Breast Cancer – Risk Factors, Genetics, Screening, Diagnosis

Bhuvaneswari Ramaswamy, MD, MRCP
Assistant Professor of Internal Medicine
Breast Cancer Fellowship Program Director
Medical Director of Clinical Trials Office for Solid Tumors
The Ohio State University Comprehensive Cancer Center
The Ohio State University’s Wexner Medical Center

OBJECTIVES

- Risks of developing breast cancer
- Screening for breast cancer in different subgroups
- Risk reduction strategies
- Diagnosis of breast cancer
CASE 1

- 72 yr old White female presenting with a left breast mass.
- Gravida 2 Para 2.
- Took hormone replacement therapy for 7 yrs (50-57yrs) after natural menopause.
- Her maternal GM had breast cancer at the age of 58. Maternal Aunt had breast cancer at the age of 78.
- Biopsy was consistent with invasive ductal carcinoma.

- What is the most important risk factor predisposing her to developing breast cancer?

AGE

The probability of developing breast cancer in the next 10 yrs for a

40 yr old is 1.5%

70 yr old is 4.1%
CASE 2

- 52 yr old Ashkenazi Jewish female on routine mammogram was found to have bilateral breast mass.
- Gravida 2 Para1.
- Daughter was diagnosed with breast cancer at the age of 30. Mother had ovarian cancer at the age of 45.

What is her greatest risk factor for developing breast cancer?

Family History

- 5-10% of all breast cancers are associated with cancer predisposition syndromes
**RISK FACTORS**

- **Age**
- **Family History**
  - 1st relative = 1.8 fold
  - 2nd relative = 2.93 fold
  - Relative < 40 yrs = 5.7 fold
- **Prolonged Estrogen Exposure**
  - Exposure to ionizing radiation
  - Abnormal breast biopsies
  - Obesity
  - Alcohol

**Estrogen-Induced Proliferation and Spontaneous New Mutations**

- Estrogen stimulation
- Normal breast cell
- Mistake in DNA duplication
- Increased proliferation
Summary of established risk and protective factors for breast cancer

<table>
<thead>
<tr>
<th>Risk factors (increased hormone exposure)</th>
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<tbody>
<tr>
<td>Early menarche</td>
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<td>Late menopause</td>
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<tr>
<td>Alcohol consumption</td>
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<td>Post-menopausal obesity</td>
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<td>Hormone replacement therapy</td>
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<table>
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<tr>
<th>Protective factors (decreased hormone exposure)</th>
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<tr>
<td>Young age at first full term pregnancy</td>
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<tr>
<td>Prolonged lactation</td>
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<td>Exercise</td>
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Genetic syndromes and breast cancer

- **Hereditary Breast and Ovarian Cancer Syndromes (80% of all inherited breast cancer)**

  - **BRCA 1**
    - 17q12-21
    - DNA repair
    - General population - 0.06%
    - Ashkenazi Jews - 2%

  - **BRCA 2**
    - 13q12
    - 3-8% of BC in Ashkenazi Jewish population
    - Other cancers associated - prostate, ovary, male breast, cervix, colon/GI, ureter, melanoma

  Lifetime risk 85% - Breast cancer
  45% for ovarian cancer
  58-fold increase in risk for male breast cancer
**BRCA1**
- Tumor suppressor gene on chromosome 17
- Autosomal dominant transmission
- Protein has role in genomic stability
- >600 different mutations reported

**BRCA2**
- Tumor suppressor gene on chromosome 13
- Autosomal dominant transmission
- Protein has role in genomic stability
- ~450 different mutations reported
OTHER GENETIC SYNDROMES

- Multiple hamartomas
- Sarcomas, brain tumors
- Melanocytic Macules in the lips
- Diffuse gastric cancer
- Ataxia, Immunodeficiency
- Cowden’s Syndrome (10q22-33)
- Li Fraumeni syndrome (TP53)
- P-J syndrome (19p13.4- STK11/LBK1)
- Hereditary Diffuse Gastric Cancer (CDH1)
- Ataxia-Telangiectasia (ATM gene)

ALERT SIGNS: Young breast cancers in family, Bilateral cancers, Triple negative cancers, Other cancers in young relatives, skin lesions.

Why should we attempt to identify these high risk women?

- Improved screening measures
- Referral to High-risk breast cancer clinic
- Consideration of chemoprophylaxis
- Genetic counseling
- Risk reduction strategies
  - Avoid excess estrogen exposure
  - Exercise
  - Moderate alcohol intake
HIGH-RISK BREAST CANCER SCREENING

AGE < 25 y
- Annual clinical breast exam
- Periodic breast self-exam

AGE > 25 y
- Clinical breast exam every 6-12 months
- Periodic breast self-exam
- Annual mammogram beginning

Age 25- Hereditary breast ovarian cancer syndromes
8-10yrs after RXT
5-10 yrs prior to youngest breast cancer case
- Consider MRI as an adjunct
- Consider risk reduction strategies
Annual MRI Screening

- BRCA mutation
- First-degree relative BRCA carrier
- Lifetime risk 20-25% or greater

Questionable indications-

Radiation to chest between ages 10 and 30
Other cancer genetic syndromes
Lifetime risk of 15-20%
Biopsy proven LCIS/ADH
Women with extremely dense breast on mammography
Women with personal history of breast cancer or DCIS

Recommend against MRI screening- Women with a lifetime risk < 15%

Bleicher et al Review. MRI in breast cancer: Role in detection, diagnosis, and staging. Oncology 2007

RISK REDUCTION STRATEGIES

Risk Reduction Mastectomy
- BRCA 1 or 2
- Compelling F/H
- LCIS

Risk Reduction Salpingo-oophorectomy
- Premenopausal
  - Tamoxifen
  - Age<35y- Unknown
- Postmenopausal
  - Tamoxifen
  - Raloxifene

Risk Reduction Agents
Estimated reduction in US overall breast cancer mortality is 28-65% (Breast cancer mortality RR >50 y- 0.78 and 40-49 y- 0.85)

Berry et al NEJM 2005

Cumulative incidence rates for all breast cancers and invasive estrogen receptor (ER)-positive breast cancers according to treatment arm

CONCLUSION

- Use of 5 yr tamoxifene reduces the risk of developing breast cancer by 50%

- 10 yr FU Tamoxifen prevention studies- 27-39%RR in ER +ve tumors

STAR Trial
The NSABP study of tamoxifen and raloxifene (STAR) P-2 trial

Figure 2. Cumulative Incidence of Invasive and Noninvasive Breast Cancer

Vogel et al, JAMA, 2006
Side-effect profile

Current recommendation: for PM women is 5 yrs of raloxifene

Vogel et al, JAMA, 2006

How to identify these pts in your practice?

- Gail model risk

http://www.cancer.gov/bcrisktool/

Review: Gail et al Weighing the risks and benefits of tamoxifen treatment for breast cancer prevention JNCI 1999 19(2) 1829-46

Quick pickup:

Family history
Multiple biopsies
LCIS
Bilateral breast cancers
CASE # 3

- 45 yr old AA female presents with a large right breast mass. She had TAH/BSO at the age of 32 and has been on HRT since then. Mass measures 5cm and 2 lymph nodes are palpable in the R axilla. She has no other symptoms.

- What is the clinical staging?

- How do you confirm your diagnosis and staging?

Clinical/TNM staging

- Stage I - Node negative, Tumor ≤ 2cm
- Stage II - Node positive, Tumor size 2-5 cm
  - (T > 5cm + node negative)
- Stage III - Tumor > 5cm, node positive- matted LN, Internal mammary LN, SCLN.
  - Inflammatory breast cancer
- Stage IV - Distant metastases.
**DIAGNOSIS**

- Core needle biopsy is the preferred method
- Sentinel LN biopsy is the preferred method for axillary staging
- Bone scan - indicated for localized symptoms or elevated alkaline phosphatase
- CT scans - Not routinely indicated
  - Consider in locally advanced tumors
- Tumor markers - No role at all.

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**SENTINEL LYMPH NODE BIOPSY**

SLN is the first node to receive lymphatic drainage from the area with the breast tumor. Most likely to harbor metastases in the axilla. Current techniques - Isosulphan blue dye, detection of radiolabelled technetium sulfur colloid with a hand-held probe or both.
SENTINEL LYMPH NODE BIOPSY

- Predictive power is the same as ALND
- Better QOL with less complications
- Long-term effects unknown

New Diagnosis of Breast Cancer

- Risk factors
- Confirmation of diagnosis
- Stage of disease
- Biology and prognostic and predictive factors
Breast Cancer Treatment and Survivorship

Maryam B. Lustberg, MD, MPH
Assistant Professor of Internal Medicine
The Stefanie Spielman Comprehensive Breast Center
The Ohio State University Comprehensive Cancer Ctr.
The Ohio State University’s Wexner Medical Center

Objectives

- Discuss the most common treatment modalities in breast cancer
- Review common toxicities experienced by breast cancer survivors
- Discuss breast cancer survivorship care in the primary care setting
Initial Presentation

- The majority of breast tumors found on screening mammograms
- Rest are found by clinical breast exams and patient/partner awareness of a breast abnormality
- Other imaging modalities: US and MRI

Breast cancer treatment modalities

- Treatment of Operable Breast Cancer
  - Local Control
    - Surgery
      - Lumpectomy
    - Radiation Therapy
    - Mastectomy
  - Distant Control
    - Chemotherapy
    - Endocrine Therapy

Factors Influencing Surgical options

- What factors influence the type of surgery therapy selected?
  - size of tumor, grade
  - lymph node involvement
  - metastatic disease
  - patient age and co morbidities
  - contraindication to radiation therapy
  - Patient preference

- How do different breast cancer subtypes influence therapy choices?
  - Triple negative breast cancer
  - HER2 positive breast cancer

Primary Therapy: Breast Surgery

- Lumpectomy with needle localization
- Mastectomy (simple mastectomy, modified radical mastectomy, radical mastectomy)
- Negative margins
- Evaluation of axilla
  - Axillary node dissection
  - Sentinel node evaluation:
    - Z0011 Randomized trial (Giuliano et al JAMA 2010)
Breast Cancer Systemic Therapy Options
Individualizing care

- Endocrine Therapy
- Chemotherapy
- Biologics (Trastuzumab)
- Experimental therapies
  - Anti-angiogenesis: bevacizumab
  - Bisphosphonates (zoledronic acid)
  - Rank ligand monoclonal antibodies (denosumab)
  - PARP inhibitors

Endocrine Therapy

- ER and/or PR positive only
- Pre-menopausal
  - Tamoxifen
  - Ovarian suppression
- Post-menopausal
  - Aromatase inhibitor
  - Tamoxifen
  - Sequential therapy
Tamoxifen

- SERM (selective estrogen receptor modulator)
- Agonist and Antagonist activity
- 20 mg daily for 5 years
- Recommended for pre-menopausal women and in select post-menopausal patients

Tamoxifen – Potential Benefits

- Decrease contralateral invasive and non-invasive hormone receptor positive breast cancers by approximately 50%
- Significantly improved disease free and overall survival with 5 years of therapy
- Improves bone density in post-menopausal women
  - P1 trial – fracture RR 0.68
## Tamoxifen - Toxicity

- **Hot flashes** – approx 80%, 30% severe  
  - CYP2D6
- **Endometrial cancer** (7 cases/10,000 treated women)  
  - Higher risk in women > 50 y/o, obesity  
  - Progressive risk with time of exposure
- **Uterine Sarcoma** (1 – 8 cases / 10,000)
- **Venous thromboemolism** (10 cases/10,000)
- **Net bone loss** in pre-menopausal women
- **Cataracts**

## Sources of estrogen in Premenopausal and Postmenopausal Women

- **Ovaries**: in premenopausal
- **Aromatase** (Cyp 19) in postmenopausal women
  - present in adipose tissue, adrenal glands, breast tissue

![Chemical structure of testosterone and estradiol](http://www.wikipedia.org/)
Aromatase Inhibitors (AIs)

- FDA approved for postmenopausal women with ER/PR + breast cancer
- 2005, ASCO recommended that optimal endocrine therapy included AI as initial therapy or after therapy with tamoxifen based on superior disease free survival relative to tamoxifen.
- Three approved drugs in this class:
  - Non-steroidal (anastrozole, letrozole)
  - Steroidal (exemestane)

Toxicities of AIs

- Hotflashes (30-50%)
- Arthralgias (30%)
- Vaginal dryness and atrophy (20-30%)
  - Intravaginal estrogen at low doses prescribed after discussion with patient
- Bone loss
- Fractures
- Cardiovascular toxicities?
Fractures with AIs

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>F/U (mo)</th>
<th>Treatment</th>
<th>Clinical Fracture Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AI vs. TAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>9366</td>
<td>100</td>
<td>ANA vs. TAM</td>
<td>11.0 vs. 7.7 [p&lt;0.001]</td>
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<tr>
<td>BIG 1-98</td>
<td>4922</td>
<td>51</td>
<td>LET vs. TAM</td>
<td>8.6 vs. 5.8 [p&lt;0.01]</td>
</tr>
<tr>
<td><strong>AI after 2-3 years of TAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>4724</td>
<td>58</td>
<td>EXE vs. TAM</td>
<td>7.0 vs. 5.0 [p=0.003]</td>
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<tr>
<td>ABCSG8/ARNO</td>
<td>3224</td>
<td>28</td>
<td>ANA vs. TAM</td>
<td>2.0 vs. 1.0 [p=0.015]</td>
</tr>
<tr>
<td><strong>AI after 5 years of TAM</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA-17</td>
<td>5187</td>
<td>30</td>
<td>LET vs. Placebo</td>
<td>5.3 vs. 4.6 [p=0.25]</td>
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Breast Cancer Systemic Therapy Options
Individualizing care

- Endocrine Therapy
- Chemotherapy
- Biologics (Trastuzumab)
- Experimental therapies
  - Anti-angiogenesis: bevacizumab
  - Bisphosphonates (zoledronic acid)
  - Rank ligand inhibitors (denosumab)
  - PARP inhibitors
**General Chemotherapy Recommendations**

- **ER +/- PR positive**
  - ≤ 0.5 cm or grade 1 0.6 -1.0 cm – no chemo
  - 0.6 – 1.0 cm grade 2/3 or any grade > 1 cm – consider Oncotype DX
  - LN + Consider chemotherapy, Consider Oncotype DX

- **Triple negative (ER-, PR-, HER2-)**
  - < 0.5 cm – no chemo
  - 0.6 – 1.0 cm – consider chemo
  - ≥ 1.0 cm or LN+ – recommend chemo

- **Her-2 positive**
  - < 0.5 cm no chemo
  - 0.6 – 1.0 cm consider chemo + trastuzumab
  - ≥ 1 cm or LN+ - recommend chemo + trastuzumab

**Chemotherapy for Hormone Receptor Positive Breast Cancer**

- **Lymph node involvement**
- **Lymph node negative**
  - Consider based on prognostic factors, age, co-morbidities
  - Adjuvant! online program
  - Oncotype Dx testing
Individualizing therapies

• Multigene tests: Tests in which samples of tissue are studied to look at the activity of many genes at the same time. These tests may help predict risk of recurrence as well as benefit from chemotherapy

• Oncotype DX is the most commonly used assay in the United States for this purpose
Chemotherapy Regimens

Node positive
• Dose dense Adriamycin/Cytoxan (AC) q 2 weeks with growth factor support + Weekly Paclitaxel x 12 or Paclitaxel q 2 weeks
• Taxotere/cytoxan q 3 weeks x 4 doses

Node negative
• AC x 4 doses
• TC x 4 doses

Toxicity from Chemotherapy

• Most common: Fatigue and hair loss
• Nausea
• Diarrhea/constipation
• Mouthsores
• Neuropathy
• Chemotherapy induced ovarian failure
• Infection/neutropenic fever
• Therapy related bone loss
• Rare: cardiomyopathy, treatment related MDS/leukemia
Chemotherapy induced ovarian failure (CIOF)

- Greatest risk >50% in women ages 40 or older
- Young women not done with childbearing at risk
- Consultation with fertility specialist recommended.
- Insufficient evidence that concurrent GnRH agonist therapy protective

Breast Cancer Systemic Therapy Options

**Individualizing care**

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**HER2-neu Oncogene**

- Located chromosome 17q21
- Encodes a 185 kd transmembrane glycoprotein. Tyrosine kinase-like activity
- Overexpression (or amplification) in 20-25% of tumors
- Independent adverse prognostic factor
- Trastuzumab is the first monoclonal antibody FDA approved for HER2 positive disease. Other HER2 targeted therapies include lapatinib, pertuzumab, and TDM-1.

**Chemotherapy + Trastuzumab**

- Addition of trastuzumab to chemotherapy, decreases recurrences by 50% and improves survival by 30%
- AC TH vs TCH
- Reversible cardiotoxicity with trastuzumab (4-8%)
- Serial cardiac monitoring with trastuzumab every 3 months in the adjuvant setting
Breast Cancer Systemic Therapy Options

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Individualizing Therapy in Breast Cancer

- As a consequence of both early screening and adjuvant therapies, more women are living with breast cancer than ever before.
Declining Deaths from Breast Cancer


Relative Hazard Rates of Breast Cancer Mortality According to Estrogen Receptor (ER) Status

10 Million+ US Cancer Survivors

Approximately one-fourth are breast cancer survivors

Female breast
Prostate
Colorectal cancer
Gynecologic
Other genitourinary
Hematologic
Melanoma
Lung
Other

Partnership Between Primary Care Physicians and Oncologists

- Importance of close collaboration between primary care providers and oncologists to optimize breast cancer survivor care
- Treatment summary and care plan
- James/ Stefanie Spielman Comprehensive Breast Center will be organizing workshops on this topic in the future

Key follow up milestones
Breast cancer and primary care go hand in hand

- Annual mammograms
- Routine oncology visits
- Bone density every 2 years in postmenopausal women on AIs
- Annual pap and pelvic for women on tamoxifen
- Annual flu shot
- Colonoscopy after age 50
- Blood pressure monitoring
- Cholesterol monitoring
- Vaccines up to date
- Weight management
- Smoking cessation
- Increase physical activity