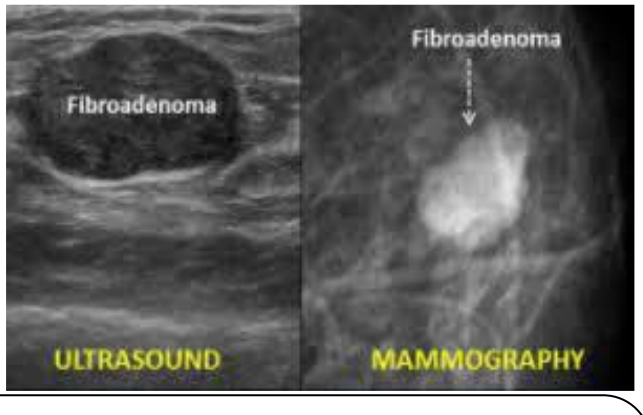
The most important thing is when these conditions produce a mass and abnormal mammogram you should investigate them more to confirm that they are benign.

Stromal neoplasms

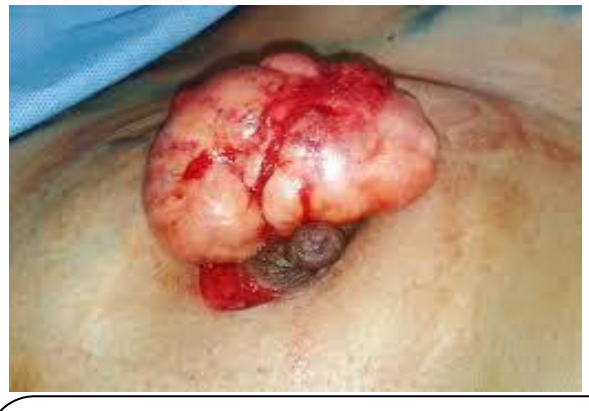
They are very common benign tumors which are fibroadenoma and phyllodes tumor. Some people considered them as one tumor and called it fibroepithelial neoplasm and other people said that there are differences between them. For classical teaching, we will study them independently.

Fibroadenoma

- From its name, (fibro) means fibroblastic proliferation and (adenoma) means glandular proliferation; both are benign. So it's a ***biphasic tumor***.
- The stroma of fibroadenoma has ***low cellularity***
- ***Slit like glands*** (we will see them later)
- It is ***Well-circumscribed mobile mass***. Usually young patients can hold the mass and it escape from them, so it's called ***breast mouse***
- Presents mostly in ***young age*** and is always ***bengin***
  - ✓ So, mobile mass in a young patient is fibroadenoma until proven otherwise. The only one who can confirm the diagnosis is the pathologist.
- Usually we remove it surgically to relief anxiety and rule out malignancy.
  - ✓ Fibroadenoma is always benign but they found in some cases cancer in fibroadenoma but this cancer are from other cell lines not from fibroadenoma itself, but they occur with each other.



24 years old women palpated an escaping mass. The doctors thought that this is fibroadenoma and did ultrasound and mammography. They found a well-circumscribed mass with sharp edges. This is how fibroadenoma looks like.



When the surgeon opened he just did inoculation

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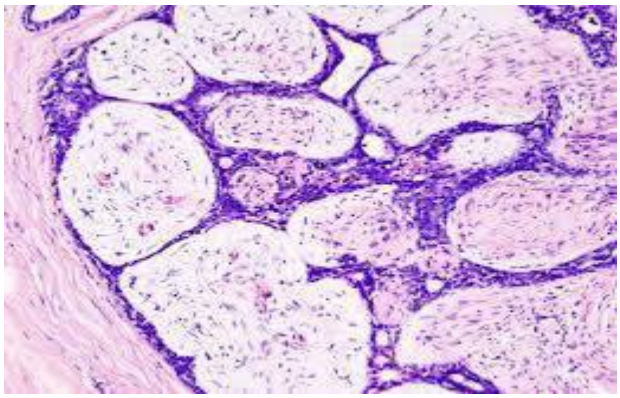
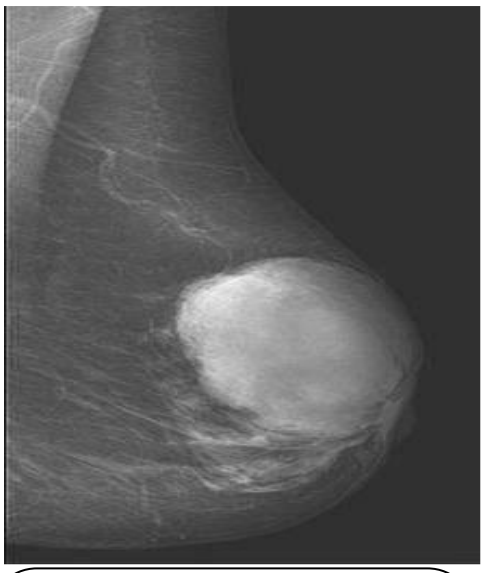
This is how it looks like after excision.Well-circumscribed, slippery and smooth.



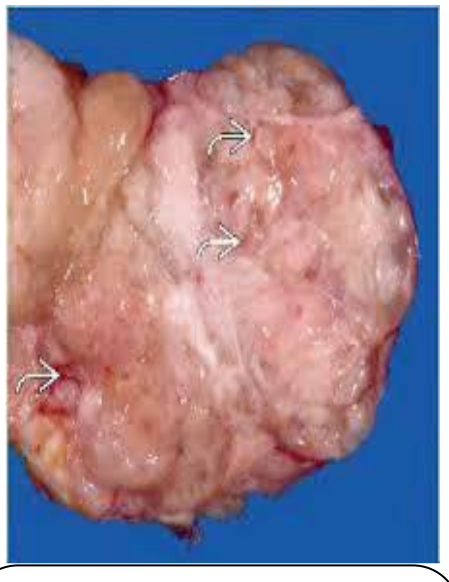
Under the microscope, stroma and slit like glandular epithelium (blue).The stroma is not hypercellular and there are no features of malignancy in the form of necrosis and high mitotic activity.

Phyllodes tumors

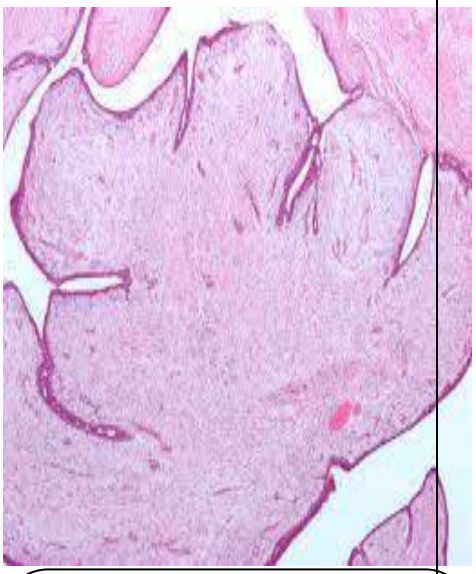
- From its name, (phyllodes) means tree leafs, it appears like a leaf in low power.
- It's a ***biphasic tumor*** like fibroadenoma, but stroma is much more than epithelia.
- ***Stromal hypercellularity.***
- It's ***well circumscribed*** BUT NOT as well as fibroadenoma
- ***Older age*** and can be ***high grade and malignant*** (based on malignant features of stroma (sarcoma)). Once you see well circumscribed mass in 50 years old woman you have to rule out the presence of phyllodes tumor.
- Surgical removal with safe margin to avoid the recurrence.



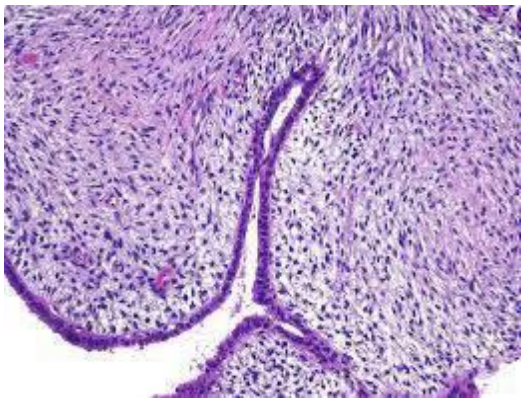
This is a mammogram of phyllodes tumor, it is well circumscribed but not as sharply as fibroadenoma



Upon excision, the surgeon must take 0.5 to 1 cm free margin around it (normal tissue) to avoid recurrence & we have to sample it very well to rule out if there is stromal malignancy



Leaf like structure under the low power



In high power the stroma is hypercellular. 80-85% of phyllodes tumors are benign, no excessive mitotic activity, no necrosis and no infiltration to adjacent tissue. 10-15% are malignant.

Subclassification of phyllodes tumors

	Benign	Borderline	Malignant
Mitosis	0-3	4-9	10 or more
Stromal cellularity/atapia	Mild	Moderate	Marked
Stromal overgrowth	-	-/+	+
Tumor interface	circumscribed	Circumscribed or infiltrative	Infiltrative

Benign epithelial lesions:

Now we will start talking about benign epithelial proliferations which are the major source for breast carcinoma.

Non proliferative disease: cysts and fibrocystic change, now we consider it as physiologic change with aging. (Very common)

No increased risk for malignancy (like normal epithelium the lifelong risk for cancer is up to 3%; discussed later)

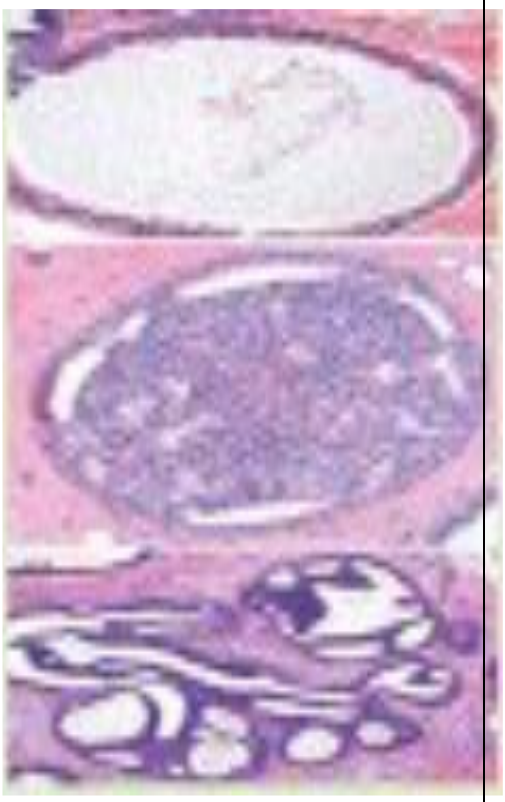
Proliferative disease without atypia: usual type epithelial hyperplasia, no atypia.

Slight increased risk of malignancy, 5-6% life time risk

Proliferative disease with atypia: atypical ductal hyperplasia (ADH) & atypical lobular hyperplasia (ALH), atypia present

Modest increased risk of malignancy, 13-17% life time risk.

These lesions usually give rise to ductal carcinoma in situ and progress to invasive carcinoma, so we want to find them early



Note: we notice atypia depending on cellular, nuclear and architectural features.

Unfortunately, this table is important XD and you have to know the risk factors & understand them, but I think that percentages are not important.

- A USMLE question was about the higher risk factor for breast cancer, the options were first degree relatives with breast cancer and patient who have breast cancer in the other side (this one was the answer).

- ***Germline tumor suppressor gene mutation (BRCA1, BRCA2),*** we now have a blood test to find these mutations.

- ***Menstrual history***: *early* menarche and *late* menopause

- ***Pregnancy***: whenever a woman gets pregnant at *earlier age* and has *more children*, the risk is less (protective) even less than that for a woman with no risk factors :o & ***breast feeding*** is also considered slightly protective. For women who have been pregnant but did not breast-feed have higher risk of getting breast cancer.

TABLE 19.6 Factors Associated With Development of Invasive Carcinoma

Factor	Relative Risk[a]	Absolute Lifetime Risk[a]
Women with no risk factors	1.0	3%
First-degree relative(s) with breast cancer[b]	1.2–9.0	4%–30%
Germline tumor suppressor gene mutation (e.g., *BRCA1* mutation)	2.0–45.0	6% to >90%
Menstrual History		
Age at menarche <12 years	1.3	4%
Age at menopause >55 years	1.5–2.0	5%–6%
Pregnancy		
First live birth <20 years (protective)	0.5	1.6%
First live birth 20–35 years	1.5–2.0	5%–6%
First live birth >35 years	2.0–3.0	6%–10%
Never pregnant (nulliparous)	3.0	10%
Breast-feeding (slightly protective)	0.8	2.6%
Benign Breast Disease		
Proliferative disease without atypia	1.5–2.0	5%–6%
Proliferative disease with atypia (ALH and ADH)	4.0–5.0	13%–17%
Carcinoma in situ (ductal or lobular)	8.0–10.0	25%–30%
Ionizing radiation	1.1–1.4	3.6%–4.6%
Mammographic density	3.0–7.0	10%–23%
Postmenopausal obesity and weight gain	1.1–3.0	3.6%–10%
Postmenopausal hormone replacement	1.1–3.0	3.6%–10%
Alcohol consumption	1.1–1.4	3.6%–4.6%
Alcohol consumption	1.1–1.4	3.6%–4.6%

- ***Benign breast disease:*** proliferative diseases *without atypia* slightly *increase* the risk & *with atypia* the risk is *more*. Carcinoma in situ has very high risk.

- ***Ionizing radiation***, ***mammographic density***: the more the density the more the risk.

- ***Postmenopausal obesity & hormone replacement*** (especially unopposed estrogen): the more fat in the body the more peripheral conversion of estrogen. Menopausal symptoms may be treated with estrogen pills; and such pills may increase the risk of breast cancer development.

- ***Alcohol consumption*** increases the risk for cancer.

- ***(Development of cancer on one side, the highest risk to develop cancer on the other side)***

Mammary carcinoma:

- When we say breast cancer we mean by that mammary carcinoma (***invasive ductal carcinoma,*** mainly)
- It's the most common women malignancy if we exclude basal cell carcinoma & squamous cell carcinoma of the skin (non-melanotic skin tumors). It used to be the major cause of death in females, but now the major cause of death is lung cancer, due to increased smoking among women.
- Incidence is stable in USA and western country; however, the incidence and mortality is increasing worldwide due to:
  - ✓ Delayed childbearing
  - ✓ Fewer pregnancies
  - ✓ Reduced breast feeding
  - ✓ No access to proper healthcare
- Lifetime risk is 1/8 (USA); one woman from 8 women will have cancer.
- Cancer death; 2nd after lung
- Mortality decreases from 30 to 20% due to:
  - ✓ Better screening
  - ✓ Diagnosing more early stage
  - ✓ Better treatment

Classifications of mammary carcinoma:

We classify breast cancer depending on multiple factors:

- Histological appearance under the microscope:
  - ✓ Ductal & lobular
- Receptor status:
  - ✓ Estrogen receptor (ER) positive and HER2 negative
  - ✓ HER2 positive (ER positive or negative)
  - ✓ Triple negative (ER, HER2, and progesterone receptor (PR) negative)
- DNA-based classification:
  - ✓ When specific DNA mutations or gene expression profiles are identified in the cancer cells this may guide the selection of treatments.
- Compination of the above classifications

We will talk about them in details in the next lecture ☺

*GOOD LUCK ^_^*