Breast Pathology

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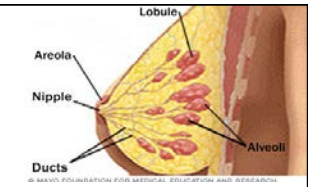
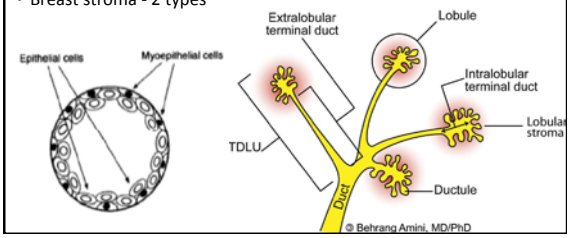
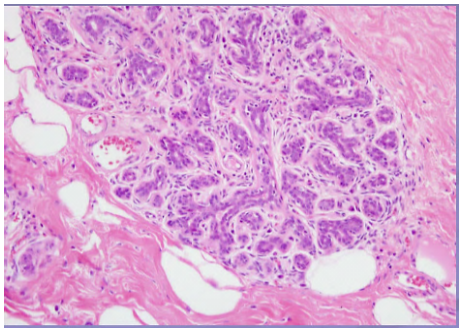
Normal breast anatomy

- Modified skin appendage
- terminal duct lobular unit (TDLU)
- 2 cell types line TDLU
- Breast stroma - 2 types



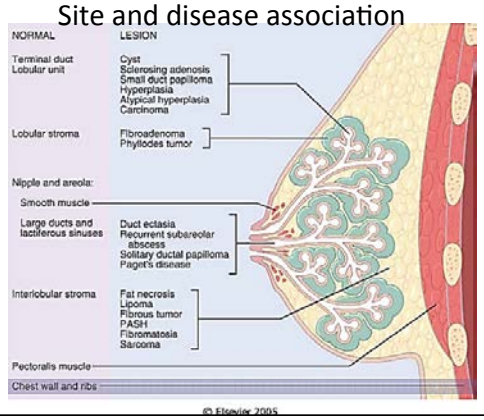


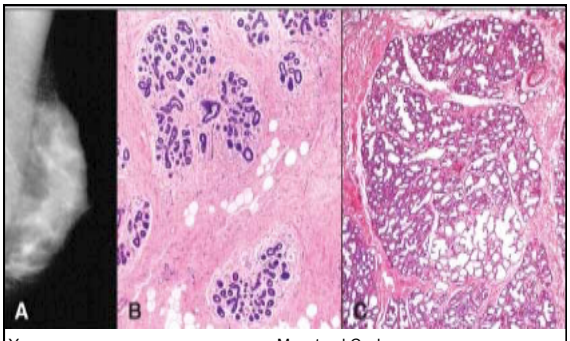
Terminal Duct Lobular Unit (TDLU)



Post-pubertal female breast TDLU >>male or pre-pubertal female

Site and disease association

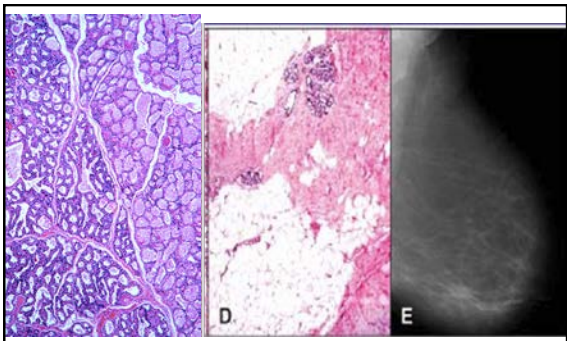




Young women
- Radiodense,
- Predominance fibrous interlobular stroma

Menstrual Cycle

Pregnancy
- Branched ducts
- Larger lobules



Postpartum/Lactation
- Colostrum (high protein) → Milk (higher fat and calories) over 10 days.
- Maternal antibodies (IgA)

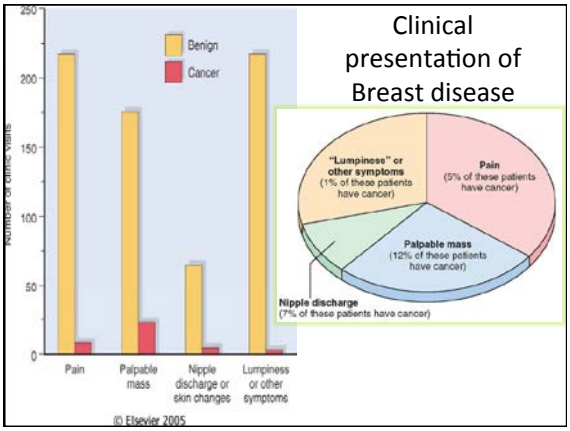
Senescence:
- Lobular atrophy and ↑ Fatty replacement
- Increased radiolucency

Disorders of Development

- Milk Line Remnants
  - Axillary fold to perineum
  - Supranumery nipples

- Accessory Axillary Breast Tissue
- Congenital Nipple Inversion
  (distinguish from acquired inversion – cancer)

Clinical presentation of Breast disease



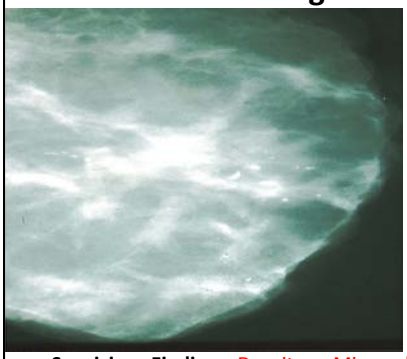
Common Causes of Mass Lesions by Age Group

Age Group	Most Common Lesion
15-35	Fibroadenoma
35-50	Fibrocystic change > cancer
>50	Cancer till proven otherwise
Pregnant/Lactating	Lactating adenoma > cyst> mastitis > cancer

Diagnostic Modalities: Evaluation of Breast Masses

- Self examination
- Radiologic Imaging
  - Mammography
  - Ultrasound
  - MRI
- Tissue diagnosis
  - Core needle biopsy
  - Excision

Mammogram

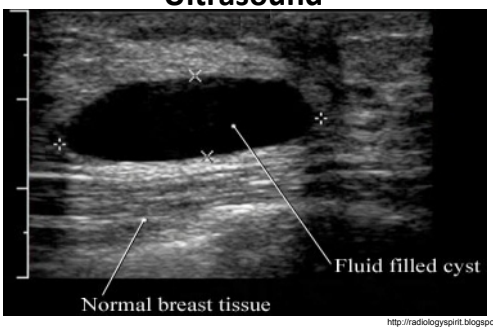


Screening

- 40-50 y: annual/ biannual
- >50 y: annual
- 1st degree relative : 10 y prior

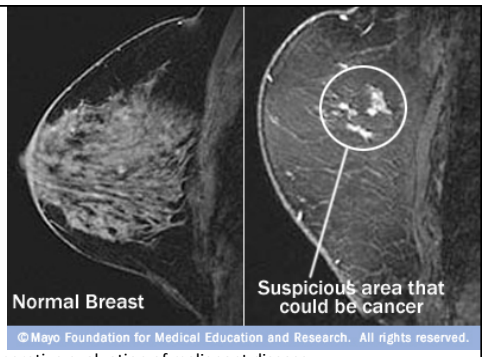
Suspicious Findings: Density or Microcalcifications

Ultrasound



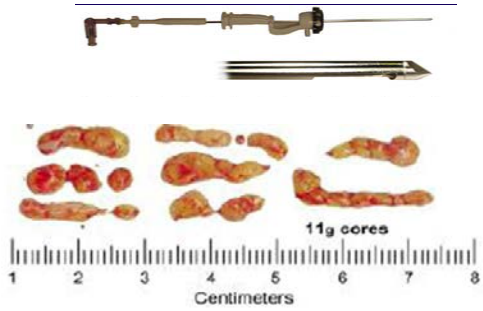
- Younger women usually clinically benign lesion

MRI

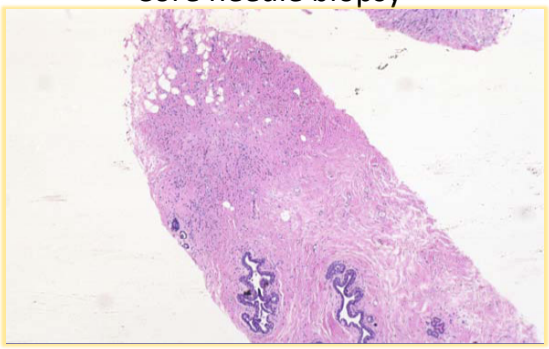


- Pre-operative evaluation of malignant disease.
- Eval tumor response to radiation therapy or chemotherapy

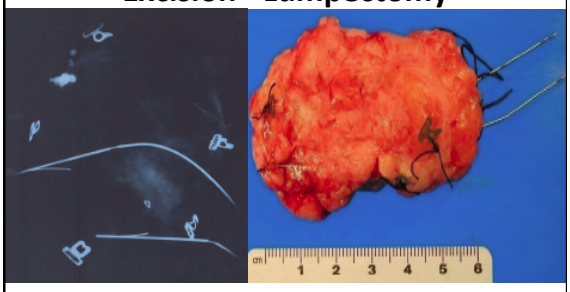
Core Needle Biopsy



Core needle biopsy



Excision - Lumpectomy



Benign Breast - Inflammatory

- Acute mastitis
- Periductal Mastitis
- Mammary duct ectasia
- Fat necrosis

Acute Mastitis

Incidence:
- Lactation

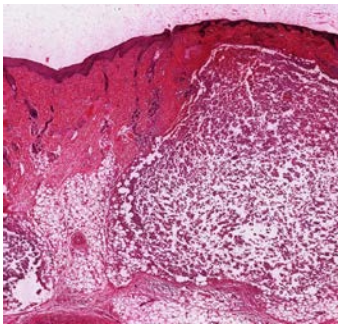
Clinical:
- Erythema, Pain, Fever

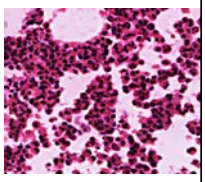
Causes:
- Staph. aureus > Streptococci

Therapy:
- Antibiotics, expression of milk

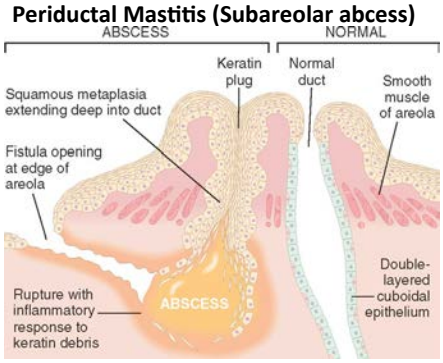
DDx Inflam carcinoma

Acute Mastitis





Periductal Mastitis (Subareolar abcess)

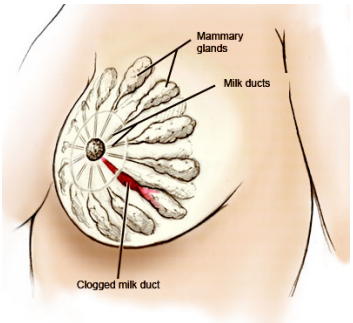


- **Clinical**: Pain, erythema, subareolar mass
- **Cause**: 90% smokers

Mammary duct ectasia (plasma cell mastitis)

Incidence:
- 50 - 60 y, multiparous

Clinical:
- Mass-like
- Thick secretions,
- Lymphadenopathy



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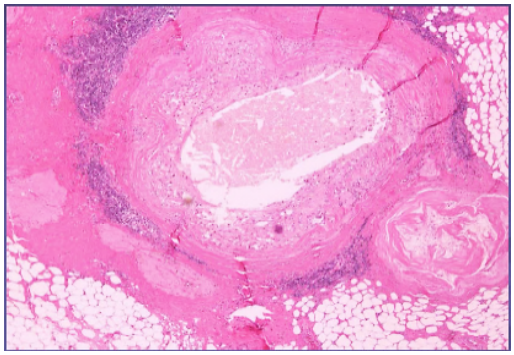
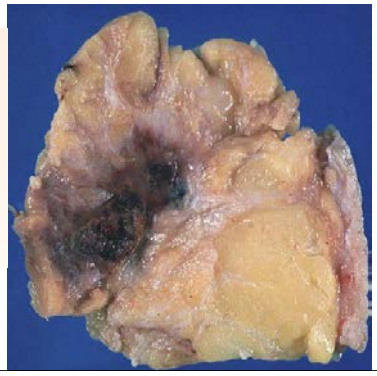


Fat necrosis

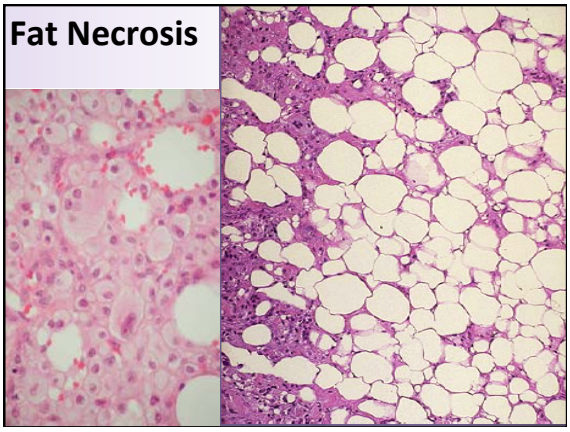
Definition:
- Nodular dead adipose

Incidence:
- Prior trauma/ surgery

Clinical:
- Painless palpable mass



Fat Necrosis



Hematoxylon

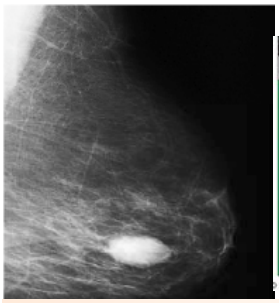
"Benign" Breast

- Stromal lesions/tumors
  - **Fibroadenoma**
  - **Phylloides tumor**
    - **Low-grade**
    - **High grade**
- Epithelial lesions
  - **Nonproliferative Breast Changes (Fibrocystic)**
  - **Proliferative Breast disease without atypia**
  - **Proliferative Breast disease with atypia**

Risks for Breast cancer

Disease		Risk Ratio
Nonproliferative	Fibroadenoma Fibrosis Cysts Apocrine metaplasia	No increased risk
Proliferative No atypia	Papilloma Sclerosing adenosis Usual ductal hyperplasia	**1.5-2x**
Proliferative with atypia	Atypical Ductal Hyperplasia (ADH) Atypical Lobular Hyperplasia (ALH)	**4-5x**
Ductal Carcinoma In-Situ (DCIS) Lobular Carcinoma In-Situ (LCIS)		**8-10x**

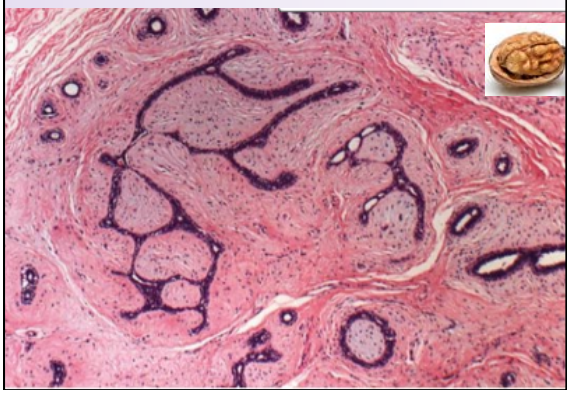
Fibroadenoma



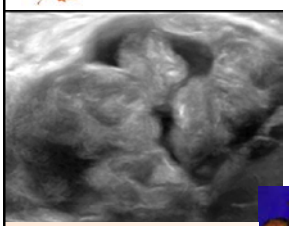
Incidence:
- 3rd decade
- Most common tumor young adults

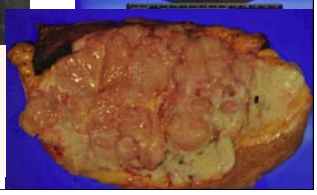
Clinical:
- Well-circumscribed
- Mobile
- Mostly painless

Fibroadenoma



Phylloides tumor



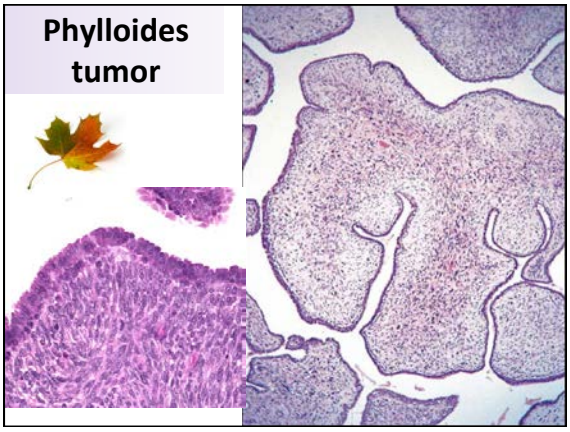


Incidence
- 50-60 y,
- Latin 3 - 4x incidence

Clinical
- Rapid growth

Other info
- <1% of breast tumors
- 15%

Phylloides tumor

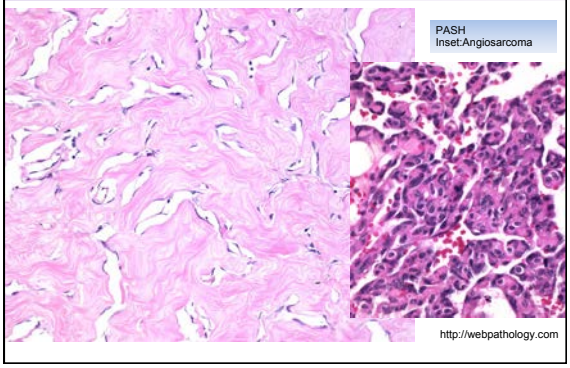


Pseudoangiomatous stromal hyperplasia (PASH)

Clinical:

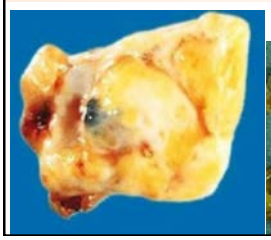
- Benign, incidental, nodule-like

Pseudoangiomatous stromal hyperplasia (PASH)

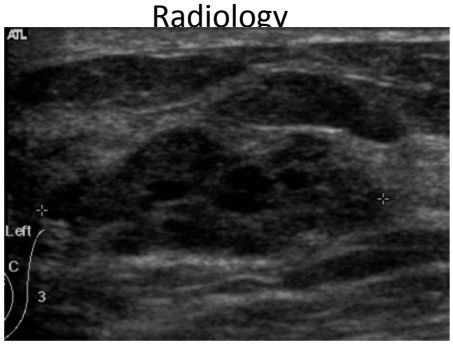


Non-proliferative Breast Changes (Fibrocystic Changes)

- **Most common breast lesion**
- Premenopausal
- Pain from swelling tied to menstrual cycle
- Nipple discharge
- Lumpy bumpy
- No cancer risk

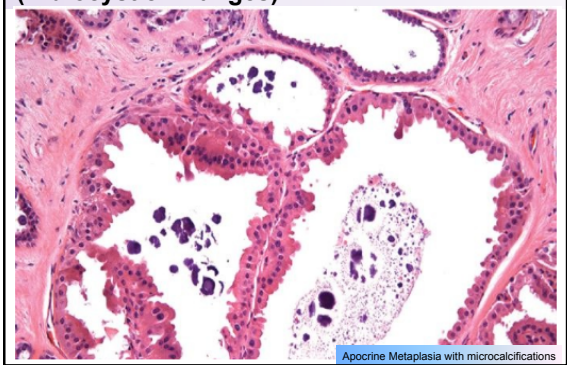


Radiology



multiple ill-defined densities usually bilaterally, no calcifications

Non-proliferative Breast Changes (Fibrocystic Changes)



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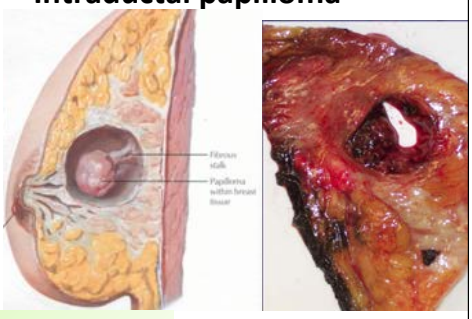
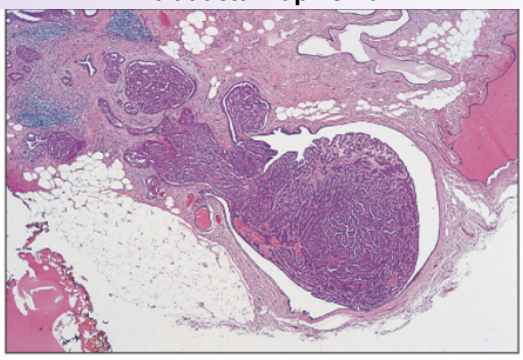
Prolif Breast Disease W/O Atypia
Intraductal papilloma

Clinical:
- Bloody, nipple discharge

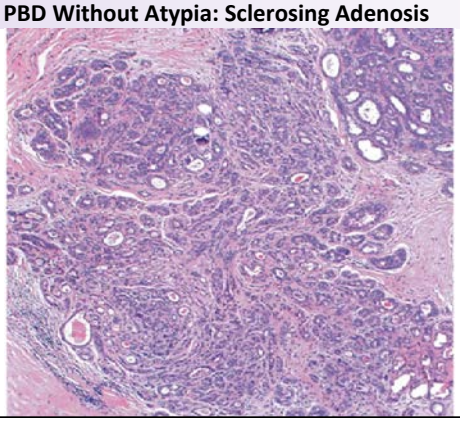


- Radiology: densities, calcifications

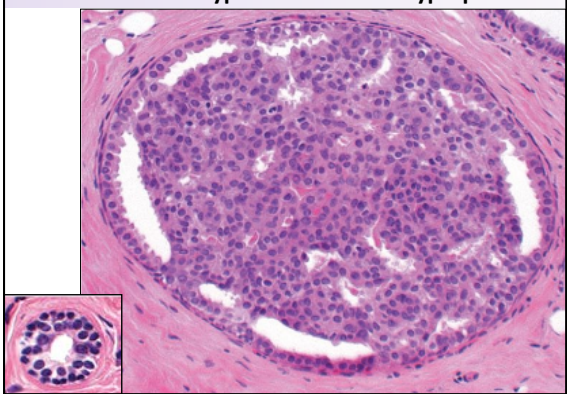
Intraductal Papilloma



PBD Without Atypia: Sclerosing Adenosis



PBD Without Atypia: Usual ductal hyperplasia



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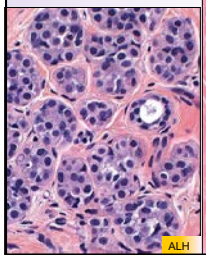
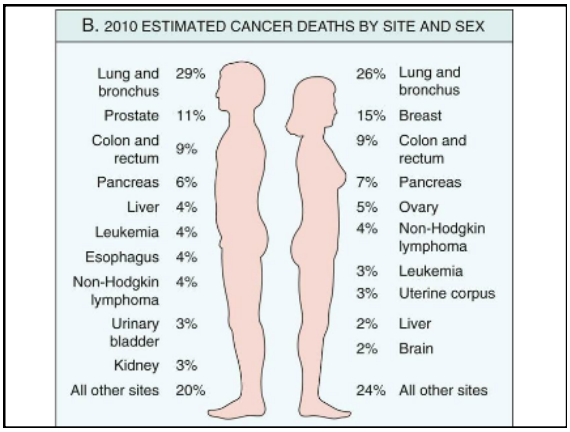
Proliferative Breast Disease with Atypia

ADH: Often associated with ductal carcinoma in-situ

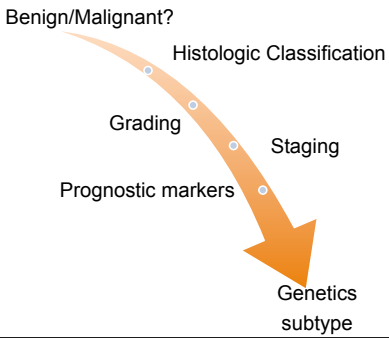


Malignant Breast Tumors

- Carcinoma (95%)
  - In-situ
  - Invasive
    - 75%, ductal adenocarcinomas
    - Genetic subclassifications
    - Other histologic subtypes



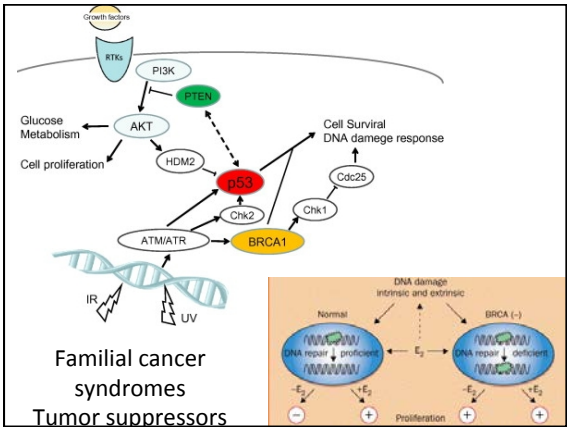
Diagnosis of Neoplasms



Risk factors

Risk factor	Mechanism	Description
Age	Estrogen exposure	70% > 50 y
Age of menarche	Estrogen exposure	Earlier, greater risk
First live birth	Estrogen exposure	>35y, Later greater risk
1st degree relative	Heredity	1° relative with cancer
Biopsy results	Tumor biology	E.g. Atypical ductal hyperplasia
Race	Socioeconomic	AA present later stage

Additional: exogenous estrogen exposure, radiation, carcinoma of the opposite breast or endometrial cancer, geography, diet, obesity, breast feeding, toxins

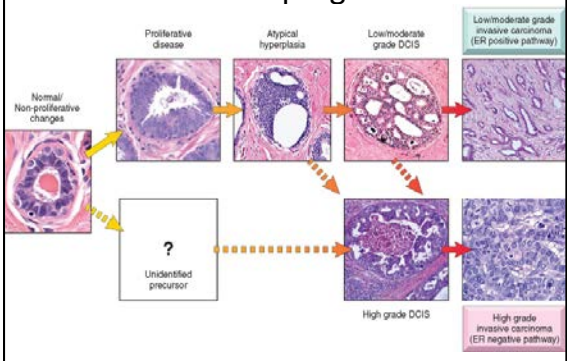


Familial cancer syndromes
Tumor suppressors

Hereditary Breast Carcinoma

Gene	Locus	Assoc cancers	Function	Comment
BRCA1	**17q21**	Breast Ovarian Male breast	Tumor suppressor, dsDNA repair	• 50% hereditary cancers. • 2% of breast cancers • Usually basal-like (Triple neg). • More common: medullary and poorly differentiated carcinoma • Majority have both breast and ovarian carcinoma
BRCA2	**13q12**	Same as above	Same	• 32% hereditary breast cancers • 1% of breast cancers • 14% both breast and ovarian carcinoma • Male breast cancer
p53	**17p13**	Li-Fraumeni syndrome	As above and + cell cycle + apoptosis	Most common mutation in sporadic cancer

Carcinoma progression



Histologic types of breast cancer

Total Cancers	Percentage
CARCINOMA IN SITU*	
Ductal carcinoma in situ	75
Lobular carcinoma in situ	25
INVASIVE CARCINOMA	
No-special-type carcinoma ("ductal")	Most common
Lobular carcinoma	
Tubular/cribriform carcinoma	
Mucinous (colloid) carcinoma	
Medullary carcinoma	
Papillary carcinoma	
Metaplastic carcinoma	Least common

Modifiedd from Dixon JM et al, Br J Surg 72:445, 1985.

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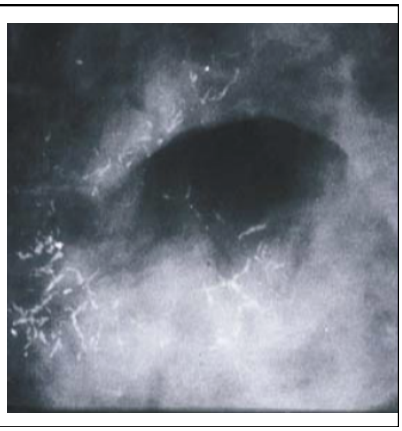
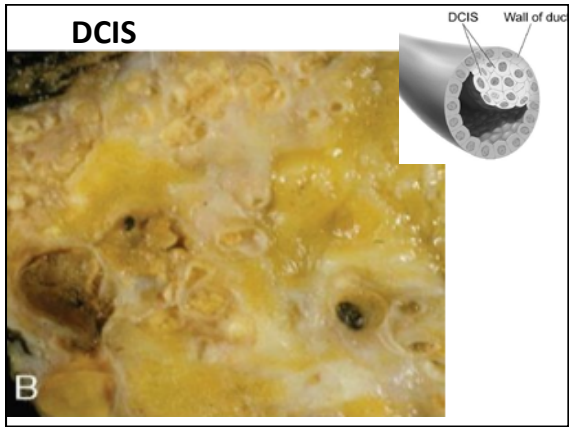
Ductal Carcinoma in Situ (DCIS)

Radiology:
- Linear/branching calcifications
- Screening, increased dx 5% - 30%

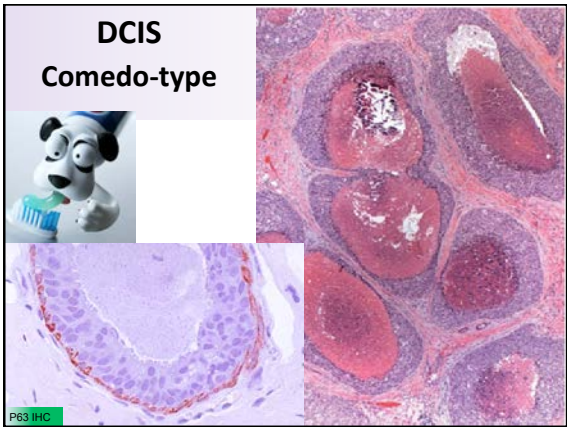
Therapy:
- Hormone, Radiation, Surgery



DCIS

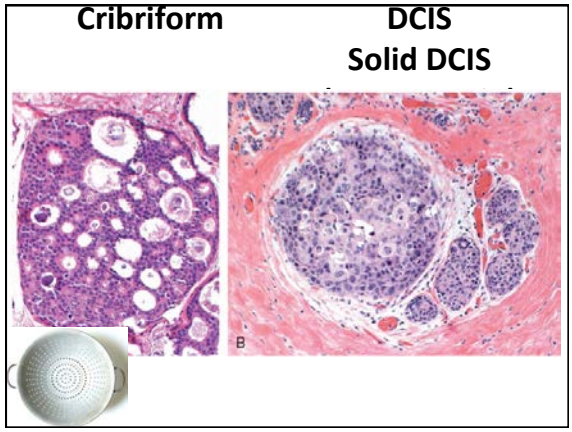


DCIS
Comedo-type

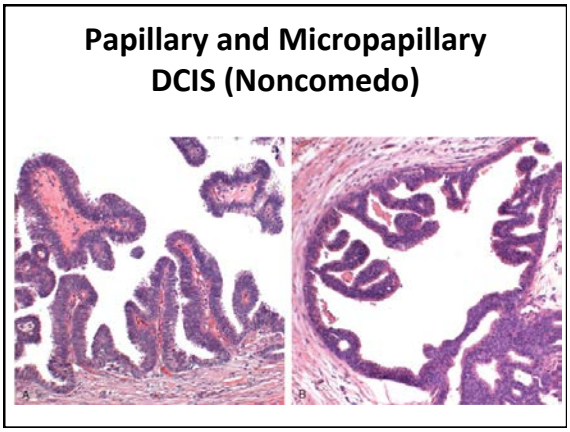


Cribriform

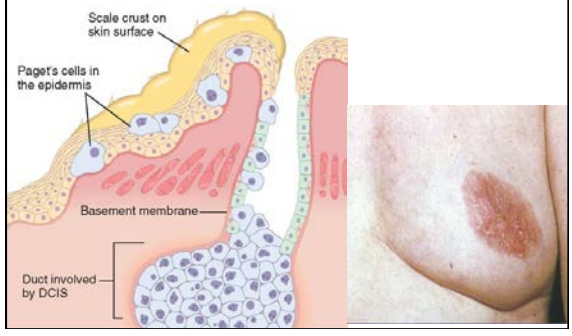
DCIS
Solid DCIS



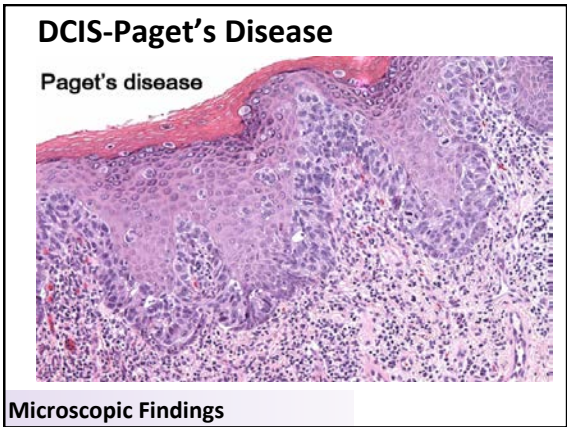
Papillary and Micropapillary DCIS (Noncomedo)



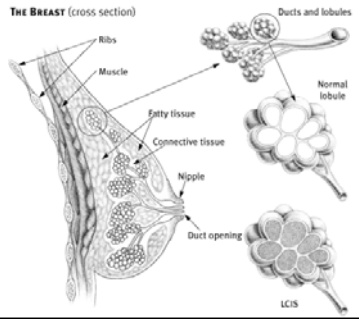
Paget's disease of the breast/nipple (DCIS)



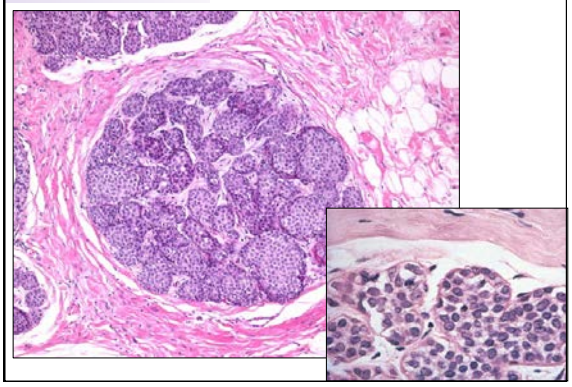
DCIS-Paget's Disease



Lobular Carcinoma In Situ (LCIS)



LCIS



Invasive ductal carcinoma NOS,NST

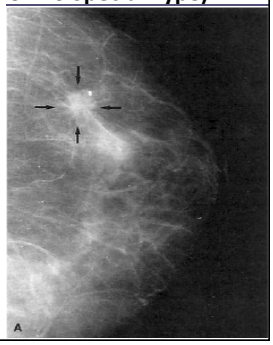
(Not otherwise specified or No Special Type)

Incidence:
- 75% >50 y
- Lifetime risk is 1 in 8

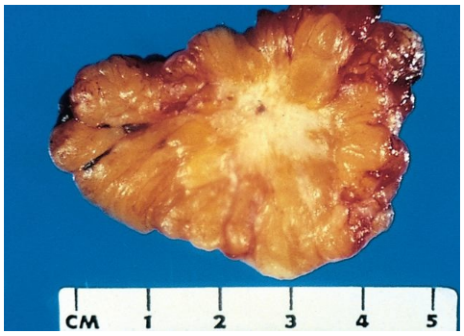
Clinical:
- Palpable mass
- Retraction of the nipple

Prognosis
- 85%, 5 year survival

Radiology:
- Mass with irregular borders, calcifications



- **Invasive ductal carcinoma NOS**



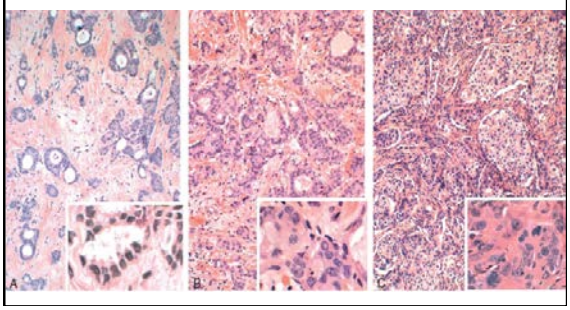
Prognostic Factors in Breast Cancer

- **Stage** (TNM)
  - Size, lymph node involvement, distant metastasis
- **Grade**
  - 3 questions: Making ducts?, ugly nuclei?, mitoses?
- **Histological type**
  - ductal, lobular, mucinous, metaplastic…others
- **Hormone receptors**
  - Therapeutic/prognostic (theranostic) markers

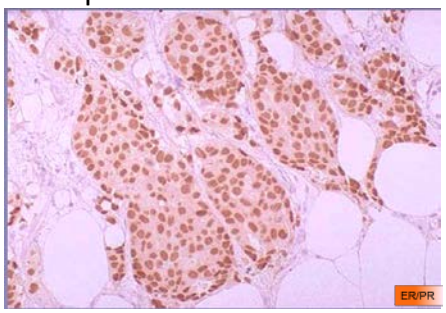
Invasive ductal carcinoma NOS

Microscopic Findings:

Grade 1 | Grade 2 | Grade 3

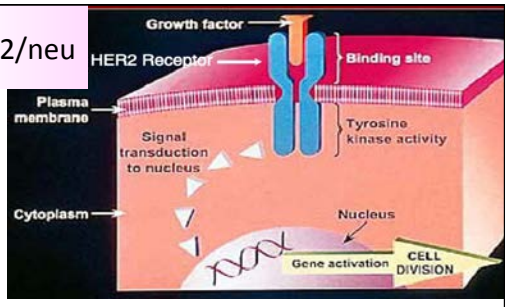


Therapeutic markers: Hormones



- Estrogen receptor (ER)
- Progesterone receptor (PR)
- Predict response to tamoxifine

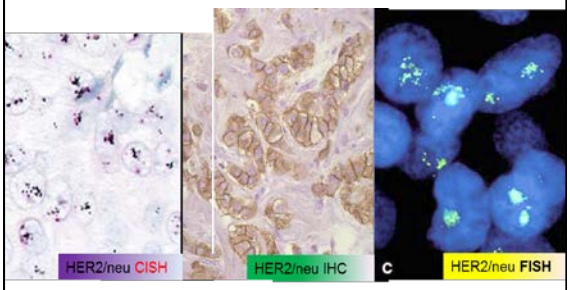
Her2/neu

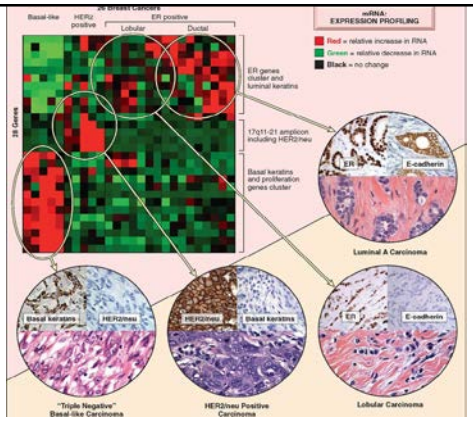


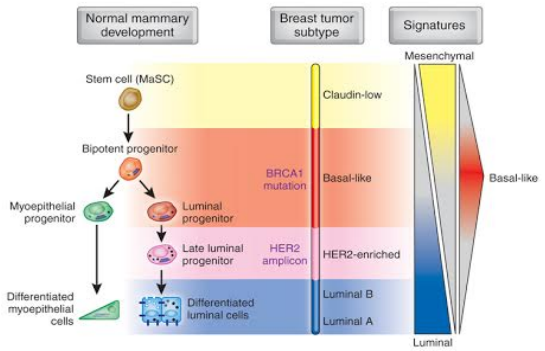
- Chromosome 17q21; synonym: hEGFR, ERbB-2
- Signaling pathways activated by HER2 receptor
- 30% breast cancer, Her2 amplified

Herceptin (Trastuzumab) antibody inactivates HER2 protein

Her2/neu - methods







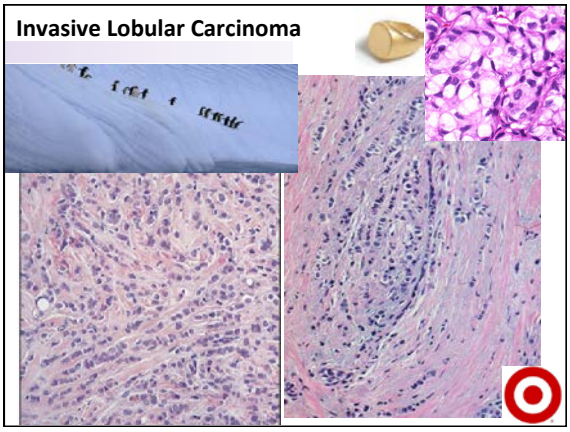
- Cells of origin for the intrinsic subtypes of breast cancer
- Expression patterns: luminal, **mesenchymal /claudin-low**, and basal-like.
- Gradients of expression (not 'on' or 'off').

Molecular/ genetic subtypes

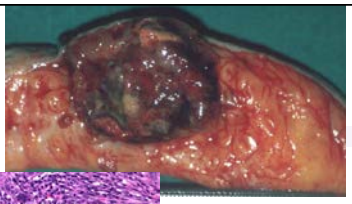
Type	ER	Her2	Cells	Other
Basal-like	-	-	Genes similar to ovarian serous carcinoma.	20% Triple negative Many BRCA1 Medullary and Metaplastic
Her-2	-	+	Poorly differentiated	10% Herceptin responsive, aggressive, poor differentiated, brain mets
Luminal A	+	-	Genes similar to lumen cells	50% in this group, ductal/lobular Tamoxifen responsive
Luminal B	+	+	Genes similar to lumen cells	20% Triple positive Standard chemotx

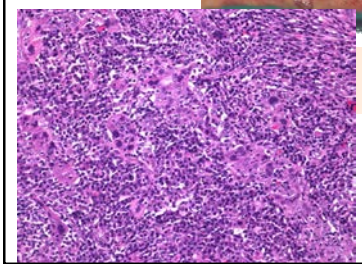
Molecular cancer groups correlate prognosis and therapy response.

Invasive Lobular Carcinoma



Medullary Carcinoma

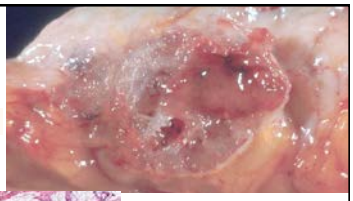


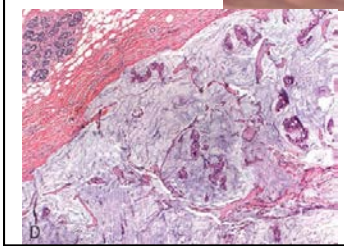


- Often BRCA1 gene +
- All triple negative Basal-type
- Better prognosis than ductal

Mucinous (Colloid) Carcinoma

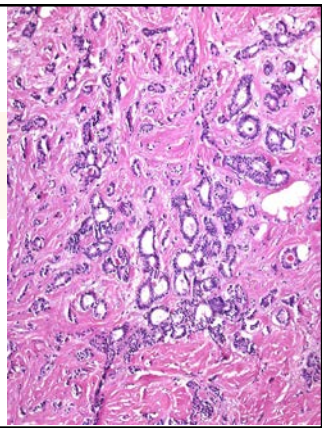
Excellent prognosis





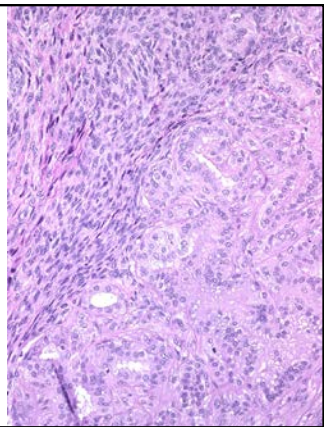
Tubular Carcinoma

- Excellent prognosis
- Comma shaped groups, low nuclear grade



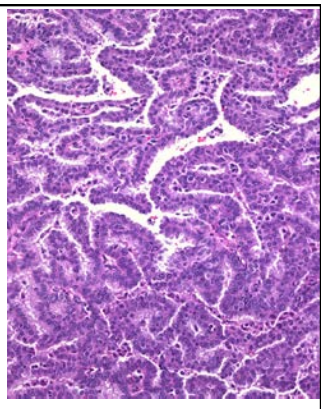
Metaplastic Carcinoma

- More aggressive than invasive ductal NOS
- Triple negative Basal-type
- Myxoid areas, mesenchymal elements



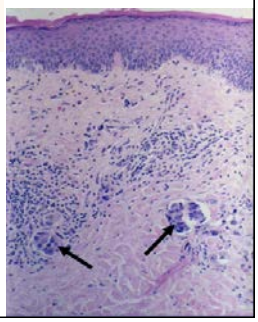
Papillary carcinoma of breast

Micro Papillary structures with vascular cores

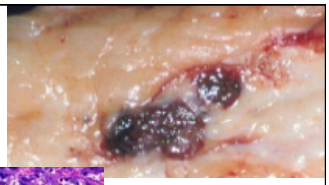


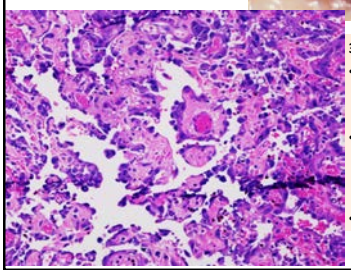
Inflammatory Carcinoma

- **Clinical diagnosis: Not histological subtype, skin with underlying carcinoma**
- **Bad prognosis**
- **Tumor plugging lymphatics**
- **DDx: acute mastitis**



Angiosarcoma





3 settings

- Spontaneous
- Post radiation :<0.5% risk post-radiation treatment
- Stewart- Treves syndrome: Chronic lymphedema from lymph node dissection
- Bad prognosis

Male Breast - Gynecomastia

Clinical

- Breast enlargement
- Palpable subareolar mass

Syndromes

- Klinefelter – XXY

Systemic disease (High estrogen)

- Cirrhosis
- Drugs
- Anabolic steroids

Carcinoma

- Rare: 0.1% (vs 1 in 8 women)
- Associated with BRCA2 mutations
- Present @ late stage

Staging-TNM

Stage	T (tumor size): Primary cancer	N:Lymph nodes	M:Distant metastasis	5-year survival
0	DCIS/LCIS	No metastasis	Absent	92
I	Microinvasive carcinoma (< 2 cm)	No metastasis	Absent	87
II	Invasive carcinoma > 2 cm	No metastasis	Absent	75
	Invasive carcinoma < 5 cm	1 – 3 positive LNs	Absent	
III	Invasive carcinoma > 5 cm	1 – 3 positive LNs	Absent	46
	Any size Invasive carcinoma		Absent	
	Invasive carcinoma with skin or chest wall involvement or inflammatory carcinoma	0 to >10 positive LNs	Absent	
IV	Any size Invasive carcinoma	Negative or positive	Present	13

Axillary lymph node status: most important prognostic factor in the absence of metastases.

Treatment

- Surgery
  - Lumpectomy (conservative)
  - Mastectomy
  - Lymph node dissection, Sentinel Lymph nodes
- Radiation
- Systemic treatment
  - Chemotherapy
  - Hormonal therapy
- Neoadjuvant :Presurgical Radiation and Chemotherapy

Treatment of high risk patient (BRCA positive)

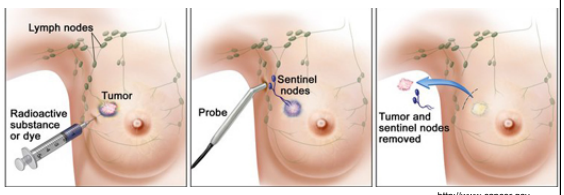
- Bilateral prophylactic mastectomy (50-90% risk)
- Oopherectomy is optional (40% risk Ovarian cancer)

- Chemoprevention (Tamoxifen)
  - Side effects
    - Venous thromboembolism
    - Increased risk endometrial cancer
    - Cataracts

Axillary node dissection

- Axillary lymph node status: important prognostic factor
- Axillary lymph node dissection
  - Stage breast cancer
  - Prevent regional recurrence of the disease.
- Risk of Lymphedema, risk of Stewart-Treves syndrome (angiosarcoma)

Sentinel node biopsy (SLNB)



http://www.cancer.gov

1-Radioactive materail +/- blue dye injected near tumor.

2-Injected material is located visually and/or with Geiger

3-Sentinel node (first lymph node to take up the material) is removed and checked for

Sufficient for staging breast cancer without signs of axillary metastasis.

?