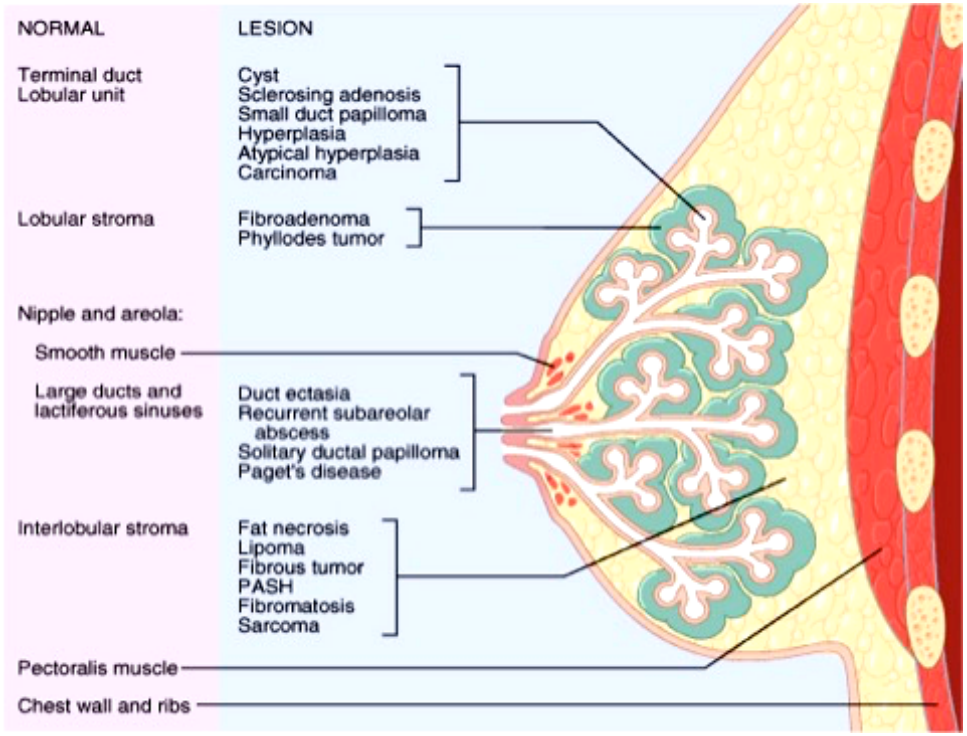
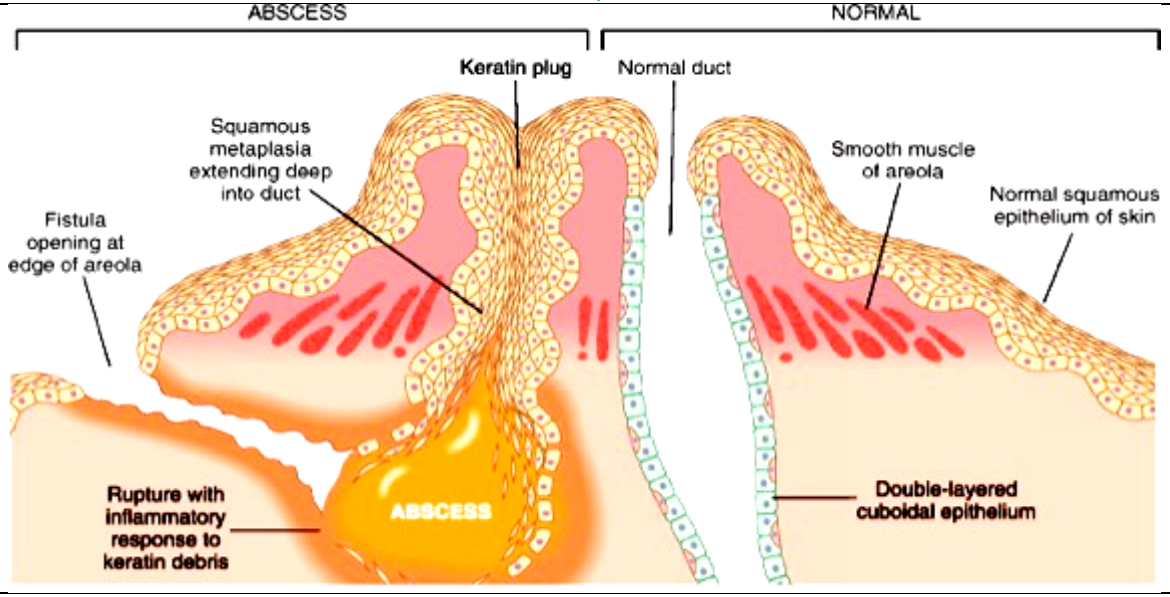
Breast Path

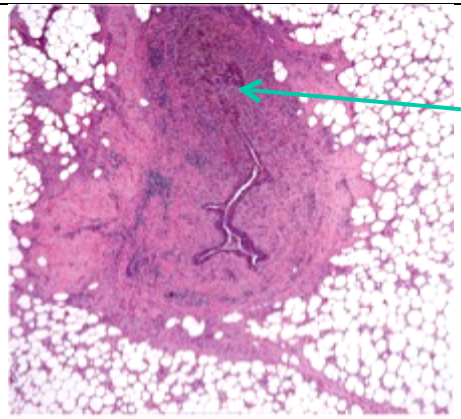
NORMAL BREAST ANATOMY



1. Disorders of Development	
MILKLINE REMNANTS	Extra nipples along the milk lines
ACCESSORY AXILLARY BREAST TISSUE	"Tail of Spince" that goes into axilla – the ectopic breast tissue is found to have a higher propensity to develop malignancy & occurs at a younger age
CONGENITAL NIPPLE INVERSION	*Remember: nipple inversion does not always mean cancer; it is important to get a patient history*
MACROMASTIA	Excessive breast growth that can be seen in pregnancy; can lead to back pain; may need reconstruction

2. ACUTE MASTITIS 1st few weeks of Breastfeeding	
DEFINITION	Seen in nursing because nipple pores are open to allow microbes, like *S. aureus*, to get in
CLINICAL	Purulent nipple discharge can lead to abscess formation (*fluctuant abscess*)
PATHOGENESIS	Usually caused by ***Staph aureus*** (rarely by GAS)
GROSS	EARLY: Breast is swollen, red, & diffusely tender LATE: localized, soft, fluctuant swelling (abscess)
MORPHOLOGY	Single or multiple abscesses seen
COURSE/ TREATMENT	Large abscesses: heals with large **SCAR** which may cause significant **skin retraction** *simulating a breast cancer* **Any benign lesion that is associated with significant scarring can mimic breast cancer because it will also be a hard mass* Antibiotics; Drain the abscess

3. SUBAREOLAR ABSCESS Smokers; Vitamin A Deficiency	
DEFINITION	
MORPHOLOGY	**Keratin plugs** due to squamous metaplasia extending deep into duct

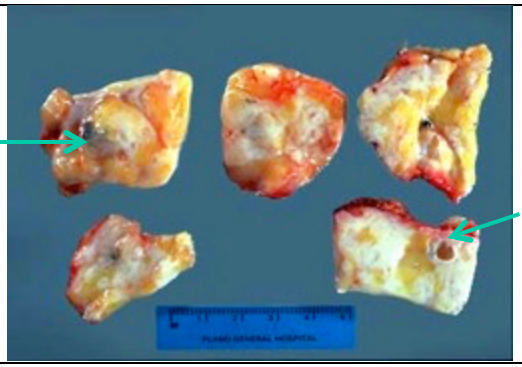
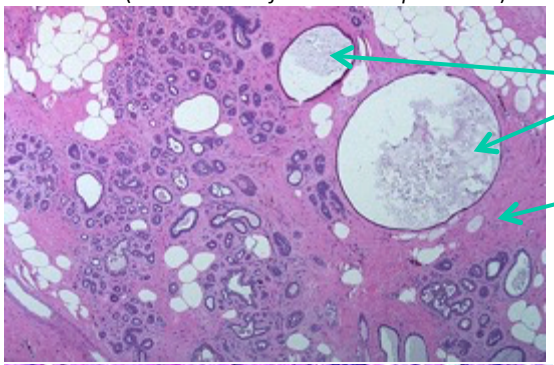
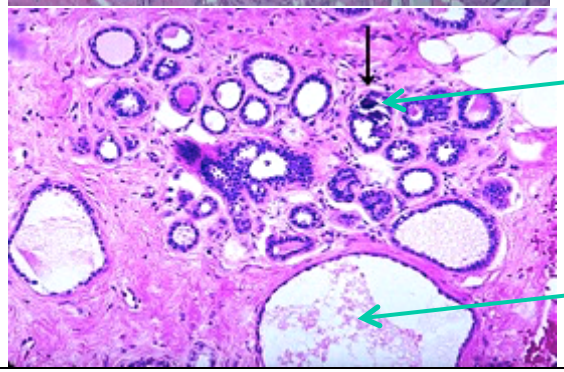
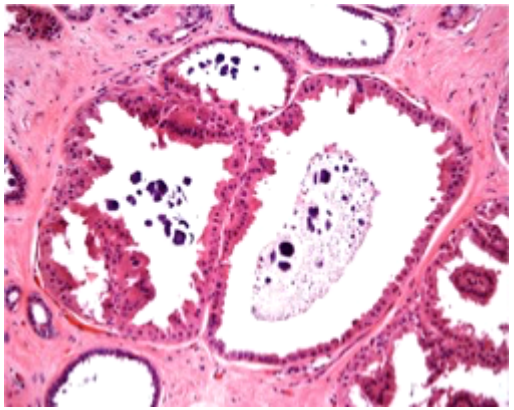
4. MAMMARY DUCT ECTASIA (Plasma Cell Mastitis) Elderly Women	
DEFINITION	Occurs when milk duct beneath your nipple widens, the duct walls thicken, & the duct fills with fluid. Duct may become blocked with a thick, sticky substance. (*Mayo)*
CLINICAL	Usually asymptomatic, but may have nipple disease, breast tenderness, or inflammation of the clogged duct – periductal mastitis (*Mayo Clinic)*
PATHOGENESIS	**Duct obstruction** → duct dilation → rupture → **periductal chronic GRANULOMATOUS inflammation** with preponderance of **plasma cells**
MORPHOLOGY	 **Ruptured duct** (this can lead to scarring and can mimic breast cancer later on)
COURSE/ TREATMENT	**No increased risk of cancer;** If scarring occurs, it can mimic breast cancer later on

5. FAT NECROSIS	
DEFINITION	Death of fat cells leading to necrosis
CLINICAL	Usually a **PAINLESS**, firm lump
PATHOGENESIS	1. Enzymatic (typically occurring in the liver) 2. Response to **REPEATED TRAUMA** of the breast → inflammation → **INDURATED mass formation** *i.e. car accident + breast hits steering wheeling
MORPHOLOGY	**GRANULOMATOUS inflammation** w/ many lipid-laden **"FOAMY" MACROPHAGES**, multinucleated giant cells, & increased **FIBROCOLLAGENOUS TISSUE** **DYSTROPHIC CALCIFICATION** may be present – *damaged tissue with **normal Ca^{2+} levels***
COURSE/ TREATMENT	Can heal as scar tissue & *mimic breast carcinoma* **No increased risk of cancer;**

6. FIBROCYSTIC CHANGE

Most common palpable breast lesion

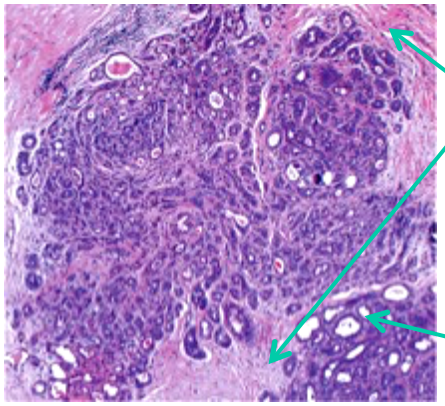
Females 30-50 y/o (Pre-menopausal)

DEFINITION	**BILATERAL, LUMPY, mobile** breast lesion that changes with menstrual cycle **This distinguished it from cancer, which is usually a unilateral, fixed mass that does not change with cycles*
CLINICAL	**PAINFUL** lumpy mass that *changes with menstrual cycle*
GROSS	**BLUE DOME CYST**  Cystically dilated ducts
MORPHOLOGY	**ADENOSIS** (*increase in # of acinar units per lobule*)  Cystic **dilation** of the **ducts** **STROMAL FIBROSIS** between ducts  **CALCIFICATION** – *indicated chronicity* **NOTE:** calcifications associated w/ cancer will be described as "small, fine cluster" calcifications. In benign lesions, the calcifications are large & coarser in appearance Benign ducts  **APOCRINE METAPLASIA:** looks like sweat glands w/ *eosinophilic cytoplasm*
COURSE	Generally, has no relative risk for cancer. But if there are proliferative changes, then the relative risk goes UP (next).

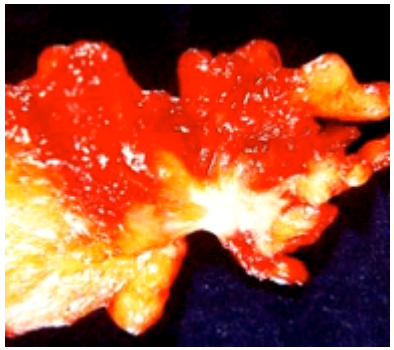
PROLIFERATIVE FIBROCYSTIC CHANGES

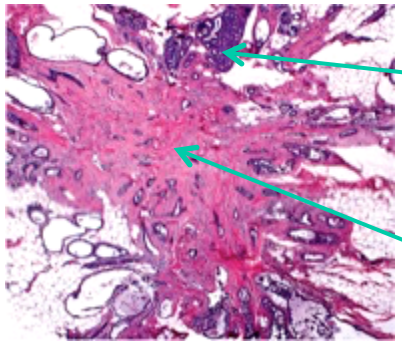
- Fibrocystic change with epithelial atypia (atypical hyperplasia) = **5-FOLD INCREASE in risk of developing breast cancer**
- Atypical duct hyperplasia + history of a 1st degree relative with breast cancer = **10-FOLD INCREASE**

1. **EPITHELIAL HYPERPLASIA:** any type of hyperplasia (increase in cell #) whether atypical or not
2. **ATYPICAL DUCTAL & LOBULAR HYPERPLASIA**: *extreme proliferation;* changes in the cell – *hyperchromatic nuclei*
3. **SCLEROSING ADENOSIS:** proliferation of small duct **EPITHELIAL cells** & **MYOEPITHELIAL cells** (=BENIGN) + increased **INTRALOBULAR STROMA**; AKA increased number of glands associated with **scar tissue**



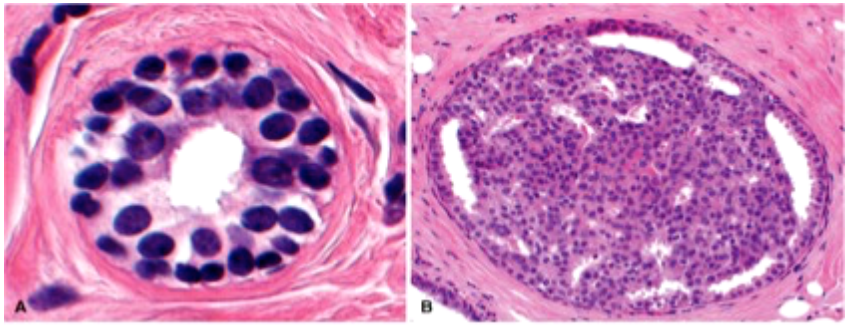
SCLEROSING ADENOSIS





RADIAL SCAR: Complex Adenosis Lesion

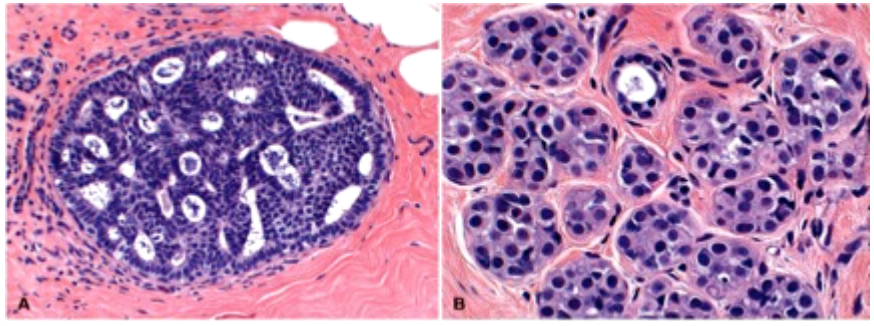
EPITHELIAL HYPERPLASIA



NORMAL: smaller, darker cells are duct cells (myoepithelial cells); if you see these you know it is BENIGN

ABNORMAL: Myoepothelial cells are the tiny cells surrounding duct & the overall number of epithelial cells is increased

ATYPICAL HYPERPLASIA: *Ductal or Lobular*

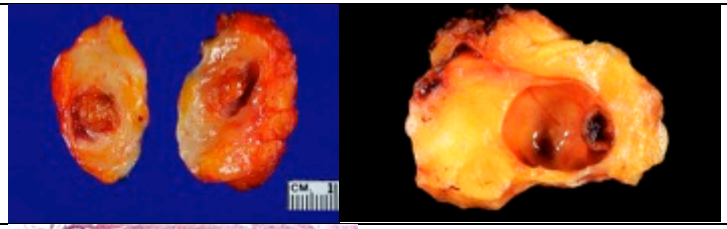
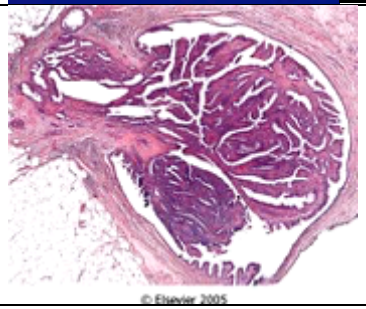


DUCTAL: 1 duct; hyperchromatic nuclei

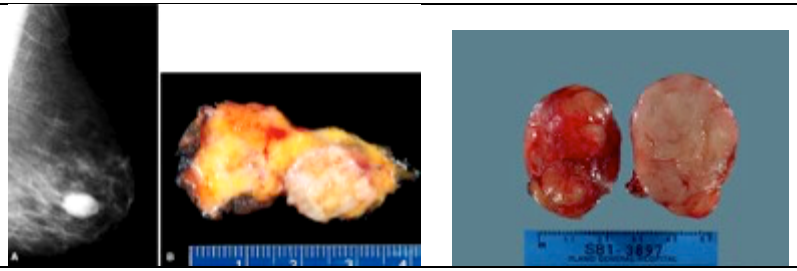
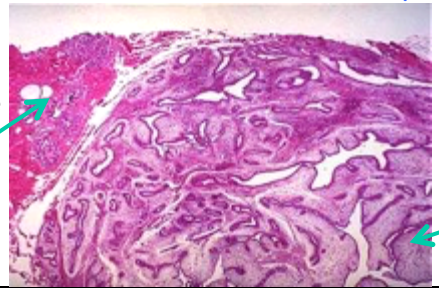
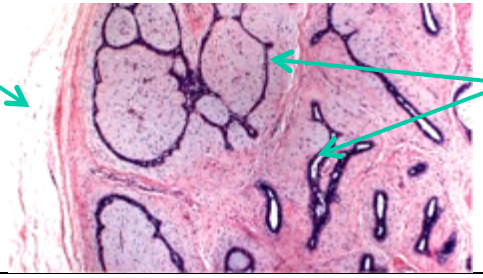
LOBULAR: all ducts; hyperchromatic nuclei

7. INTRADUCTAL PAPILLOMA

Perimenopausal Women (Mean Age: 48)

DEFINITION	Dilated, papillary lesion **(BENIGN)** usually seen in the **dilated LACTIFEROUS DUCTS**
CLINICAL	**BLOODY nipple discharge**
GROSS	 **Papillary lesion with HEMORRHAGE** – hemorrhage goes into the duct (*this is why there's blood discharge)*
MORPHOLOGY	 **Branching papilloma** lined by 2 layers of cells: Outer ductal cells & Inner myoepithelial cells (=BENIGN) w/ **cellular PLEOMORPHISM + numerous mitotic figures**

8. FIBROADENOMA

DEFINITION	Sharply demarcated, **MOBILE** lump that *"slips away from the examining fingers"*; found in **UPPER OUTER QUADRANT** *(distinguish from invasive ductal carcinoma)*
GROSS	 Ducts are **COMPRESSED** in here with stromal fibrosis around it
MORPHOLOGY	**Well-encapsulated** tumor with **fibroconnective tissue (loose, myxoid stroma** compromised of ductal tissue) + **NO FAT CELLS in Fibroadenoma**  Normal breast tissue with FAT CELLS → **Stromal fibrosis** → Capsule → **COMPRESSED DUCTS** 

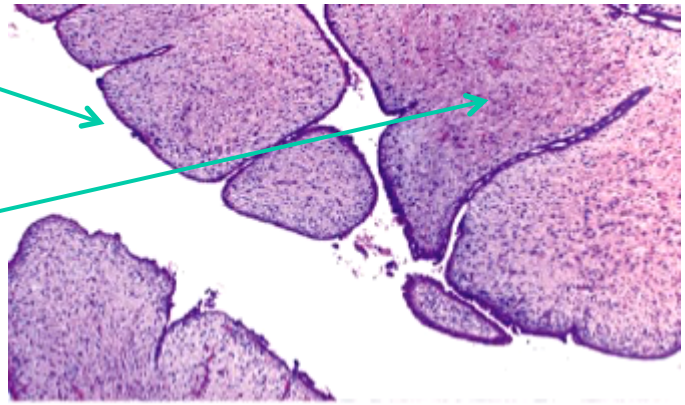
9. PHYLLODES TUMORS

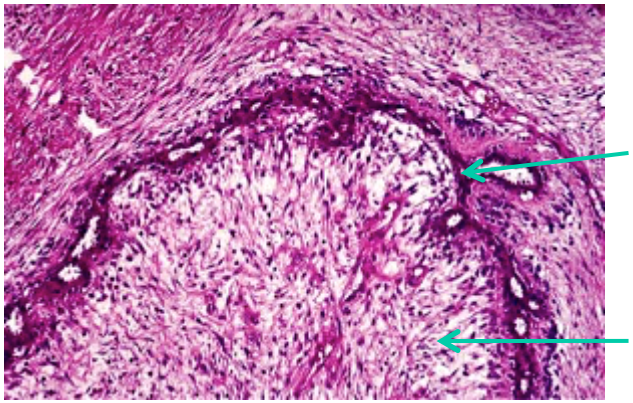
5th Decade

DEFINITION	**BENIGN (90%)** or malignant lesion composed of both stromal & ductal elements **Malignancy depends on **STROMAL CELLS** (not glandular structure) – hypercellular stroma + mitoses*
MORPHOLOGY	Lobulated tumor with cystic spaces containing **LEAF-LIKE EXTENSIONS** **BENIGN:** MONOTONOUS, UNIFORM STROMAL CELLS **MALIGNANT:** ATYPICAL STROMAL CELLS + MITOTIC ACTIVITY

BENIGN DUCTAL CELLS
**Not worried about these cells that line the duct*

STROMAL CELLS*





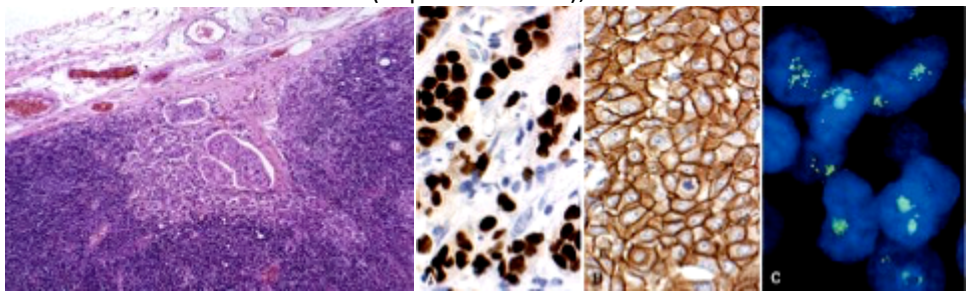
BENIGN DUCTAL CELLS

UNIFORM STROMAL CELLS
= BENIGN

BREAST CARCINOMA: Most common cancer in women in the U.S.

- **CLINICAL:** *palpable HARD, FIXED mass;* ***skin retraction, skin dimpling, nipple inversion***
- **HIGH RISK FACTORS:**
  - GENETIC: **BRCA1 (MOST AGGRESSIVE) & BRCA2 germ line mutations** (DNA repair enzymes)
  - FAMILY HISTORY: **1 first-degree relative** (3-fold), 2 first-degree relatives (5-fold)
  - AGE: median age is **65 y/o**
  - GEOGRAPHICAL: 4-fold greater incidence in Western industrialized countries
  - DIET: high fat *(obesity: fat converts to estrogen)* + alcohol intake
  - MEDICAL HISTORY: **previous cancer has 5-fold increase in developing a 2nd cancer in opposite breast;** Radiation to chest **(Hodgkin's)**
  - MORPHOLOGY: fibrocystic change w/ epithelial atypical hyperplasia (5-fold)
  - COMBINATION**: atypical ductal hyperplasia + first-degree relative (10-fold)**
  - MENSTRUAL HISTORY:
    - Early menarche <12
    - Late menopause >55
    - **Nulliparity** *(correlation w/ endometrial carcinoma)* or 1st pregnancy **>35**
  - INCREASED ESTROGEN
    - **Anovulatory cycles:** *unopposed estrogen*; most common cause dysfunctional uterine bleeding
    - Post-menopausal **obesity**: *aromatization of androgens to estrogens*
    - **Estrogen-producing ovarian tumors *(Granulosa cell & PCOS)*** + Hx of endometrial cancer
    - Exogenous, prolonged estrogen administration
- PROGNOSTIC FACTORS
  - Infiltrating/invasive ductal + infiltrating lobular carcinomas have equally *poor prognoses*
  - Medullary, colloid, & tubular carcinomas have ***good prognoses***
  - **POOR PROGNOSTIC FACTORS**
    - High grade, high stage, large tumors
    - **LYMPH NODE METASTASIS + vascular invasions** – ***in the absence of distant mets, LN metastasis is best prognostic factor***
    - **Amplifications of c-Erb B2 (HER-2/neu+)**: *aggressive nature of the tumor with multiple node metastasis & vascular dissemination*
    - **ABSENCE** of estrogen + progesterone receptors (can't treat with Tamoxifen)
    - Overexpression of cathepsin D enzyme
    - Elevated levels of GFs (TGF, EGF, IGF)
    - Aneuploidy: #chromosomes is not factor of 23 (haploid number); i.e. 51 chromosomes

With LN metastasis, axillary contents are removed. *Thus, that arm can no longer be drained. SO, they now so* ***sentinel node biopsy*** *–* ***LN closest to the tumor. If biopsy is negative, they will spare axillary LNs because there is no axillary LN involvement.***



Lymph Node Metastasis **Estrogen** **HER2**

ER+, HER2- (BRCA2): better prognosis
ER+/-, **HER2+**: poorer prognosis
ER-, HER2- (BRCA1): poorest prognosis
^African American females

10. INTRADUCTAL CARCINOMA IN SITU (DCIS)

DEFINITION

A **malignant** clonal proliferation of epithelial cells limited to ducts + lobules by the **basement membrane**; **NO STROMAL INVASION**

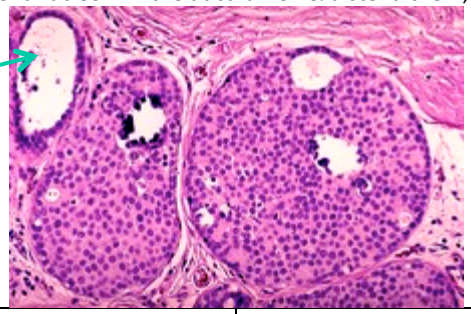
CLINICAL

Almost always **detected by mammography** – reveals **microcalcification** & tumor mass

MORPHOLOGY

Abnormal cells with **large** hyperchromatic nuclei & **prominent nucleoli fill the duct lumen & distend them**; **BM remains intact**

Normal w/ nice open lumen

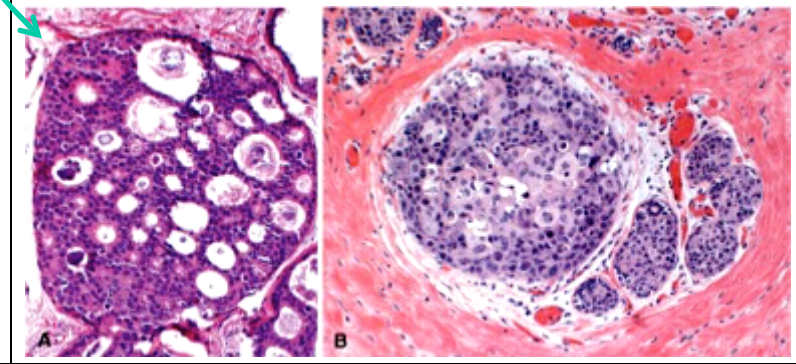


COMEDO* PATTERN: central ductal cells are necrotic

Necrotic tissue may ***calcify*** **(DYSTROPHIC)**

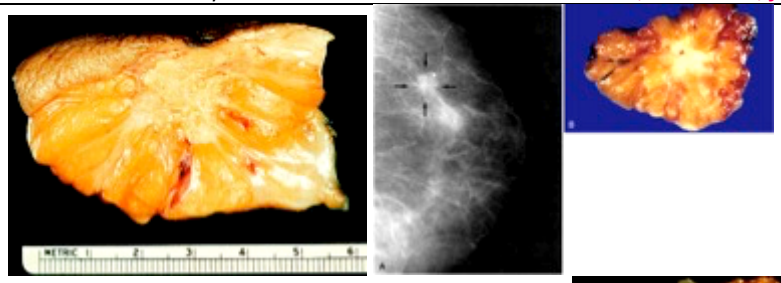
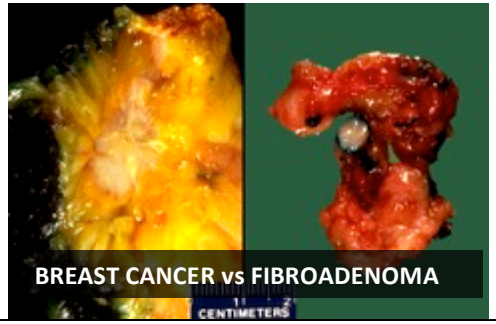
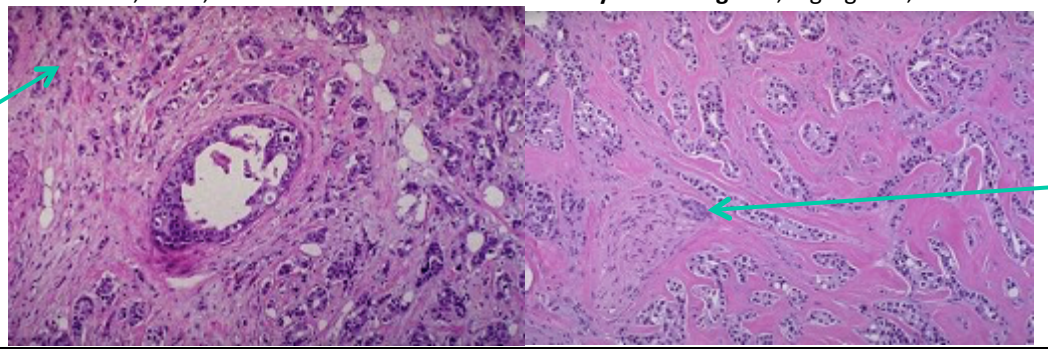
CALCIFICATION

CRIBIFORM PATTERN: multiple small round spaces, giving a SIEVE-LIKE appearance to the gland (*looks like hole)*

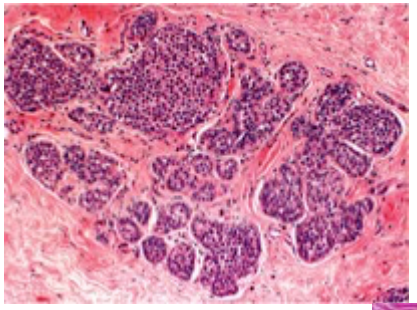
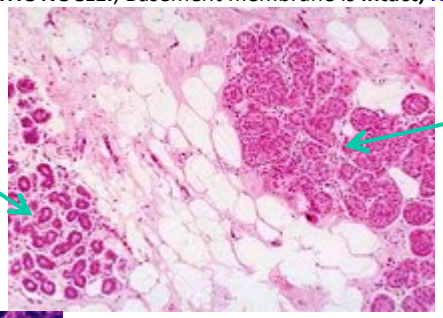
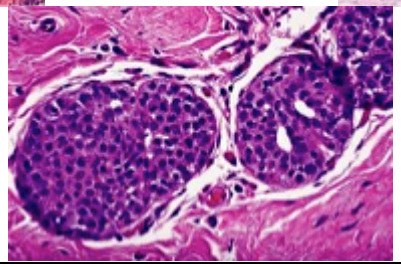


11. INVASIVE (INFILTRATING) DUCTAL CARCINOMA

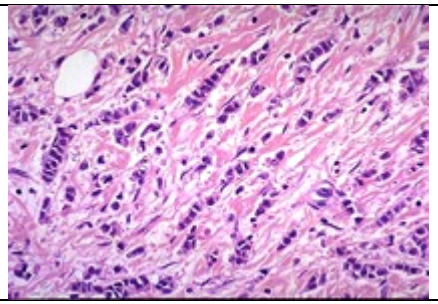
Most common type of breast carcinoma (75-80%)

DEFINITION	Most common location – **UPPER OUTER QUADRANT***; *started out as **DCIS**, but by the time it is diagnosed, it is already invasion*
CLINICAL	Nipple discharge (10%) & nipple retraction (5%) – ***subareolar*** *in location, involving lactiferous ducts* **PEAU D' ORANGE:** caused by **lymphatic infiltration*** (called ***inflammatory carcinoma*** bc grossly the tissue appears inflamed); **POOR PROGNOSIS** 90% are discovered by **self-breast examination** – PE revels a *hard, non-tender, **fixed** mass with **ill-defined margins***
GROSS	 ***Ill-defined* borders** with **STELLATE** appearance in the periphery Tumors cut with a 'gritty' sensation (due to desmoplasia + microcalcifications) 
MORPHOLOGY	*"Cells in strands or little nests going into the stroma, having left the main duct"* Cancer cells induce **dense fibrous stroma (DESMOPLASIA) –** *often termed **'Scirrhous Carcinoma'*** **HYPERCHROMATIC NUCLEI W/ PROMINENT NUCLEOLI + MITOTIC FIGURES** **WELL-DIFFERENTIATED FORM:** *dense collagenous stroma* w/ small abnormal **glandular structures** **POORLY-DIFFERENTIATED FORM:** lines, nests, & columns of abnormal cells + **many mitotic figures**; high-grade; **NO GLANDS SEEN AT ALL** Malignant cells all throughout the stroma – *This is the invasion*  *Involving the nerve cells = poor prognosis*
COURSE/ TREATMENT	**Axillary LN Mets** – *enlarged, firm, palpable mass* **Bone Mets** – ***bone pain*** *(most common cancers go to bone – prostate, breast, lung, renal cell)*

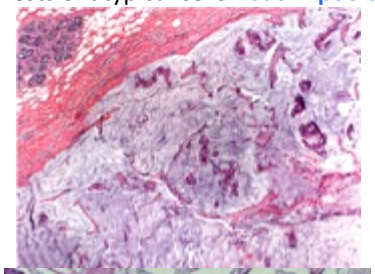
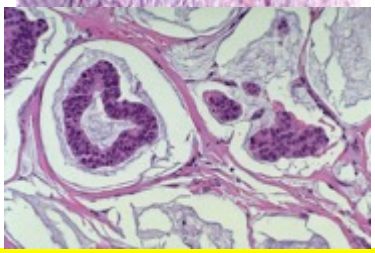
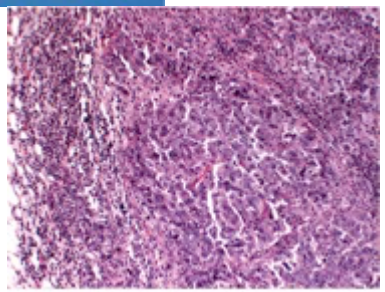
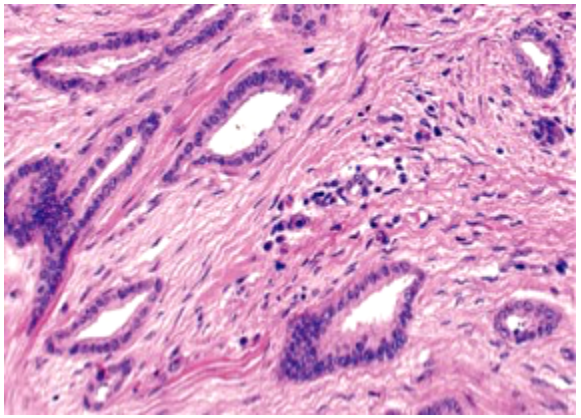
12. LOBULAR CARCINOMA IN SITU (LCIS)

DEFINITION	A clonal proliferation of cells within ducts + lobules that grow in a discohesive fashion; **MOST LIKELY TO BE BILATERAL (mirror image)** **All ducts within the lobule are involved*
CLINICAL	Diagnosis often **incidentally** made in a breast biopsy performed for other reasons – *there is no mass or calcifications seen on mammography*
MORPHOLOGY	***"There is not that much pleomorphism. They will be atypical, but they will all look kind of the same."*** TERMINAL DUCT + LOBULAR UNITS are packed with abnormal cells with **ROUND HYPERCHROMATIC NUCLEI**; Basement membrane is **intact; NO CALCIFICATIONS** "Uniform, monotonous"  Normal  **LCIS: expanded ducts w/ no lumen***  ***No tumor cells in stroma***

13. INVASIVE LOBULAR CARCINOMA

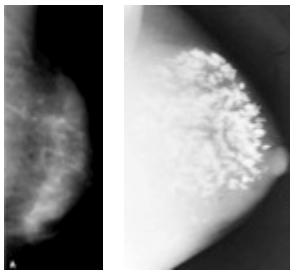
DEFINITION	Notorious for **multicentricity + BILATERALITY**
CLINICAL	Difficult to palpate or detect by mammography
PATHOGENESIS	Usually due to an acquired loss of tumor suppressive adhesion protein E-CADHERIN
GROSS	**DOES NOT FORM A DISTINCT MASS OR CALCIFY**
MORPHOLOGY	 Tumor cells infiltrate into the stroma in **SINGLE FILES** **Sometimes you can see 'single filing' in invasive ductal carcinoma, but you should really associate 'single files' with invasive LOBULAR carcinoma & 'strands' & 'nests' with ductal*

All 3 of these variants have better prognoses than infiltration ductal or lobular carcinomas!

14. MUCINOUS CARCINOMA (Colloid Carcinoma)	15. MEDULLARY CARCINOMA	16. TUBULAR CARCINOMA
Older Women		**Women in late 40s**
Will not feel hard due to mucin production		***Well-differentiated*** carcinoma w/ **well formed tubules**
Groups or nests of atypical cells **float in pools of MUCIN**	**Well-circumscribed, soft, fleshy tumors**	**LACKING MYOEPITHELIAL CELLS**
 		
***Note**: MUCIN production in breast cancer is GOOD, but in COLON cancer it has a WORSE prognosis!!*	Pleomorphic, hyperchromatic, large cancer cells Surrounded peripherally by **dense lymphoid infiltrate** ***DESMOPLASIA IS ABSENT!**	**Often misdiagnosed because it looks benign*

MAMMOGRAMS

- Used for both screen + diagnosis of breast carcinoma
- Breast Cancer Screening:
  - **Women aged 35-40 –** baseline
  - **Between 40-49**: every 1-2 years
- **MALIGNANT LESION ON MAMMOGRAPHY:**
  - **SPICULATED margin** of a *dense mass (desmoplasia, fibrous stroma)*
  - **CLUSTERS OF SMALL calcifications**; particles varying in shape & size



TREATMENT REGIMENS

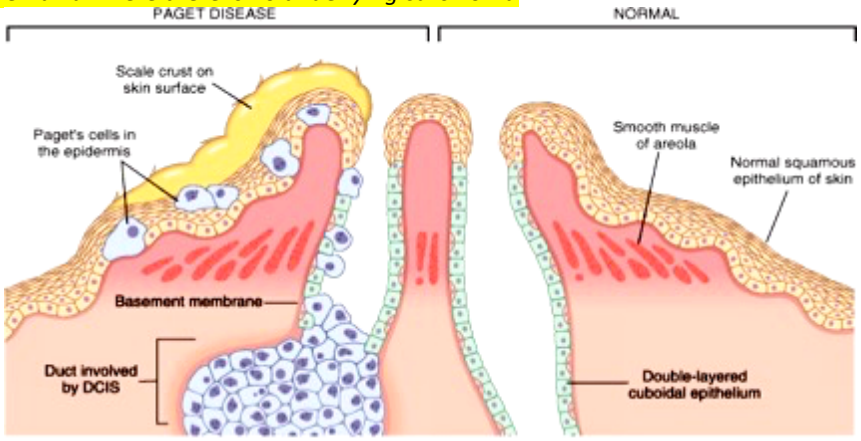
- **Radical mastectomy**: *mastectomy + axillary lymph node dissection + removal of pectoral muscles*
- Modified radical mastectomy: without removal of pectoral muscles; **mainstay treatment**
- Simple mastectomy or lumpectomy w/ radiation to preserve breast tissue, endocrine therapy (Tamoxifen, ovarian ablation), chemotherapy
- Breast implant: *could get a fibrous capsule*

17. PAGET DISEASE OF THE NIPPLE

DEFINITION

Occurs when the **underlying *In situ* or invasive ductal carcinoma extends upwards to involve the epidermis of the nipple**

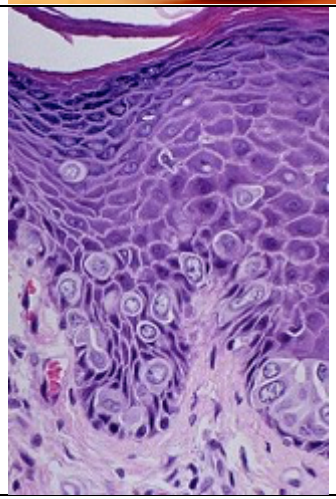
**This is different from Paget of the Vulva where there is no underlying carcinoma*



GROSS

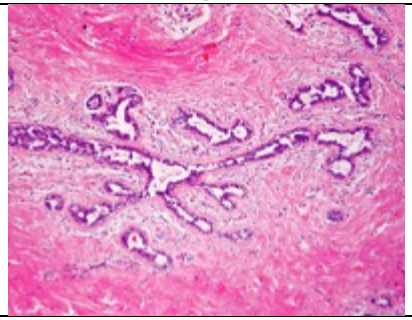
Nipple becomes **red + crusted**

MORPHOLOGY

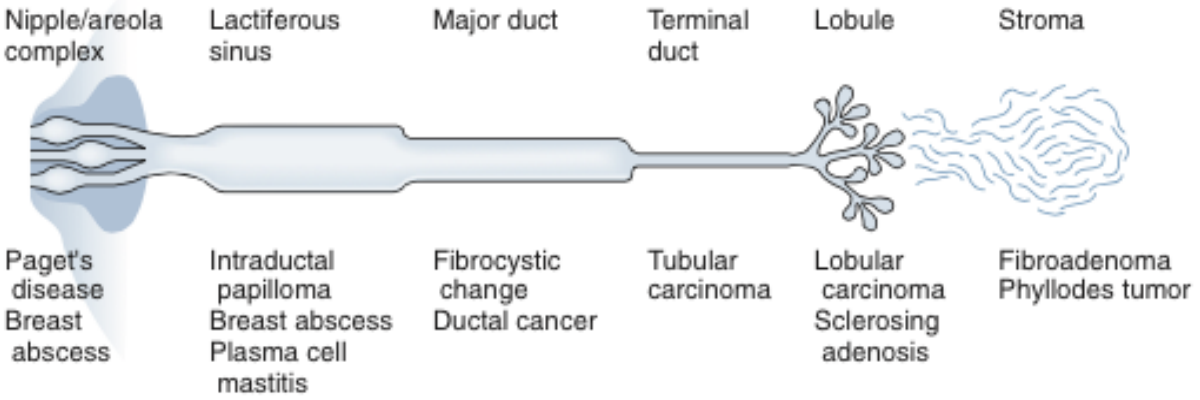


Tumor cells occur singly or in small groups in the epidermis & have a **CLEAR, vacuolated CYTOPLASM**

MUCIN +
PAS +
KERATIN +

18. GYNECOMASTIA	
DEFINITION	Unilateral or bilateral male breast enlargement
PATHOGENESIS	May be idiopathic or secondary to hormonal disturbances: – Estrogen excess due to ***testicular atrophy*** (**KLEINFELTER'S SYNDROME**) – Faulty estrogen metabolism (LIVER **CIRRHOSIS**) – Gonadotropic excess (Testicular tumor) – Prolactin excess (hypothalamic or pituitary disease) – **S**ome **D**rugs **C**reate **A**wesome **K**nockers – Spironolactone, Digoxin, Cimetidine, Alcohol, Ketoconazole
MORPHOLOGY	 Hyperplasia of the **ductal epithelium** with surrounding fibroconnective tissue; **NO LOBULES**

19. CARCINOMA OF THE MALE BREAST	
DEFINITION	Very rare (1% of all breast cancer) High risk factors & prognostic factors are similar to those in women & include Western countries, 1st degree relative w/ breast cancer, eat.
MORPHOLOGY	Similar to the infiltrating/invasive ductal carcinoma of the female breast



DISORDERS OF DEVELOPMENT	Milkline remnants, Accessory axillary breast tissue, congenital nipple inversion, macromastia
INFLAMMATORY DISEASES	Acute Mastitis Subareolar Abscess Duct Actasia (Plasma Cell Mastitis) Traumatic Fat Necrosis
FIBROCYSTIC CHANGE	Non-proliferative fibrocystic change Proliferative fibrocystic changes: Ductal Hyperplasia Sclerosing Adenosis
TUMORS (non-neoplastic)	Fibroadenoma Phyllodes Tumor Intraductal Papilloma
NEOPLASMS	Breast Carcinoma (female) High-Grade Ductal Carcinoma In situ (DCIS) Low-Grade Ductal Carcinoma In situ (DCIS) Lobular Carcinoma In situ (LCIS) Infiltrating (Invasive) Ductal Carcinoma Infiltrating (Invasive) Lobular Carcinoma Mucinous (Colloid) Carcinoma Medullary Carcinoma Tubular Carcinoma Paget Disease of the Nipple
DISEASES OF THE MALE BREAST	Gynecomastia Carcinoma of the Male Breast

1st few weeks of breastfeeding	Acute mastitis	Elongated glands from ↑glands & scar tissue	Sclerosing Adenosis
Benign papillary dilation of lactiferous ducts	Intraductal papilloma	Compressed ducts	Fibroadenoma
Mutations for breast carcinoma	BRCA-1 & BRCA-2	Strands or nests of cells going into the stroma	Invasive ductal carcinoma
Malignancy detected by mammography	Ductal carcinoma	Prognosis of mucin production in breast cancer	GOOD
Found in upper outer quadrant	Fibroadenoma & invasive ductal carcinoma	Well-defined, soft tumor w/ no desmoplasia	Medullary carcinoma
Incidental finding (breast carcinoma)	Lobular carcinoma	Hyperplasia of ductal epith + no lobules	Gynecomastia
Painless lump from repeated trauma	Fat necrosis	Mutation w/ worse prognosis (breast ca)	BRCA1
Malignancy depends on stromal cells	Phyllodes tumors	Bilateral breast malignancy	Lobular carcinoma
Well formed tubules + no myoepithelial cell	Tubular carcinoma	Estrogen-secreting lesions causing breast ca (2)	Granulosa cell tumor & PCOS
Hx of what cancer tx can cause breast ca	Hodgkin's radiation to chest	Most common type of breast carcinoma	Invasive/infiltrating ductal carcinoma
Scirrhous carcinoma	Invasive ductal carcinoma (desmoplasia = hard)	Peripheral dense lymphoid infiltration	Medullary carcinoma
Apocrine metasplasia	Fibrocystic change	Blue dome cyst	Fibrocystic change
Malignancy on mammography	Spiculated; clusters of small calcifications	Ill-defined margins + stellate appearance	Invasive ductal carcinoma
3 breast carcinomas w/ good prognosis	Medullary, Colloid, **Tubular**	Well vs poor differentiated ductal carcinoma	Well has glands, poor has NO glands
Peau d' orange	Invasive ductal carcinoma	Disease w/ underlying carcinoma	Paget Disease of the Nipple
Proliferation of duct epithelial cells & myoepithelial cells with increased stroma	Sclerosing adenosis	Fibrocystic change morphology (5)	Adenosis, apocrine metaplasia, dilation of ducts, stromal fibrosis, calcification
Fat necrosis morphology (4)	Granulomatous inflammation, foamy macrophages, fibrocollagenous tissue, dystrophic calcification	Chronic granulomatous inflammation + plasma cells + elderly	Mammary duct ectasia (plasma cell mastitis)
Encapsulated, loose myxoid stroma, no fat	Fibroadenoma		
Malignancy, but monotonous cells	Lobular carcinoma		
Caused by liver cirrhosis	Gynecomastia		
Presence of myoepithelial cells means..	BENIGN		
Often misdiagnosed because looks benign	Tubular carcinoma		
Central ductal cells necrotic	Comedo pattern of DCIS		
Soft mass of nests of atypia cells in mucin	Mucinois/Colloid carcinoma		
Invasive ductal carcinoma mets where (2)	Axillary nodes & bone		
Phyllodes tumor with monotonous stroma	BENIGN		
ER+/-, HER2+ prognosis	poor		
ER+, HER2- prognosis	better		
ER-, HER2- prognosis	worst		
Clear, vacuolated cytoplasm; PAS+	Paget Disease of the Nipple		
Nulliparity associated with... (2)	Breast & endometrial carcinoma		
Mobile lump "slips away from fingers"	Fibroadenoma		
Single file tumor cell infiltration	Invasive lobular carcinoma		
Multiple small holes in ducts	Cribiform patern of DCIS		
Caused by lymphatic infiltration in breast ca	Peau d' orange		
Malignancy w/ no calcifications	Lobular carcinoma		
Bloody nipple discharge	Intraductal papilloma		
Leaf-like extension	Phyllodes tumor		
Inflammatory carcinoma	Peau d' orange of invasive ductal carcinoma		
Common cause of acute mastitis	*Staph aureus*		