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
    - Branch 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

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Most Common Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-35</td>
<td>Fibroadenoma</td>
</tr>
<tr>
<td>35-50</td>
<td>Fibrocystic change &gt; cancer</td>
</tr>
<tr>
<td>&gt;50</td>
<td>Cancer still proven otherwise</td>
</tr>
</tbody>
</table>

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**

- **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

**Fat necrosis**

- **Definition:** Nodular dead adipose
- **Incidence:** Prior trauma/surgery
- **Clinical:** Painless palpable mass

**Periductal Mastitis (Subareolar abscess)**

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

**Fat Necrosis**
"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

<table>
<thead>
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<th>Disease</th>
<th>Risk Ratio</th>
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<tr>
<td>No increased risk</td>
<td>Nonproliferative Fibroadenoma, Fibrosis, Cysts, Apocrine metaplasia</td>
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<tr>
<td>1.5-2x</td>
<td>Proliferative No atypia Papilloma, Sclerosing adenosis, usual ductal hyperplasia</td>
</tr>
<tr>
<td>4-5x</td>
<td>Proliferative with atypia Atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH)</td>
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<td>Ductal Carcinoma In-Situ (DCIS), Lobular Carcinoma In-Situ (LCIS)</td>
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### Fibroadenoma

- **Incidence:**
  - 3rd decade
  - Most common tumor in young adults
- **Clinical:**
  - Well-circumscribed
  - Mobile
  - Mostly painless

### 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)

http://webpathology.com

Non-proliferative Breast Changes (Fibrocystic Changes)
- Most common breast lesion
- Premenopausal
- Pain from swelling tied to menstrual cycle
- Nipple discharge

Non-proliferative Breast Changes (Fibrocystic Changes)

Radiology
- Multiple ill-defined densities usually bilaterally, no calcifications

Apocrine Metaplasia with microcalcifications
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### Prolif Breast Disease W/O Atypia

#### Intraductal papilloma

- Clinical: Bloody, nipple discharge
- Radiology: densities, calcifications

#### 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

Benign/Malignant?
- Histologic Classification
- Grading
- Staging
- Prognostic markers
- Genetics subtype

Risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Mechanism</th>
<th>Description</th>
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<tr>
<td>Age</td>
<td>Estrogen exposure</td>
<td>70% &gt; 50 y</td>
</tr>
<tr>
<td>Age of menarche</td>
<td>Estrogen exposure</td>
<td>Earlier, greater risk</td>
</tr>
<tr>
<td>First live birth</td>
<td>Estrogen exposure</td>
<td>&gt;35 y, later greater risk</td>
</tr>
<tr>
<td>1st degree relative</td>
<td>Heredity</td>
<td>1st relative with cancer</td>
</tr>
<tr>
<td>Biopsy results</td>
<td>Tumor biology</td>
<td>E.g. Atypical ductal hyperplasia</td>
</tr>
<tr>
<td>Race</td>
<td>Socioeconomic</td>
<td>AA present later stage</td>
</tr>
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Additional: exogenous estrogen exposure, radiation, carcinoma of the opposite breast or endometrial cancer, geography, diet, obesity, breast feeding, tissues
**Familial cancer syndromes**

**Tumor suppressors**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Assoc cancers</th>
<th>Function</th>
<th>Comment</th>
</tr>
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</table>
| BRCA1  | 17q21 | Breast, Ovarian               | 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**

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<th>Total Cancers</th>
<th>Percentage</th>
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<tr>
<td>CARCINOMA IN SITU</td>
<td>75%</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>20%</td>
</tr>
<tr>
<td>INVASIVE CARCINOMA</td>
<td></td>
</tr>
<tr>
<td>No-special-type carcinoma (ductal)</td>
<td>Most common</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td></td>
</tr>
<tr>
<td>Tubular ductal carcinoma</td>
<td></td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td></td>
</tr>
<tr>
<td>Mucinous (colloid) carcinoma</td>
<td></td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td></td>
</tr>
<tr>
<td>Metaplastic carcinoma</td>
<td>Least common</td>
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**Ductal Carcinoma in Situ (DCIS)**

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

**Therapy:**
- Hormone, Radiation, Surgery
DCIS

Comedo-type

Cribriform
Solid DCIS

Papillary and Micropapillary
DCIS (Noncomedo)

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

Paget’s disease

Microscopic Findings
Lobular Carcinoma In Situ (LCIS)

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, 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

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:

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
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</table>
Therapeutic markers: Hormones

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

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

Gene profiles

- 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

<table>
<thead>
<tr>
<th>Type</th>
<th>ER</th>
<th>Her2</th>
<th>Cells</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like</td>
<td>-</td>
<td>-</td>
<td>Genes similar to ovarian serous carcinoma</td>
<td>20% Triple negative, many BRCA1 / BRCA2</td>
</tr>
<tr>
<td>Her-2</td>
<td>-</td>
<td>+</td>
<td>Poorly differentiated</td>
<td>12% Herceptin responsive, aggressive,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>poor differentiated, brain metastases</td>
</tr>
<tr>
<td>Luminal A</td>
<td>+</td>
<td>-</td>
<td>Genes similar to luminal cells</td>
<td>50% in this group, ductal/lobular</td>
</tr>
<tr>
<td>Luminal B</td>
<td>+</td>
<td>+</td>
<td>Genes similar to luminal cells</td>
<td>20% Triple positive, standard chemotherapies</td>
</tr>
</tbody>
</table>

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

Tubular Carcinoma

- Excellent prognosis
- Comma shaped groups, low nuclear grade

Metaplastic Carcinoma

Papillary carcinoma of breast

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

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
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)
- Oophorectomy 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)

1- Radioactive material +/- blue dye injected near tumor.
2- Injected material is located visually and/or with Geiger counter.
3- Sentinel node (first lymph node to take up the material) is removed and checked for cancer cells.

Sufficient for staging breast cancer without signs of axillary metastasis.

http://www.cancer.gov