BREAST CANCER

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Background

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

• Second leading cause of cancer death among women in the U.S.

• Women have a 1 in 9 lifetime risk of developing breast cancer.

Estimated New Cancer Cases
10 Leading Sites by Gender

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>31%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>13%</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>11%</td>
</tr>
<tr>
<td>Uterus</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>4%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>18%</td>
</tr>
</tbody>
</table>

SEER Breast Cancer Incidence and Mortality Data

180,000 / year
40,000 / year

Trends since 1950 in age-standardised death rates comparing breast and selected other types of cancer, among women in the USA

EBCTCG. Lancet 2005; 365: 1687

Stages of Breast Cancer

• **Stage 0**: Cancer cells are present in either the lining of a breast lobule or a duct, but they have not spread to the surrounding fatty tissue or DCIS.

• **Stage I**: The tumor is <2 cm, the lymph nodes are not involved.

• **Stage II**: The tumor can range from 2-5 cm in diameter or <4 lymph nodes are involved.

• **Stage III**: Locally advanced cancer; tumor may be larger than 5 cm in diameter or >4 LN.

• **Stage IV**: Known as metastatic; cancer has spread to other parts of the body, such as bone, liver, lung, or brain.

- About 15% of breast cancer diagnoses are in situ disease
- 5-year survival for early stage breast cancer is very good

Breast Cancer Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol intake (&gt;2 drinks/day)</td>
<td>1.2</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.2</td>
</tr>
<tr>
<td>HRT use (&gt;5 years)</td>
<td>1.3</td>
</tr>
<tr>
<td>Early age of first menstrual period (&lt;12 years)</td>
<td>1.3</td>
</tr>
<tr>
<td>Late menopause (&gt;55 years)</td>
<td>1.2-1.5</td>
</tr>
<tr>
<td>Age at first birth (&gt;30 years or no children)</td>
<td>1.7-1.9</td>
</tr>
<tr>
<td>Current age (&gt;65 years)</td>
<td>5.8</td>
</tr>
<tr>
<td>Benign breast disease</td>
<td>5-20</td>
</tr>
<tr>
<td>Prior breast cancer</td>
<td>6.8</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>2nd degree relative with breast cancer</td>
<td>1.5</td>
</tr>
<tr>
<td>1st degree relative, age&gt;50</td>
<td>1.8</td>
</tr>
<tr>
<td>1st degree relative, age&lt;50</td>
<td>3.3</td>
</tr>
<tr>
<td>Prior Exposure to Radiation</td>
<td>5-80x</td>
</tr>
<tr>
<td>BRCA1/2 mutation carrier</td>
<td>15-200</td>
</tr>
</tbody>
</table>

Breast Cancer Risk Assessment: Gail Model

- Age 45
- Race White
- Age of first menstrual period 13
- Age of first live birth 32
- Number of first degree relatives with breast cancer 1
- Number of breast biopsies 1
- Presence of atypical hyperplasia

5-Year Risk = 2.6%
Lifetime Risk = 21.9%

Benign Breast Disease

Dupont et al. Cancer, 1993

- Pre-Cancerous Changes in Breast Tissue
- Hyperplasia
- Atypia
- In Situ

Risk
- Non-Proliferative 1.0
- Pre-Cancerous Changes 1.5-2.0
- Hyperplasia 4.0-5.0
- Atypia 10-20
- In Situ

How Much Breast and Ovarian Cancer Is Hereditary?

- Sporadic
- Family clusters
- Hereditary
Features That Indicate Increased Likelihood of Having BRCA Mutations

- Multiple cases of early onset breast cancer
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer

Multi-modality Treatment of non-metastatic Breast Cancer

- Local therapy
  - Surgery
  - Radiation therapy
- Systemic therapy
  - Endocrine manipulations
  - Chemotherapy
  - Novel Therapies

Risk Factors Related to Breast Cancer

- Early Menarche
- Never Pregnant
- Never Breastfed
- Family History
- Benign Breast Disease
- Mammographic Density
- Never Breastfed
- Late Age at First Birth
- Late Menopause
- Lack of Exercise
- Overweight
- Alcohol
- Hormone Use (HRT, OC)

Adjuvant Systemic Therapy for Breast Cancer: Decision making

Risks:
- Adverse Events
- Organ Function, Age, Co-morbidities

Benefits:
- Risk Reduction
- Prognostic & Predictive Factors

Comparing Relative Risk to other Risk Factors

Adjuvant Systemic Therapy for Breast Cancer: Decision Making

- Prognostic Factors
  - Estimate outcome independent of systemic treatment
  - Reflect tumor biology: Who should be treated?
- Predictive Factors
  - Reflect a relative resistance or sensitivity to specific therapy
  - What specific treatment(s) should be offered to an individual?
Breast Cancer Prognostic Factors

<table>
<thead>
<tr>
<th>Strength Marker</th>
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Breast Cancer Predictive Factors

- Accepted
  - Age
  - ER
  - Grade
  - HER2

- Investigational
  - Gene arrays, proteomics
  - Novel imaging

Breast Cancer Subtypes

<table>
<thead>
<tr>
<th>Tumor subtypes (based upon Fig 1)</th>
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<tbody>
<tr>
<td>A: Basal-like</td>
</tr>
<tr>
<td>B: HER2-negative</td>
</tr>
<tr>
<td>C: HER2-positive</td>
</tr>
<tr>
<td>D: Luminal-like</td>
</tr>
<tr>
<td>E: HER2-positive</td>
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</tbody>
</table>

OncoTypeDX Recurrence Score (RS) Assay Predicts Distant Relapse Rates at 10 Years if Five Years of Tamoxifen

16 Cancer and 5 Reference Genes From 3 Studies

<table>
<thead>
<tr>
<th>PROLIFERATION</th>
<th>ESTROGEN</th>
<th>INVASION</th>
</tr>
</thead>
<tbody>
<tr>
<td>KI-67</td>
<td>ER</td>
<td>GSTM1</td>
</tr>
<tr>
<td>STK15</td>
<td>PR</td>
<td>CD68</td>
</tr>
<tr>
<td>Survivin</td>
<td>BAG1</td>
<td>HER2</td>
</tr>
<tr>
<td>Cyclin B1</td>
<td>GAPDH</td>
<td>GRB7</td>
</tr>
<tr>
<td>MYBL2</td>
<td>RPLPO</td>
<td>HER2</td>
</tr>
<tr>
<td>RS = 0.47 x HER2 Group Score + 0.34 x ER Group Score + 1.04 x Proliferation Group Score + 0.10 x Invasion Group Score + 0.05 x CD68 - 0.08 x GSTM1 - 0.07 x BAG1</td>
<td></td>
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</tr>
</tbody>
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Validation Study of OncoType DX

Tamoxifen treated patients from NSABP B-14 (N=668)
Performance exceeded standard measures of patient age, tumor size
Inhibition of Estrogen-Dependent Growth

Antiestrogens

Estrogen biosynthesis

Nucleus

Inhibition of cell proliferation

Aromatase inhibitors

Tumor cell

Tamoxifen: Oxford Overview Data

- Effective in all hormone receptor positive women:
  - ER+/PR+ > ER-/PR+ > ER+/PR-
- Regardless of age, stage, tumor grade
- Optimal duration: 5 years
  - 5 yrs > 2 yrs, but 10 yrs not > 5 yrs

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EBCTCG. Lancet 2005; 365: 1687–1717

ATAC: Disease-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>T</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+</td>
<td>424</td>
<td>497</td>
<td>0.83</td>
<td>(0.73–0.94)</td>
<td>0.005</td>
</tr>
<tr>
<td>ITT</td>
<td>575</td>
<td>651</td>
<td>0.87</td>
<td>(0.78-0.97)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Absolute difference: 1.6% 2.6% 2.5% 3.3%

Adjuvant Chemotherapy

1. Who should be treated?
2. Which regimen?
3. What duration?
4. How intense?
5. When to administer?

1. Who should be Treated?

Risks:
- Adverse Events
- Organ Function
- Age, Co-morbidities

Benefits:
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- Prognostic & Predictive Factors

EBCTCG. Lancet 2005; 365: 1687–1717

5 years of Tamoxifen vs. Not: 15-year Probabilities of Recurrence and Breast Cancer Mortality (ER-positive/unknown, n = 10,386)

Recurrence

Breast Cancer Mortality

15 year gain 11.8% (SE 1.3)
Logrank 2p<0.0001

15 year gain 3.2% (SE 1.2)
Logrank 2p<0.0001

EBCTCG. Lancet 2005; 365: 1687–1717
Polychemotherapy vs. Not, by Entry Age: 15-year Probabilities of Recurrence and Breast Cancer Mortality (Age 50-69)

Recurrence | Breast Cancer Mortality
--- | ---
EBCTCG. Lancet 2005; 365: 1687–1717

15 year gain 3.0% (SE 1.3) Logrank 2p<0.00001
15 year gain 4.1% (SE 1.2) Logrank 2p<0.00001

Polychemotherapy vs. Not, by Entry Age: 15-year Probabilities of Recurrence and Breast Cancer Mortality (Age <50)

Recurrence | Breast Cancer Mortality
--- | ---
EBCTCG. Lancet 2005; 365: 1687–1717

15 year gain 12.3% (SE 1.6) Logrank 2p<0.00001
15 year gain 10.0% (SE 1.6) Logrank 2p<0.00001

2. Which Regimen? Results from the Oxford Overview

- Polychemotherapy is superior to single agent chemotherapy
- Anthracycline-based therapy is superior to CMF-based therapy
- All women gain benefit but younger women, and those with poorly differentiated, hormone receptor negative-tumors more likely to benefit


Common Breast Cancer Treatments

- Endocrine Therapies
  - Tamoxifen
  - Aromatase Inhibitors
  - Other
- Chemotherapy
- Novel Therapies
  - Trastuzumab (Herceptin)

Trastuzumab Targets the Human Epidermal Growth Factor Receptor 2 (HER2)

- The HER2 gene is localized to chromosome 17q
- HER2 is a tyrosine kinase transmembrane growth factor receptor


HER2 Overexpression Leads to Increased Signaling


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Metastatic Breast Cancer: Goals of Therapy

- Cure
- Improve overall survival
- Improve time to progression
- Improve symptoms related to the disease
- Improve quality of life

Therapeutic options

- Endocrine therapies
- Chemotherapy
- Novel therapies
- Supportive Therapy
  - Local therapy: surgery, radiation
  - Bisphosphonates
    - For women with skeletal metastases
    - Reduces pain/risk of fracture/RT requirements
  - Symptom management

Monitoring Response

- History and physical
- Tumor markers
- Imaging
  - Standard: CT, bone scan, MRI
  - Emerging: PET, functional imaging
- Circulating cells
- Other
Conclusions and Future Directions

• Many therapies available to women with metastatic breast cancer
  - Improve overall survival, time to progression, QOL
  - Well tolerated
• Individualized treatment
• Optimal dose, schedule, combination
• Numerous emerging novel therapies

Thank You