EDUCATIONAL OBJECTIVES

• Risk factors/assessment

• Average versus high risk

• Value of screening and early detection

• Controversies in screening mammography

• Long-term follow up of Breast Cancer survivors

Epidemiology

• Breast cancer is the most common malignancy in women in the U.S.

• A leading cause of cancer deaths in women

• Incidence
  – New cases expected in 2014: 232,670 IBC
  – Deaths: 40,000
  – 1 in 8 chance of invasive breast cancer in USA
Epidemiology

- Age specific incidence increases throughout life
- More than ½ the risk occurs after the age of 60
- 5 year survival of all breast cancer patients is approximately 85%
- Mortality in U.S. has been decreasing 2.2%/year since 1990

Risk Factors

- BRCA 1 or 2 mutations
- Family history – no known mutation
- Prior breast irradiation
- Early menarche
- Late parity/nulliparity
- Combined hormonal therapy >10 years
- Atypical ductal or lobular hyperplasia
- Dense breasts
- Postmenopausal obesity

Breast Cancer Risk Tools

- Purpose: Stratify risk categories for screening
- BCRAT: Risk Assessment tool
  — Gail model – NCI
- Based on mammography – screening series of >280,000 women
- Predicts 5 year and lifetime rates both invasive and non-invasive breast cancer in a population
- Less accurate for individual women
- Result of 1.67 or more suggests further counseling
### Gail Model

- **INCLUDED IN MODEL**
  - Age
  - Age at menarche
  - Age at first live birth
  - Number of maternal first degree relatives with breast cancer
  - Number of breast biopsies
  - Presence of atypia on biopsy

- **NOT INCLUDED**
  - Age at menopause
  - Density of breast tissue
  - Use of birth control pills
  - HRT
  - High fat diet
  - Alcohol intake
  - Radiation exposure
  - Environmental pollutants
  - Paternal family history

### Mammography

- Reduces mortality by 26% in women aged 50-74

- Women with significant risk factors for early onset breast cancer should have a baseline mammogram at age 35

- Women aged 40 and older should have a yearly mammogram

### Mammography (continued)

- Women with a first degree relative with breast CA should begin having mammograms 5-10 years earlier than the relative at the age of diagnosis

- Mammography will fail to detect 10% breast cancers – consider biopsy of palpable masses

- When appropriate, mammography should be used in conjunction with ultrasonography
Radiographic Abnormalities

Mammography lesions of malignancy
- Spiculated margins
- Irregular shape
- Linear calcifications

New Diagnostic Techniques
- Ultrasound-cysts
- MRI

Biopsy Techniques and Pathologic Review

- Fine-needle aspiration (in-office)
- Core-cutting needle biopsy (in-office)
- Excisional biopsy (outpatient surgery)

- Pathologic Evaluation
  - Tumor size and histologic diagnosis
  - Estrogen/Progesterone receptors
  - HER2-neu over expression

Biology Features

- Pathology
  - Tumor Grade and Size
  - Histologic Subtype
  - Nodal Status
  - ER, PR, HER-2
  - Multigene Assay

- Patient Age
Breast Tumor Subtypes

- Analysis by genomic DNA copy number arrays, exome sequences, micro RNA
  - 4 main breast cancer classes
  - Significant molecular heterogeneity

Multigene Assay to Predict Recurrence

- Study of correlation between molecular signatures by DNA arrays to predict recurrence
- Validate 21-gene RT-PCR assay and recurrence score algorithm to quantify likelihood of distant recurrence
- Node-negative ER+ treatment with Tamoxifen on NSABP trial B-14

Panel 21 Genes
Likelihood of Distant Recurrence According to Recurrence Score Categories

<table>
<thead>
<tr>
<th>Recurrence Score Categories</th>
<th>Percentage of Patients with Distant Recurrence</th>
<th>Rate of Distant Recurrence at 10 Yr (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>22</td>
<td>4.3 (3.6-5.1)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>22</td>
<td>14.3 (10.5-20.3)</td>
</tr>
<tr>
<td>High</td>
<td>27</td>
<td>30.1 (22.4-40.0)</td>
</tr>
</tbody>
</table>

*Note: All comparisons were made for the analysis of distant recurrence after excluding patients with grade 3 tumors. The analysis was performed using Kaplan-Meier estimates and log-rank test for statistical significance. The recurrence score was calculated based on the expression levels of 12 genes (ESR1, PR, EGFR, etc.). The risk categories were defined as low (<10), intermediate (10-24), and high (>24). The rate of distant recurrence at 10 years for each category is given along with the 95% confidence interval.*

Kaplan-Meier Estimates of Distant Recurrence

Likelihood of Distant Recurrence According to Recurrence Score Categories

![Graph showing likelihood of distant recurrence over time for low, intermediate, and high risk categories.](image-url)
Rate of Distant Recurrence as a Continuous Function of the Recurrence Score

Detection

- Goal: detect malignancy early to reduce mortality
- Screening should be sufficiently sensitive, easy to obtain, safe and cost-effective
- Tools:
  - Mammography/Ultrasonography
  - Breast self-examination
  - Clinical breast examination
- Mammography detects 85-90% of biopsy proven cancers

Question 1

- Pt is a 35 yr old female who notes a 1.5 cm palpable mass in her right breast over the past month. She has just completed her menstrual period. She has no history of breast abnormalities and no family history of breast cancer. Ultrasonography shows no abnormality.
Question 1: You would recommend?

• A) A mammogram; if it is normal, follow with a clinical examination every 6 months and a yearly mammogram
• B) No further evaluation
• C) Repeat evaluation in 1 month after she has completed her next menstrual cycle
• D) A mammogram; if suspicious for malignancy, proceed to a biopsy
• E) A biopsy

Question 1: Answer

• Answer: E (proceed with biopsy)

• Mammography may not be relied on to exclude malignancy

• False positive rates in younger woman are 10-30%, but lower in women over the age of 50

How Much Breast and Ovarian Cancer is Hereditary?

Breast Cancer | Ovarian Cancer
---|---
15%-20% | 5%-10%
5%-10% | 5%-10%

Sporadic | Family clusters | Hereditary
My Medical Choice

Strategies for Screening

• Does screening with mammography decrease breast cancer mortality?
  Average Risk vs. High Risk
  Weigh benefits against costs
  Benefit: Reduction in risk of death
  Costs: Financial, pain, inconvenience, over-diagnosis

Over-diagnosis: Detection of cancer that would never have become clinically evident
Screening: Women Ages 50-69

- Universal recommendations for mammography
- Reduction in death
  14% - women in their 50's
  32% - women in their 60's
- Higher sensitivity with increased age

Screening Mammography Women 70 years and above

- Randomized trial in Sweden to study effectiveness of screening
  2 cohorts ages 40-74
  1. Invited to screen
  2. Screening 5-7 years later

Conclusion: No benefit in this age group
Reduction in mortality for younger age group 40-49 years old

Screening Mammography Women 40-49 years of age

- Controversial currently
- Prior meta-analysis suggested a reduction in mortality
- No single randomized trial shows reduction in mortality
- Lower breast cancer risk, lower mammographic sensitivity, higher number of false positives
U.S. Preventive Services Task Force

- Support decreases in use of screening mammography
- Screening for women 40-49 years old should be an individual decision taking into account the patient’s values
- Recommended frequency of screening be reduced from every 1 to 2 years to every 2 years

Effect of Three Decades of Screening Mammography on Breast Cancer Incidence

- SEER data examined trends from 1976-2008 incidence of DCIS, localized disease and late stage in women >40 years
- Screening mammography: doubling of early-stage breast cancer from 112 to 234 cases/100,000 women
- Rate in late stage decreased by 8% from 102 to 94 cases / 100,000 women

Change in the Incidence of Stage-Specific Breast Cancer among Women 40 years or Older

<table>
<thead>
<tr>
<th>Variable</th>
<th>Annual Breast-Cancer Incidence</th>
<th>Women Affected over the Three Decades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute Change</td>
<td>Estimated number of women</td>
</tr>
<tr>
<td></td>
<td>Before Mammography</td>
<td>Three Decades Later</td>
</tr>
<tr>
<td>Cases of early-stage breast cancer</td>
<td>Number of cases per 100,000 women</td>
<td>estimated number of women</td>
</tr>
<tr>
<td>DCIS</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>Localized disease</td>
<td>105</td>
<td>178</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>234</td>
</tr>
<tr>
<td>Decrease in cases of late-stage breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional disease</td>
<td>85</td>
<td>78</td>
</tr>
<tr>
<td>Distant disease</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
<td>94</td>
</tr>
</tbody>
</table>

References:
Effects of Three Decades of Mammography

- Estimated breast cancer over-diagnosed in 1.3 million US women in 30 years
- In 2008, over-diagnosed in >70,000 women or 31% of all diagnosed

Conclusion:
- Screening mammography has marginally reduced rate of presentation with advanced cancer
- Substantial over-diagnosis
- Small effect on rate of death from breast cancer

Recent Study: Canadian National Screening Study

- 25 year follow up – Breast Cancer incidence and mortality
  - Objective: To compare BC incidence and mortality for up to 25 years in women aged 40-59
  - Mammography screen or not

Design:
- Centre coordinators
- Central Office
- Cancer Registries
- Vital Statistics Database

Measured Outcome: Deaths from Breast Cancer

Canadian National Screening Study

Setting: 15 screening centers in 6 Canadian provinces

Participants: 89,835 women aged 40-59

Assigned Mammography
No Mammography
Canadian National Screening Study: Interventions

Women aged 40-59
• Mammography arm: MG and annual breast exams
• Control arm: Single examination and usual care in the community

Women aged 50-59
MG and annual breast exams

Results of Randomized Screening Trial
Breast cancers in screening period
Total: 1190
666 – MG; 180 died
524 – control arm; 171 died

Follow up period
Total: 5193
2584 – MG
2609 – control arm

Results of Canadian National Trial
Findings for women aged 40-59 and 50-59 were nearly identical

Mammography arm:
3250 – BC; 500 died of Breast Cancer
Control arm:
3133 – BC; 505 died of Breast Cancer
-Cumulative mortality similar
-After 15 years follow up:
excess of 106 cases of over-diagnosis
Conclusion: annual mammography did not result in reduction in Breast Cancer mortality for ages 40-59.
Evolution of HER2-Positive Disease
• Overexpression of human epidermal growth factor receptor 2 (HER2) causes an aggressive course in breast cancer
• Humanized anti-HER2 monoclonal antibodies Pertuzumab and Trastuzumab active in combination
• Example: Cleopatra Trial

Case Study
62 year old female
• Mammography reveals mass in right breast
• Biopsy positive for invasive ductal carcinoma
• Tumor 0.9 cm, grade III, on right modified radical mastectomy
• 3/38 lymph nodes positive
• Stage IIA
• ER 92%, PR 80%, HER2 3+

Cleopatra Trial
• Phase III Randomized, double-blind, placebo controlled

© 2013 Rising Tide
Breast Cancer Screening, Diagnosis, Biology and Long-Term Follow-Up

Cleopatra Trial: Enrollment and Outcomes

Overall Survival

Breast Cancer Treatments Received by Patients Who Discontinued Study Treatment

Table 1: Breast Cancer Treatments Received by Patients Who Discontinued Study Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count Cancer</th>
<th>Restart Cancer</th>
<th>Count Overall</th>
<th>Restart Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>453 (52.8)</td>
<td>435 (51.3)</td>
<td>634 (74.2)</td>
<td>618 (72.2)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>208 (24.2)</td>
<td>173 (20.5)</td>
<td>299 (35.6)</td>
<td>270 (32.7)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>17 (2.0)</td>
<td>11 (1.3)</td>
<td>24 (2.8)</td>
<td>18 (2.2)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>14 (1.6)</td>
<td>10 (1.2)</td>
<td>21 (2.5)</td>
<td>16 (1.9)</td>
</tr>
<tr>
<td>Trastuzumab-eribulin</td>
<td>14 (1.6)</td>
<td>10 (1.2)</td>
<td>21 (2.5)</td>
<td>16 (1.9)</td>
</tr>
<tr>
<td>Eribulin</td>
<td>14 (1.6)</td>
<td>10 (1.2)</td>
<td>21 (2.5)</td>
<td>16 (1.9)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>14 (1.6)</td>
<td>10 (1.2)</td>
<td>21 (2.5)</td>
<td>16 (1.9)</td>
</tr>
<tr>
<td>Hormonal treatment</td>
<td>14 (1.6)</td>
<td>10 (1.2)</td>
<td>21 (2.5)</td>
<td>16 (1.9)</td>
</tr>
</tbody>
</table>

* Data are based on the number of patients in the intervention arm who discontinued study treatment.
Post Treatment Follow-Up: Breast Cancer

• 3 million women – history

• Over 40% of female cancer survivors

• Risks
  – Recurrence
  – New Primary Cancer
  – Short-term adverse events
  – Long-term effects

Survivorship Care

• Coordination between specialists and primary care physicians

• Interventions for sequelae of treatment
  – Fatigue
  – Pain
  – Lymphedema
  – Insurance, disability
  – Employment
  – Surveillance for recurrence and second primary cancer

Long-term Effects:

• Psychological

• Genetic

• Social

• Reproductive/Sexual

• Employment
ASCO Guidelines

• Women with early stage breast cancer tumor
  – <5 cm and <4 positive nodes

• Transition to PCP at one year

• Input from Oncologist

• Age appropriate screening and preventive care

Follow Up

• History and Physical
  – Every 3 to 6 months after primary therapy
  – Every 6 to 12 months for two years
  – Then annual

• Specifics: Constitutional Symptoms of History
  – Bone Health
  – Pulmonary/Neurologic Symptoms
  – GI and GU
  – Psychological
  – Reproductive

• Education re: Symptoms of recurrence

Physical Exam

• Complete examination

• Attention to breast, chest wall, axilla

• Lung, musculoskeletal

• Abdominal: RUQ

• Cardiac: CHF

• Neurologic

• Gynecologic
Follow-Up Breast Imaging

**Purpose:** Detect ipsilateral local recurrence after BCT
- Detect contralateral breast recurrence
- Surveillance mammography associated with reduction in mortality
  - Women >65 years: case control study who lived >30 months were less likely to die of breast cancer

**Surveillance Recommendation – Imaging Mammography**

Breast conservation
- Post treatment mammogram no earlier than 6 months after radiation therapy
- Subsequent mammograms every 6-12 months
- Mammogram yearly if stable

**Breast MRI**
- Not recommended for survivors
- 2012 review of 10 case series
- No advantage over mammogram
- However, recommended for high risk BRCA mutation or strong positive family history
Role of Laboratory and Imaging Post Treatment

- Intensive surveillance not indicated for asymptomatic patients
- Meta-analysis: 2005 - randomized trial between routine follow up versus intensive surveillance

<table>
<thead>
<tr>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFTs</td>
</tr>
<tr>
<td>Tumor Markers</td>
</tr>
<tr>
<td>Chest Imaging</td>
</tr>
<tr>
<td>Bone Scan</td>
</tr>
<tr>
<td>CT</td>
</tr>
<tr>
<td>PET</td>
</tr>
</tbody>
</table>

Healthy Lifestyle

- Exercise
- Avoidance of obesity
- Minimal Alcohol intake
- Coordination of care

Guidelines for Breast-Cancer Screening

<table>
<thead>
<tr>
<th>Organization</th>
<th>Year Guidelines Issued</th>
<th>Mammography</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF</td>
<td>2009</td>
<td>Age 40-74 yr, every 2 yr; age 40-49 yr and age &gt; 75 yr, individualize the decision (every 2 yr, if performed)</td>
</tr>
<tr>
<td>American Cancer Society</td>
<td>2010</td>
<td>Age &gt;40 yr, annually</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>2011</td>
<td>Age &gt;40 yr, annually</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>2010</td>
<td>Age &gt;40 yr, annually</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>2007</td>
<td>Age 50-69 yr, every 2 yr; age 40-49 yr, individualize the decision (every 2 yr, if performed)</td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists</td>
<td>2003</td>
<td>Age 40-49 yr, every 1-2 yr; age &gt;50 yr, annually</td>
</tr>
<tr>
<td>American College of Radiology</td>
<td>2008</td>
<td>Age &gt;40 yr, annually</td>
</tr>
<tr>
<td>Canadian Task Force on Preventive Health Care</td>
<td>2000-2001</td>
<td>Age 40-49 yr, every 2 yr; age 40-49 yr, individualize the decision (every 1-2 yr, if performed)</td>
</tr>
<tr>
<td>National Health Service, UK</td>
<td>2011</td>
<td>Age 40-74 yr, every 1 year</td>
</tr>
</tbody>
</table>