Lecture Objectives

1. Understand the epidemiology of breast cancer
2. Illustrate common breast anatomy
3. Discuss gene susceptibility mutations
4. Know the screening and diagnostic modalities
5. Discuss the common benign breast diseases
6. Know the classification, diagnosis and therapeutic approach to benign breast disease, non-invasive and invasive breast cancers
Epidemiology of breast cancer

2018: 268,670 new cases/Deaths 40,920

Females: 266,620 most common (30%)
Females: 40,920 deaths (14%)  2nd only to lung cancer
Males: 2550 new cases; 480 deaths (1%)
AGE

Birth - 39: 1 in 207  
40-59: 1 in 24  
60-79: 1 in 13  
Birth to death: 1 in 7


2% of breast cancers <30; 70% Dx’d > 50

Kearny & August: ACOS Breast Disease Curriculum, 2003

NO AGE GROUP IN WHICH THE PROBABILITY OF HAVING BREST CA IS ZERO

Proven Risk Factors

• Gender  F:M-100:1  
• Age  
• Family history  
• High risk lesions (ADH, ALH, LCIS)  
• Early menarche, late menopause  
• Nulliparity or first birth after age 30  
• Radiation exposure  
• HRT

Kearny & August: ACOS Breast Disease Curriculum, 2003

Risk Estimation Models - Gail

• Based on age, menarche, age at 1st life birth, previous biopsies, atypical hyperplasia, breast cancer in 1st relatives  
• Provides 5-yr and life time (to age 90) risk estimate  
• If for example, 5-yr risk ≥1.66%, consider chemoprevention  
• Overestimates risk in women not screened regularly  
• Not useful in pts with prior breast cancer, DCIS or LCIS  
• Not applicable if family history suggests HBC

Kearny & August: ACOS Breast Disease Curriculum, 2003
Risk Estimation Models- Claus

- Includes information about:
  - Age at onset
  - No. of breast ca.
  - Paternal and maternal relatives

- Useful for women with a strong family hx of breast cancer with unknown BRCA1 and BRCA2 status

Kearny & August: ACC Breast Disease Curriculum, 2003

Primary Prevention of Breast Cancer

Lifestyle prevention strategies
  - smoking, alcohol, obesity, estrogen replacement

Chemoprevention
  - Endocrine (anti-hormonal therapy)

Prophylactic surgery
  - Gene susceptibility (BRCA1&2, ?PALB-2)
  - Risk reduction-benign breast

Primary Prevention of Cancer - Nutrition

Overweight and obesity as risk factors for cancer outweigh the impact of any other dietary consideration

Obesity – associated cancer:
  - Postmenopausal breast
  - Endometrial cancer
Primary Prevention of Cancer - Nutrition

<table>
<thead>
<tr>
<th>Carcinogenic processes influenced by diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free radical formation</td>
</tr>
<tr>
<td>Antioxidants: Tocopherols, carotenoids, ascorbic acid, uric acid, selenium as a cofactor</td>
</tr>
<tr>
<td>DNA adduct formation</td>
</tr>
<tr>
<td>Folate deficiency and folic acid depletion and DNA adducts</td>
</tr>
<tr>
<td>Chemical Carcinogen potency</td>
</tr>
<tr>
<td>Raw vegetables contain phytochemicals which induce Phase II enzymes, promoting excretion</td>
</tr>
<tr>
<td>Abnormal growth promotion</td>
</tr>
<tr>
<td>Cherries, citrus, berries contain monoterpene &amp; polyphenol, inhibiting G protein anchoring</td>
</tr>
<tr>
<td>Abnormal hormone control</td>
</tr>
<tr>
<td>Retinoic acid, retinoids to modulate complex with the retinoid X receptor to promote cell differentiation and induce cell cycle arrest; phytoestrogens in many fruits/vegetables</td>
</tr>
<tr>
<td>Abnormal immune surveillance</td>
</tr>
<tr>
<td>Immune function promoted by low-energy diet, low fat diet, high omega-3 to omega-6 fatty acid ratio, adequate intake of vitamins and carotenoids</td>
</tr>
</tbody>
</table>

Primary Prevention of Breast Cancer (Chemoprevention)

Five-year Gail model risk must be 1.7 % or above

Drug Choices

- Tamoxifen – premenopausal women/ women who have had a hysterectomy
- Raloxifene - postmenopausal women

Primary Prevention of Breast Cancer (Chemoprevention)

Efficacy
49% relative risk reduction after a five year course of therapy

Interpretation Estimate for Patient:

- "After 5 years of treatment, your lifetime risk can be reduced almost in half."
- Use now extending out to 10 years in selected instances
- So if Gail model lifetime risk was 20%, it could be reduced to almost 10%
TRIAD OF BREAST CANCER SCREENING

MAMMOGRAPHY

SELF EXAM

CLINICAL EXAM

Breast Cancer Stage and Five-Year Survival

99% survival rate

Localized

83% survival rate

Spread to regional lymph nodes

Efficacy of Mammography Screening

20 – 25%

Mortality Reduction in Screened Populations
Clinical Breast Examination

Reasons to perform annual screening CBE:

- High-quality patient care
- Good risk management
- Improved quality of life for patients

Breast Self-Exam (BSE)

Randomized Studies: No effect

Reasons to promote BSE:
- Reinforces provider-patient partnership
- Reinforces patient’s role in her healthcare
- Good risk management

Mammography Screening Guidelines

Normal Risk Women

<table>
<thead>
<tr>
<th>Age</th>
<th>AAFP</th>
<th>ACOG</th>
<th>ACR</th>
<th>ACS</th>
<th>USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 49</td>
<td>Counsel</td>
<td>Annual</td>
<td>Annual</td>
<td>*See below</td>
<td>1-2 Yrs</td>
</tr>
<tr>
<td>50 - 74</td>
<td>Biannual</td>
<td></td>
<td></td>
<td></td>
<td>NR#</td>
</tr>
<tr>
<td>≥ 75</td>
<td></td>
<td></td>
<td>Annual</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ACS: 40-44: Counsel
45-54 Annual
55 and older every 1-2 years

NR# = No Recommendation
ACS Breast Ca Screening Guidelines

• Age 20–39
  CBE; monthly BSE (optional); MGM baseline at 35 and at >25 if risk is increased
• Age ≥ 40
  Annual MGM, CBE; monthly BSE (optional)

• MGM and CBE are complementary as 10–15% of breast cancers are only detected by CBE

Screening in High Risk Populations

Annual Screening MGM & MRI beginning at age 30 for:

Evidence Based
• known BRCA carriers
• 1st degree relative of BRCA carrier (untested)
• >20-25% lifetime risk

Expert Consensus Opinion
• Radiation to chest between age 10 and 30 years
• Li-Fraumeni syndrome and first-degree relatives
• Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives

Screening MRI:
Insufficient Evidence for or against

• Lifetime risk 15–20%, as defined by BRCAPRO

• Lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH), atypical ductal hyperplasia (ADH)

• Heterogeneously or extremely dense breast on mammography
Effect of Screening on Mortality from Breast Cancer

- In the US, 1975-2000: total reduction in mortality rate using 7 statistical models - 28 to 65% (median, 46%).
- By 2000, approx. 70% of women >40 had MGM in the previous 2 yrs.

Berry et al: NEJM 2005;353: 1784-1792

Findings Suggestive of Hereditary Breast Cancer (HBC)

- HBCs constitute 5-10% of all breast ca.
- Multiple generations
- Multiple 1st relatives
- Premenopausal breast ca
- Bilateral breast ca
- Family h/o ovarian ca
- Family h/o other cancers


Proportion of Breast Cancer Attributable to Known and Unknown Germline Genetic Mutations

Genes Associated with HBC

- BRCA1
- BRCA2
- P53 (Li-Fraumeni syndrome)
- CD1 (Cowden Syndrome)
- Possibly ATM (Ataxia Telangiectasia Mutated)

BRCA1 & BRCA2 Genes

**BRCA1**
- Chromosome 17q21
- 40-50% of HBC
- 50-85% risk of female breast ca
- 2nd breast cancer risk up to 65%
- Ovarian ca - 20-40%
- Male breast cancer-up to approx. 6%
- Probable increased risk of prostate ca
- Possible increased risk of colon ca

**BRCA2**
- Chromosome 13q12
- 33-50% of HBC
- 50-85% risk of female breast ca
- 2nd breast cancer risk 50%
- Ovarian ca - 10-20%
- Male breast ca - 6%
- Increased risk of prostate ca
- Possible increased risk of colon ca

HBC Management

- Monthly BSE starting at age 18 y
- CBE, semiannually, starting at age 25
- Annual MGM and breast MRI screening starting at age 25, or individualized based on earliest age of onset in family
- Discuss option of risk reducing mastectomy on case-by-case basis and counsel regarding degree of protection, reconstruction options
- Consider chemoprevention, discussing risks and benefits
- Advise about risk to relatives, genetic counseling and possible testing for at-risk relatives
- Education regarding signs and sx of cancer(s) esp. those associated with BRCA gene mutations

NCCN Practice Guidelines v.1.2006
Classification of Breast Disease

Malignant
- In-situ: ductal or lobular
- Invasive: ductal or lobular

Benign
- Fibrocystic change
- Fibroadenoma
- Cyst
- Papilloma
- Inflammatory conditions

Signs & Symptoms of Breast Disorders

Non-palpable mammographic abnormalities
- Breast pain
- Mass or asymmetrical thickening
- Nipple discharge
- Skin or nipple changes on observation

Signs & Symptoms of Breast Disorders:

- Non-Palpable
- Mammographic
- Abnormalities
Screening Mammogram

• Asymptomatic pts
• Craniocaudal (CC) and Medial-lateral oblique (MLO)
• Previous images essential

• If screening is abnormal or inconclusive additional diagnostic imaging (special views and US) may be necessary
**BIRADS—Breast Imaging Reporting And Data System**

0-incomplete study  
1-normal  
2-benign  
3-probably benign (get follow-up study 3-6 months)  
4-suspicious  
5-highly suspicious  
6-known cancer

---

**Occult Mammographic Abnormalities**

5-10% of screening mammograms need “call back” for diagnostic views  
50-60% of diagnostic studies will resolve the initial problem

---

**Two major types of mammographic abnormalities**

Calcifications  
Densities
Occult Mammographic Abnormalities

INITIAL WORK UP – BIRADS 0 - Density

1. Diagnostic mammogram - Cone or spot compression
   Magnification views

2. +/- Ultrasound

Occult Mammographic Abnormalities

BIRADS 3 Mammogram - OPTIONS

Interval mammography/ultrasound*
(usually 6 months interval)
Image-guided biopsy*
Surgical removal

Occult Mammographic Abnormalities

BIRADS 4 or 5 Mammogram OPTIONS

Image-guided biopsy
Surgical removal
Occult Mammographic Abnormalities--Work-up
Interventional Procedures

Image-guided biopsy
  Ultrasound
  Stereotaxic

Surgical excision
  Needle localization/biopsy
Signs & Symptoms of Breast Disorders

Non-palpable mammographic abnormalities
Breast pain
Mass or asymmetrical thickening
Nipple discharge
Skin or nipple changes on observation

TAKE A 10 MINUTE BREAK

DISEASE PROCESSES AND THERAPY
BREAST PAIN

Most common breast complaint
Precipitates anxiety and worry
Etiology often unknown
Self-limited in 80% - 85% of patients

Management of Breast Pain

Reassurance
no sign of breast cancer
common symptom
self-limited

Eliminate caffeine may affect pain, but not nodularity or cancer

Lower estrogen dose, wean from estrogen, or substitute different estrogen

Evening primrose oil (3 gram/day)

Signs and Symptoms of Breast Disorders:

Breast Mass

Benign
Cyst
Fibroadenoma
Fibrocystic mass

Malignant
Asymmetrical Thickening
Breast Mass/Asymmetry
Management of a Breast Cyst

Mass Resolves or Fluid Not Bloody
Discard Fluid Follow-up 4-6 wks
No Recurrence
Routine Screening

FNA Cyst & Fluid Bloody
Recurrence
Biopsy

Residual Mass after FNA

Breast Mass/Asymmetry
Mass Solid
Core BIOPSY

Signs and Symptoms of Breast Disorders
NIPPLE DISCHARGE
Non-Spontaneous
Normal Physiology (cyst, duct ectasia, papilloma)
Spontaneous
Pathology (intraductal papilloma, malignancy)

bloody
white
green

clear (watery)
yellow
Breast Evaluation

• The ultimate goal is to classify findings as:
  ➢ Normal
  ➢ Clearly benign
  ➢ Possibly malignant
  ❖ *Not always readily apparent hence, consultation is necessary*

Breast Evaluation

abscess or cancer?

BLOODY NIPPLE DISCHARGE
NON-HEALING NIPPLE ULCER (Paget's)

Neglected locally advanced

INFLAMMATORY CANCER
PEAU D’ORANGE
(breast swelling – Cooper’s ligaments)

Dimpling

Neglected Advanced Breast Cancer
Diagnostic Studies

- Diagnostic MGM
- Breast US
- Breast MRI
  - Percutaneous Bx
  - FNAB
  - Needle core bx
  - Image guided vs non image guided
  - Open bx

Diagnostic MGM

- Done when signs or symptoms are present
- Review of previous images when available
- Often includes specialized views such as spot compression and magnification

Breast U/S

- *Not used for screening*
- Distinguishes a solid from cystic lesion
- Adjunct to MGM
- Used for guiding percutaneous bx of solid
- Nodules palpable and nonpalpable
- *Not useful* for bx of microcalcifications
Breast MRI

- Very limited use—**no role for screening**
- High risk young women with very dense breasts with nondiagnostic MGM
- Post neoadjuvant chemotherapy to assess for BCT
- Pts with silicon breast implant
- Must be done in a dedicated center with experience in interpreting breast MRI and capable of MRI directed bx

FNA

- Image guided—US or stereotactic but not absolutely necessary
- Simple, low morbidity and expeditious - can have the result at time of visit if a cytopathologist is available
- Sensitivity 65-98%
- False positives rare, about 0.2%
- Requires a skilled cytopathologist
- **Gives cytology and NOT histology** -cannot distinguish invasive from noninvasive ca
- **Unless it is clearly benign, suspicious, or shows cancer cells, it is nondiagnostic; Repeat FNA or use alternative bx technique**

Needle Core Bx

- Image guided—stereotactic or US but not necessary for an easily palpable mass
- **Gives histology, thus, can distinguish in situ from invasive cancer**
- Requires at least 24hrs to have the result
Stereotactic Bx

- Smaller scar than open bx and minimal anesthesia
- Accuracy=99%, similar to wire localized excisional bx; however, if malignant, wire localized excision will be required
- Discordant results require further evaluation
- MGM follow up of benign bx at 6 months
- Contraindicated if pt cannot lie prone, lesion too faint or superficial for digital imaging

U/S Guided BX

- More comfortable and quicker than stereotactic bx
- Not useful for lesions not seen on U/S such as microcalcifications
- Discordant results require further evaluation
- US and MGM follow up benign bx at 6 months

Excisional Open Bx

- The highest accuracy for DX but more invasive than percutaneous bx
- Combined with wire localization for nonpalpable lesions
- Specimen imaging mandatory for wire localized excision
Specific Benign Entities

- Fibrocystic condition
- Mastodynia
- Simple cyst
- Complex cyst
- Fibroadenoma
- Gynecomastia
- Nipple Discharge
- Breast Abscess

Fibrocystic Condition (Changes)

Clinical manifestations of breast tissue response to cyclical hormonal changes

Often associated with mastodynia or mastalgia

Pathological Changes Sometimes Associated with Fibrocystic changes

- Non-proliferative changes (RR=1.0) - cysts, mild hyperplasia of the usual type
- Proliferative lesions without atypia (RR=1.5-2.0)-moderate or florid hyperplasia, intraductal papilloma, sclerosing adenosis
- Atypical hyperplasia (RR=4.0-5.0) - ADH, ALH
Noninvasive Breast Cancer-Ductal Carcinoma in Situ (DCIS)

- **Precursor** of invasive ductal cancer
- Age of occurrence same as for invasive cancer
- Usually presents as microcalcifications on MGM
- Rarely presents as palpable mass
- Incidence is rising probably due to increasing use of MGM
- Dx’d by stereotactic core or wire localized bx

Treatment of DCIS

- BCT consisting of breast conserving surgery (margin free excision) if pt has unicentric disease and RT or
- Total mastectomy if BCT is contraindicated
- Axillary staging not needed
- Recurrences after BCT can be invasive ca or noninvasive
- Tamoxifen if patient is hormone receptor positive.

Lobular Carcinoma In Situ- LCIS

- **Marker of pts at increased risk of having invasive breast cancer**
- >80% occur in premenopausal women
- **Not apparent on CBE or MGM**
- Incidental microscopic finding
- Relative risk 6-12 for developing invasive breast cancer in either breast
- 1% per yr risk of developing invasive ca
- Family hx may further increase the risk to 2% per year
Management of LCIS

- Close observation (CBE Q 6 months, annual MGM, monthly BSE)
- Tamoxifen
- Bilateral, prophylactic mastectomy with or without reconstruction in select pts

Invasive Breast Cancer (IBC)

- Invasive ductal (70-75%)
- Invasive lobular (5-10%)
- Special types: medullary, tubular, mucinous or colloid, papillary (less biologically aggressive)

Neoadjuvant, Induction or Primary Chemotherapy- Indications

- Locoregionally advanced breast cancer as part of multimodality therapy, then MRM followed by RT; enhanced survival
- To downsize a tumor for BCT, particularly for tumors large relative to the breast- no survival advantage
Treatment of Invasive Breast Cancer (IBC)

• Dependent on TNM stage, hormone receptor status, menopausal state, overexpression HER2/neu receptor

• Locoregional and Systemic

AJCC Staging (Early Stage, 2010; 7th edition)

• Stage 0 TisN0M0
• Stage IA T1N0M0
• Stage IB T0-T1 N1miM0
• Stage IIA T0-1N1M0, T2N0M0
• Stage IIB T2N1M0, T3N0M0

AJCC Staging (Advanced)

• Stage IIIA T0-3N2M0, T3N1M0
• Stage IIIB T4 N 0-2M0
• Stage IIIC Any T N3M0
• Stage IV Any T Any N M1
Locoregional Therapy

- Locoregional: Surgery + Radiation Therapy (RT)
- Breast Conserving Therapy (BCT) = Breast Conserving Surgery (BCS) + RT
- Total mastectomy (if BCT is contraindicated) + reconstruction
- Axillary staging - sentinel lymph node bx and/or level 1 and 2 ALND

Mammosite (Partial brachytherapy)

- Age > 45 years old
- Tumors < 3 cm
- Skin thickness > 7 mm
- 2 times daily for 5 days

Contraindications to BCT

- Diffuse malignant appearing microcalcifications
- Previous breast irradiation
- Pregnancy (unless radiation is provided after delivery)
- Multicentric cancers
- Collagen vascular disease (relative contraindication)
Mastectomy for Primary Operable Breast Cancer

- Patient preference for mastectomy
- Multicentric tumor
- Difficulty with follow-up anticipated
- Inability to achieve negative margin with BCS
- Contraindication to radiation therapy

Skin-sparing mastectomy

Young women with strong family histories

28 y.o. AA

27 y.o. AA
Indications for Postmastectomy Radiation

• Tumor > 5cm
• T4
• > 3 +LN

Sentinel Lymph Node Dissection (SLND)

Systemic Therapy

• **Chemotherapy**—CMF; AC; AC + Taxol

• **Hormonal**—Tamoxifen (anti-estrogen)
  Arimidex (aromatase inhibitor); Femara (AI)

• **Immunologic**—Trastuzumab (Herceptin)—
  monoclonal Ab vs HER2/NEU receptors

• **Bevacizumab** (Avastin)—humanized
  monoclonal Ab vs VEGF
Neoadjuvant, Induction or Primary Chemotherapy
-Indications-

• Locoregionally advanced breast cancer as part of multimodality therapy, then MRM followed by RT; enhanced survival

• To downsize a tumor for BCT, particularly for tumors large relative to the breast-no survival advantage

Adjuvant Systemic Therapy

- Cytotoxic
- Hormonal
- Biologic

Oncotype DX
A multigene (21 gene) assay to predict recurrence of tamoxifen-treated, node-negative breast cancer
3 risk categories
- Low risk—<18 (Benefit from hormonal therapy)
- Intermediate risk—18-31 (Don’t know - study patients)
- High risk—>31 (Benefit from chemotherapy)
**Prognostic Factors in Breast Cancer**

- Axillary Lymph Node Status
- Tumor size
- Estrogen Receptor, Progesterone Receptor Status
- HER-2/neu expression
- Ploidy
- S-phase fraction
- Cathepsin-D expression
- p-53 expression

**Local Treatment**

- Lumpectomy (often done at excisional biopsy)
  - tumor-free margins must be achieved
  - tumor:breast ratio a consideration for eligibility
  - not applicable to
    - pregnant patients
    - patients with previous chest wall irradiation
    - patients with multifocal disease
    - Some connective tissue disorders
- Mastectomy necessary in:
  - cases of Stage III breast cancer
  - Multicentric disease (cancer in multiple quadrants)
  - when patient is not eligible for breast preservation
  - when patient prefers mastectomy

**Systemic Treatment for Breast Cancer**

**Targeted Therapy**

- If HR + (ER+/PR+, ER+/PR-, ER-/PR+)

  - Tamoxifen or an Aromatase Inhibitor
  - Aromatase Inhibitors are not used in premenopausal women
Systemic Treatment for Breast Cancer

Targeted Therapy

If HER2/neu+

Herceptin

3+ by immunohistochemistry (IHC)
or if 2+ (borderline)
then FISH or DISH to determine positivity

Chemotherapy

Cytoxan
Adriamycin
5-FU
Methotrexate

If node-positive

Taxol

Who Needs Cytotoxic Chemotherapy?

- All women with node-positive breast cancer
- Most women with hormone-receptor negative disease
- Decision-making for women with ER/PgR + node - breast cancer based on recurrence prediction models using gene profiling techniques
- Oncotype > 30 (discuss use between score 19-30)
CONCLUSION

✓ Until gene Rx is available to prevent or treat the somatic or germline mutation leading to breast carcinogenesis
✓ Screening - the key element both in early diagnosis and greater probability of cure with less toxic therapy
✓ FIGHT ON THE GOOD FIGHT!!!!!!