Today’s Goals:
By the end of the lecture you will be able to:

1. Describe the clinical presentation of common breast pathologies
2. Explain what "fibrocystic change" means and discuss several of the most common benign lesions of the breast
3. Recognize and describe the pathology associated with the common types of breast cancer
4. List and discuss the major prognostic factors in breast cancer
5. Explain why testing for expression of estrogen receptor and Her2/neu is an important part of breast cancer analysis
Structure of Lecture

1. Review anatomy/histology
2. Clinical presentations of breast disease
3. Benign breast diseases
4. In-situ neoplasms
5. Malignancies
   a. Classification
   b. Prognosis/treatment
6. Additional topics (not covered in lecture)
   a. Special presentations of breast cancer
   b. Male breast
Embryology of the Breast

• Modified sweat gland
• Mammary ridge in embryo -- multiple potential breasts
• Only one on each side develops normally
• Accessory breasts 1% of population, male or female, anywhere on mammary ridge from axilla to groin

breast is a modified sweat gland that forms on the mammary ridge

multiple nipples in development--as for cats and dogs--but people usually only develop one on each half of the body

you will see the mammary ridge on the next slide
Accessory Breast

usually just cosmetic addition, but anything that can occur in a normal breast can occur in an accessory breast (e.g., cancer)
Breast, Anatomy

basically two components: ducts and lobules

what you see in the following slides is NORMAL

lobules (which aren't super distinct in the breast tissue) make milk that empty into ducts
Breast, Normal TDLU

whole bunch of lobules pictured here

Terminal duct lobular unit
Terminal Duct Lobular Unit

- **Lobule** composed of small glands (acini)
- Acini grow at **puberty**; suppressed by even low levels of testosterone
- Acini and duct lined by **2 cell layers**
  - **Myoepithelial** cells (outer cell layer)
    - Flattened cells, often clear cytoplasm
  - **Epithelial** cells (inner cell layer)--most cancers derived from this layer

TDLU is a lobule composed of acini that develops at puberty (though suppressed by testosterone in men)--composed of two cell layers.
Breast Anatomy

Myoepithelial cells
Epithelial cells
Normal Lobule
Normal Acini
Stroma

- Large variation in amount of fibrous stroma
- Varies between individuals, and with menopause/hormone status within individual over time.
Normal Breast

Both images are totally normal: fatty and fibrous
Variation in normal mammograms

Fatty--radiolucent

"easier" to pick out cancer amidst dark background

Fibrous--radiodense

very difficult to pick out cancer in this background

Mixed-heterogenous

a bit harder to pick out cancer amidst background

examples of how variation in normal stroma from individual to individual can challenge current mammography
Benign Breast Lesions

• Non-neoplastic
  – Inflammatory
  – Fibrocystic changes
  – Proliferative breast changes
  – Proliferative breast disease with atypia

• Benign neoplasms
Benign Breast Lesions

Why do we care?

• Many can **mimic malignancy**:
  – Lumps on physical exam
  – Microcalcifications or masses on mammograms
  – Bloody nipple discharge

• Some are **risk factors** for developing future breast cancer

• **Benign** lesions are much **more common** than cancers.
Breast Disease:
A common reason to see the Doctor!

- 16% of women in large group practice sought medical attention for breast symptoms over 10 year period
- Only 4% of visits for breast symptoms resulted in dx of cancer

again, benign breast lesions are COMMON
Breast Disease:
Most common clinical presentations

- Pain
  - Rarely is sole sign/symptom of CA
- Palpable mass ("lump")
- Bloody nipple discharge
- Mammographic Abnormalities
  - Density (mass)
  - Microcalcifications.
Unlike medical school professors, most breast lesions are benign.
Mastitis is inflammatory condition that can be described as ACUTE (bacterial) or PLASMA CELL (non-bacterial)

Inflammatory Conditions

Mastitis

• **Acute mastitis:** Bacterial infection, usually while beginning nursing
  – Red, hot, swollen, painful breast
  – Can develop abscess, extensive tissue destruction

• **Plasma cell mastitis:** Non-bacterial, chronic irritation from secretory products
  – Usually in multiparous woman, nursing

we’re talking about INFLAMMATORY conditions for the next several slides

usually when skin breaks
Fat Necrosis—occurs after trauma to fat, release of fatty acids, with marked inflammatory response. Heals by scarring. Excellent cancer mimic—rock hard, spiculated mass; microcalcifications on mammogram.

The trauma doesn't have to be "that severe" for this to occur.
Histology of fat necrosis

*macrophages full of fat help to distinguish Fat Necrosis from Breast Cancer--phew!*
Mammogram, fat necrosis

horrifying image: dense white spiculated lesion>>looks for all the world like BC but it's Fat Necrosis
Inflammatory Conditions

Duct Ectasia

- Inflammation destroys duct wall
- Common cause of nipple discharge
- Microcalcifications can mimic cancer

Duct Ectasia: inflammation destroys duct wall, nipple discharge, microcalcifications mimic cancer
Duct Ectasia: low power

Duct ectasia

Normal duct

fibrous capsule around it
Duct Ectasia: high power

- Lumen is full of macrophages
- Inflammatory cells around rim
- Hemosiderin down here
Benign Epithelial Lesions

• Nonproliferative changes
  – Fibrocystic change
  – Fibroadenoma

• Proliferative breast disease
  – Epithelial hyperplasia
  – Sclerosing Adenosis
  – Radial Scar
  – Intraductal papilloma
Fibrocystic Change

- **Not a disease!** Normal change, doesn't hurt patient at all; starts 30s-40s in women
- A group of processes which are related only by the fact that they tend to occur together.
- Represents exaggerated response to hormonal stimulation
- **Present in most women** (>80%) common
- **No increased risk** for cancer

Fibrocystic change is not a disease; rather, it's a common exaggerated response some women have to hormonal stimulation. No increased risk for BC.
Fibrocystic Change
aka Non-Proliferative Breast Changes

- Fibrosis
- Cysts
- Metaplasia
  - Apocrine
  - Columnar

three characteristics of fibrocystic change: Fibrosis and cysts (hence the name); also, metaplasia
Fibrocystic Change

“Fibrosis”

1/3 parts of FCC

- Localized areas of fibrous tissue is common cause of lump
- This gets called “fibrosis” implying an increase over normal... but it is just normal breast tissue.
- Fibrous tissue in breast is NORMAL
Breast, fibrosis

lots of collagen >> dense fibrosis
Fibrocytic Change
Cysts

• Cysts are extremely common
• Multiple, bilateral
• Fluctuate over time
• Disappear with fluid aspiration
Fibrocystic Change

Cysts

- Translucent “blue dome” cysts
- Clear colorless fluid
- Lined by simple cuboidal epithelium

can be quite dramatic clinically--multiple cysts/breast
Fibrocystic Change

Apocrine Metaplasia

• **Replacement** of ducts or lobules with apocrine-type epithelium
  – Apocrine epithelium *normal in axillary and groin sweat glands*
  – **No clinical significance**
  – Often seen in cysts
Cyst with Apocrine Metaplasia

Cyst

Apocrine Metaplasia (pink!)

Cyst

very "eosinophilic"/pink

we want to see only one layer

apocrine metaplasia: very eosinophilic (pink)
**Fibroadenoma**

- **Most common benign** neoplasm of the breast
- Most common in **teens and twenties**; second peak around **menopause**
- Proliferation of ducts AND stroma -- **"biphasic neoplasm"**
- Hard, round, well circumscribed nodule; can mimic cancer
- Often **diagnosed clinically**, not biopsied

Pop quiz: name the characteristics of fibrocystic change
Fibroadenoma

proliferating DUCTS and STROMA
it is pushing things out of the way,
NOT invading
(these are classic features for a
"benign" neoplasm)
Proliferative Breast Disease

A group of benign proliferative processes, distinct from non-proliferative change because they are markers for a slightly increased risk (1.5-2x) for breast cancer in the future, not concurrently.

- Moderate to florid epithelial hyperplasia
- Sclerosing adenosis
- Radial scar/complex sclerosing lesions
- Papilloma

We're going to look at the four listed.

Now we're talking about lesions that DO INCREASE THE RISK for BC.
Proliferative Breast Disease
Epithelial Hyperplasia

- Proliferation of epithelial cells within ducts and acini
- Classified as ductal (usual type) or lobular
Proliferative Breast Disease
Epithelial Hyperplasia

- Always an **incidental** finding
- Does not make lump or microcalcifications
- Graded from mild to severe (florid)
- **Important mostly as risk factor**
  - Patients with moderate/florid hyperplasia have 1.5-2.0 relative risk for developing breast cancer over 20 year f/u.
Mild Epithelial Hyperplasia

increase in ductal epithelial cells
Florid Epithelial Hyperplasia

remember, still "benign" only serves as a risk factor
Proliferative Breast Disease
Sclerosing Adenosis

- **Adenosis** = Proliferation of small acini and terminal ducts

- **Sclerosing** Adenosis: Most common type
  - Adenosis with associated *stromal fibrosis*
  - Found in 12% of biopsies
  - Can *mimic cancer*, mass and microcalcifications

SA: more ducts and fibrous tissue by definition; fairly common, can mimic cancer
Sclerosing Adenosis

- Big lobule, expanded terminal duct
- Pink stuff is vast sclerosis (fibrosis)
- Again, increased risk of breast cancer
Proliferative Breast Disease

Radial Scar

- **Misnomer**, not related to trauma
- Stellate proliferation of ducts and acini around a central scar-like area of fibrous and elastic tissue.
- Often **mimics cancer** mammographically (**spiculated mass** with microcalcifications)
Radial Scar

- scar-like, has "arms"
- epithelial, glandular stuff around periphery, trapped by the radial scar

not a scar in literal sense
Intraductal Papilloma

- Proliferation of papillary fronds within dilated duct
- Large ducts beneath nipple
- Most common cause of bloody nipple discharge

"cauliflower"

Typically resected because bloody nipple discharge often signify something terrible wrong.
Intraductal Papillomas

- Typically grows in large ducts

- bloody, necrotic
Intraductal Papilloma

totally benign, but causes bloody nipple discharge

stalk, branching "cauliflower-like" branching within duct
Proliferative Breast Disease With Atypia

A group of benign proliferative processes, distinct from fibrocystic change because they are markers of high risk (4-5x) for breast cancer in the future.

- **Atypical** Ductal Hyperplasia
- **Atypical** Lobular Hyperplasia
Proliferative Breast Disease With Atypia

Atypical Ductal Hyperplasia

- Has some but not all features of in-situ carcinoma
  - Probably precursor to in-situ carcinoma, like dysplasia in cervix
- Usually detected because of Ca++
- Approximately 5% of biopsies
- Moderate increase in risk for cancer
Atypical Hyperplasia

atypical because the punched out lumen is pattern for in situ carcinoma
that's all for benign--they increase RISK
Malignant Neoplasms of the Breast
Breast Cancer

- Subject of intense scientific investigation
- Major advances in breast-conserving therapy and reconstruction
- Major focus of cancer screening (mammography, self-exam)
- Only recent years have seen a modest impact on mortality rate
Malignant Neoplasms

- Basic epidemiology
- In-situ carcinoma
  - Ductal carcinoma in-situ
  - Lobular carcinoma in-situ
- Invasive carcinoma
  - Ductal
    - Special ductal subtypes
  - Lobular
- Prognostic and treatment factors
  - ER/PR, Her2/neu, genomic
- Special presentations of breast cancer
Breast Cancer
Fast Facts

• 192,370 est. new cases 2009
  – 40,170 deaths

• **One in 8 women** will develop breast cancer

• **One in 35 women** will die from breast cancer

• **31%** of all cancers in women

*excluding skin cancers, which are always excluded it seems*
Cancer Death Rates* Among Women, US, 1930-2005

Death Rate--mostly stable but now have downward trend

*Age-adjusted to the 2000 US standard population.
Cancer Incidence Rates* Among Women, US, 1975-2005

*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Risk Factors for Breast Cancer

• Age
• Family history
• Specific gene mutations: BRCA1, BRCA2, p53
  – very high risks (50-80%) for affected families, but uncommon causes of breast cancer overall
  – also have increased risk of other cancers (ovary, other)

most breast cancer is SPORADIC--the above mutations are relatively rare and contained intrafamilially
Risk Factors...

- Prolonged *estrogen* exposure
  - early menarche, late menopause, birth control pills
- **Late or no** pregnancy  
  lactation is protective
- High risk *findings* in previous breast biopsy
- **Radiation**, esp. as teenager or young adult
- Breast feeding is **protective**

**Notes:**
- more RFs for BC: estrogen, late/no pregnancy, previous breast findings, radiation
- breastfeeding DECREASES the risk for BC
Pre-invasive Malignancy

• Ductal Carcinoma in Situ (DCIS)
  – Synonym: Intraductal Carcinoma
  – Direct precursor to invasive carcinoma.
  – Malignant cells proliferating within duct, no invasion through basement membrane (no metastatic potential)
  – Spread within duct system; can involve very large area
  – Microcalcifications on mammogram

DCIS: precursor to invasive carcinoma; can be very widespread, microcalcifications
Ductal Carcinoma In Situ

dilated ducts, with central necrosis common in some kinds of DCIS

necrosis

large, pleomorphic, mitoses

mitosis
Mammogram, DCIS

Microcalcifications
Pre-invasive Malignancy...

• **Lobular** Carcinoma in Situ (LCIS)
  – Proliferation of **small** bland cells within lobule
    small and uniform, grows in lobule as opposed to duct
  – **Probably not direct precursor**
    • patients have high risk of developing invasive cancer (10x), but risk is **bilateral**, not at site of LCIS
    • Not really carcinoma in situ --just marker of risk
  – **Treated differently** than DCIS

LCIS: likely NOT a direct precursor but rather a marker of risk; pts have increased risk of BILATERAL invasive cancer>>thus, it is treated differently
Invasive Neoplasms
Invasive Adenocarcinoma Classification

- Invasive Ductal adenocarcinoma
  - No special type (NST, NOS)
  - Special subtypes -- better prognosis
    - Medullary
    - Mucinous
    - Tubular
- Invasive Lobular adenocarcinoma

Two types of invasive Adenocarcinoma: ductal and lobular>>ductal is divided into not special and special
Invasive Ductal Adenocarcinoma

- **Most common**, 70% of breast cancers
- Incites prominent fibrous reaction ("desmoplasia") -- accounts for clinical presentation
  - Rock hard, "scirrhous" or chalk-like, spiculated mass
  - Grows into surrounding tissue--skin dimpling, nipple retraction
- **Poorest prognosis**
Invasive Ductal Adenocarcinoma

Spiculated Mass

IDA-spiculated mass
spreads out and pulls surrounding breast tissue into the lesion
Invasive ductal adenocarcinoma

Mammogram

"fingers radiating out, strings pulling breast tissue into itself"

feels very hard and "chalky"
Invasive Ductal Adenocarcinoma

- **Irregular and complex** duct or gland-like structures
- **Malignant** epithelial cells
  - nuclear enlargement, pleomorphism
  - prominent nucleoli
  - frequent mitoses
  - no myoepithelial cell layer

always think of these characteristics when describing cancer histologically

also for prostate
Invasive Ductal Carcinoma

irregular branching glands going thru surrounding stroma

"adenocarcinoma"
Special Types...

• **Medullary carcinoma**
  
  – Well circumscribed, soft
  
  – Prominent lymphoid infiltrate
  
  – Paradoxically, despite relatively good prognosis, most anaplastic tumor cells of any type.
    
    • No ducts or glands
    
    • High grade nuclei
  
  – Rare, less than 1% of breast cancers
Medullary Carcinoma

note that it is well-circumscribed
Special Types...

- **Mucinous Carcinoma**
  - Synonym: Colloid carcinoma
  - *Well circumscribed, mucinous* consistency
  - “*Islands* of tumor floating in a sea of mucin”
  - Approximately 1-5% of breast cancers
Special Types...

• **Tubular Carcinoma**
  - Extremely well differentiated ductal carcinoma
  - Composed entirely of **simple tubules** lined by a **single layer** of cells
  - Can be confused with benign lesions (radial scar)
    - No myoepithelial cell layer
  - Extremely good prognosis; no deaths reported when <1cm
  - 5% of breast cancers

Tubular: extremely well-differentiated ductal cells; can be confused with benign lesion; great prognosis with excision
Tubular Carcinoma

Which is the Cancer?
Tubular Carcinoma

Which is the Cancer?

Carcinoma ➔

Normal (note ME cell layer)

single layer!!!
Invasive Lobular Carcinoma

- **5-10%** of breast cancers
- Originates in **TDLU**, same cell type as ductal
  - often mixed with ductal carcinoma
- **Does not incite fibrous response**; may be difficult to detect
  - Single file pattern of spread-”Indian file”
- Prognosis similar to ductal carcinoma, NST
Invasive Lobular Carcinoma

- Normal dense fibrous stroma of breast up here
- Blue are tumor cells
Invasive Lobular Carcinoma

Note the single file pattern of invasion.

little to no stromal response to cancer cells

Entrapped benign duct
Behavior of Breast Carcinoma

- **Local recurrence**
  - Can ulcerate through skin, invade chest wall

- **Lymphatic/hematogenous metastases**
  - Local metastases to axillary nodes (most common); internal mammary nodes, supraclavicular nodes less common
  - Distant metastases to lung, liver, bone, brain common sites
Breast Cancer - Local recurrence

Breast cancer ulcerating through skin
Breast cancer metastases in vertebra
Key Prognostic Factors

- **Stage** of disease
  - Tumor size
  - **Axillary node status** -- single most important prognostic feature, predicts distant metastases
- **Tumor grade:** well differentiated vs. poorly differentiated
- **Margins** of resection: local recurrence likely if tumor in margins

For prognosis, we need to know stage and grade--axillary node status is CRITICAL
Estrogen/Progesterone Receptors

Important for both prognosis AND treatment

- ER/PR negative tumors have worse prognosis
- ER/PR positive tumors respond to anti-estrogen agents (e.g. tamoxifen, raloxifene, aromatase inhibitors)
Estrogen Receptor Immunostain

(Brown nuclear staining)
Her2/neu

• Aka c-erb-B2, human epidermal growth factor receptor 2
• Gene is amplified in 25% of breast cancers, with associated protein overexpression
• Her2 amplified tumors respond to treatment with anti-Her2 antibody (Herceptin)
Her2 in Breast Cancer

Immunohistochemistry

Strong membrane staining

FISH - Her2 amplified

Her2 signal >> Centromere 17 signal
Molecular Studies

- Oncotype Dx
- 21 gene rtPCR molecular test
- First of many likely molecular tests for breast cancer
  - **Prognostic:** Predicts 10 year disease free survival in ER positive tumors
  - **Predictive:** Likelihood of response to chemotherapy.
Summary

• Described the clinical presentation of common breast pathologies
• Explained what "fibrocystic change" means and described several of the most common benign breast lesions.
• Described the common types of breast cancer
• Discussed major prognostic factors in breast cancer
• Explained why testing for expression of estrogen receptor and Her2/neu is an important part of breast cancer analysis
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For more details Pathology 448C—Practical Surgical Pathology (4th year elective)
Additional slides for those who have an unquenchable thirst for knowledge
Unique Manifestations of Breast Cancer

Or two things to know about that will help you avoid unpleasant encounters with malpractice lawyers!
Paget’s Disease

- Eczematous, scaly, red rash around nipple
- Represents ductal carcinoma in-situ invading epidermis of nipple
- Frequently not recognized clinically—diagnosis of breast cancer delayed
Paget’s Disease
Diagram of Paget's

skin surface (Epidermis)

Intraductal carcinoma cells grow out duct orifice onto skin surface

Nipple Duct
Paget’s Disease of the Nipple

Epidermis

Tumor cells
Remember...

1. Rashes around the nipple can represent breast cancer.
2. When your patient discovers that you’ve been treating her breast cancer with topical steroids, she will not be pleased!
Inflammatory Carcinoma

- Diffusely red, swollen, hot breast
- Associated with very poor prognosis (considered T4 disease)
- Skin biopsies show plugging of dermal lymphatics by tumor cells
- Closely mimics infection (cellulitis) but does not respond to antibiotics; often not recognized clinically—diagnosis delayed
Inflammatory Carcinoma
Inflammatory Carcinoma

Skin Biopsy

Tumor in dermal lymphatics
Remember…

1. “Cellulitis” in the breast can represent breast cancer
2. Six weeks of antibiotics will not cure breast cancer!
Male Breast

• Gynecomastia
  – Enlargement of male breast
  – Relative estrogen excess: puberty, old age, cirrhosis, estrogen secreting tumors.

• Carcinoma -- rare
  – <1% of breast cancer occurs in men
  – Strong association with BRCA2

• Other pathology rare
Gynecomastia

Note absence of lobules!
The End (Really!)