BREAST CANCER

Epidemiology

- Commonest cancer in women
- About 235,000 new cases/year in United States
- About 45,000 deaths/year

Epidemiology

- Incidence high in U.S., Canada, Europe, Australia
- Incidence low in Japan, China, Africa
- Migration studies indicate an environmental factor(s)

Figure 6: Female Breast Cancer Incidence Rates* by Race and Ethnicity, SEER, 1975-2000

Figure 7: Female Breast Cancer Death Rates* by Race and Ethnicity, SEER, 1975-2000

*Rates are age-adjusted to the 2000 U.S. standard population.
Breast Cancer

Epidemiology
Risk *increased* with:
4. Prolonged use of post menopausal estrogen replacement therapy
5. Obesity - postmenopausal

Risk *decreased* with:
1. Late age first menstrual cycle (menarche > age 14)
2. Early age last menstrual cycle (menopause < age 45)
3. First pregnancy before age 20
4. Breast feeding > 16 months

Risk *increased* with:
Prolonged use of OCPs / HRT
Daily alcohol intake - increased estradiol levels - other mechanisms – effects on folate

Family history breast cancer, especially first degree relatives (mother, sister)

How Much Breast and Ovarian Cancer Is Hereditary?

<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer</th>
<th>Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>15%–20%</td>
<td>5%–10%</td>
</tr>
<tr>
<td>Family clusters</td>
<td>5%–10%</td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BRCA1**

Tumor suppressor gene on chromosome 17
Autosomal dominant transmission
Protein has role in genomic stability
~500 different mutations reported

Breast Cancer Information Core
**BRCA1-Associated Cancers: Lifetime Risk**

- Breast cancer 50%–85% (often early age at onset)
- Second primary breast cancer 40%–60%
- Ovarian cancer 15%–45%

Possible increased risk of other cancers (e.g., prostate, colon)

**BRCA2**

Tumor suppressor gene on chromosome 13
Autosomal dominant transmission
Protein has role in genomic stability
~300 different mutations reported

**BRCA1-Associated Cancers: Lifetime Risk**

- Breast cancer (50%–85%)
- Male breast cancer (6%)
- Ovarian cancer (10%–20%)

Increased risk of prostate, laryngeal, and pancreatic cancers (magnitude unknown)

**BRCA2-Associated Cancers: Lifetime Risk**

- Breast cancer
  - 50%–85%
  - 40%–60%
  - 15%–45%
- Second primary breast cancer
- Ovarian cancer
- Male breast cancer

Increased risk of prostate, laryngeal, and pancreatic cancers

**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

**Comparing Breast Cancer Risk Estimates in BRCA Mutation Carriers**

<table>
<thead>
<tr>
<th>General population</th>
<th>BRCA1+ carriers (BCLC)</th>
<th>BRCA1+ carriers (Ashkenazi Jews)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>General population</th>
<th>BRCA1+ carriers (BCLC)</th>
<th>BRCA1+ carriers (Ashkenazi Jews)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>60</td>
<td>70</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>80</td>
<td>90</td>
<td>100</td>
<td>110</td>
</tr>
</tbody>
</table>

**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)
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- Ashkenazi Jewish heritage
- Male breast cancer

ASCO
Causes of Hereditary Susceptibility to Breast Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Contribution to Hereditary Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>20%–40%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>10%–30%</td>
</tr>
<tr>
<td>TP53</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>PTEN</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Undiscovered genes</td>
<td>30%–70%</td>
</tr>
</tbody>
</table>

BREAST CANCER

Epidemiology
Risk increased with:
- Exposure to Ionizing Radiation
  1. Fluoroscopy for monitoring TB therapy in 1940’s
  2. Atomic bombings 1945
  3. Radiation therapy for Hodgkin’s disease

Pathology
1. Description of:
   i. Histological type
   ii. Size of primary
   iii. Axillary nodal metastases
2. Hormone receptors
3. Over expression her-2/neu

Axillary Dissection
Complications
1. Dysesthesia and paresthesia in axillary skin and medial upper arm
2. Arm/hand edema; cellulitis
3. Limited shoulder mobility
**BREAST CANCER**

Pathology

Hormone receptors
- steroid binding proteins
  1. Estrogen receptors
  2. Progesterone receptors

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**Classic Pathway of Estrogen Signal Transduction**

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**BREAST CANCER**

Pathology

Hormone receptors
  1. Measured by immunohistochemical test
  2. Expressed as percentage positive cells
  3. Over 10% reported as a positive test

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**BREAST CANCER**

Pathology

Hormone receptors
  1. Prognostic factor
     - Improved if receptors present
  2. Predictive factor
     - If receptors present, hormonal therapy may be effective
**BREAST CANCER**

**Pathology**

Her-2/Neu

1. Prognostic factor
   - Worse if her-2/Neu is over expressed
2. Predictive factor
   - If her-2/Neu over expressed, may respond to trastuzumab

**MANIFESTATIONS**

**Local tumor growth**

i. Changes detectable on imaging studies (mammography, sonography, MRI)
ii. Lump found by patient
iii. Lump found by physician

**Diagnostic Methods**

- Radiologic
  - Mammography
  - Sonography
  - MRI
- Histologic
  - FNA/core biopsy
  - Stereotactic biopsy
  - Excisional biopsy

**MANIFESTATIONS**

**Mechanisms of spread**

i. Direct extension
   - skin, chest wall
ii. Lymphatic
   - axillary, others
iii. Hematogenous
   - skeleton, lungs, liver, CNS, skin, LN, anywhere

**TREATMENT**

1. Surgery
2. Radiation therapy
3. Medical therapy (Pharmaceuticals)
BREAST CANCER
TREATMENT GOALS
1. Control primary lesion in breast
2. Control systemic micrometastases

TREATMENT PRIMARY LESION
1. Surgery alone (total mastectomy)
2. Limited surgery (lumpectomy) and radiation therapy

Breast Cancer: Primary Surgery Options / Outcomes
- Halsted: radical mastectomy
- Fisher: MRM vs lumpectomy +/- XRT

<table>
<thead>
<tr>
<th>Event</th>
<th>MRM</th>
<th>LE</th>
<th>LE+XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence - n (%)</td>
<td>219 (37)</td>
<td>239 (42)</td>
<td>271 (47)</td>
</tr>
<tr>
<td>Local</td>
<td>60 (10)</td>
<td>58 (9)</td>
<td>17 (3)</td>
</tr>
<tr>
<td>Regional</td>
<td>27 (5)</td>
<td>35 (6)</td>
<td>34 (6)</td>
</tr>
<tr>
<td>Distant</td>
<td>132 (22)</td>
<td>138 (23)</td>
<td>153 (26)</td>
</tr>
<tr>
<td>Total</td>
<td>371 (63)</td>
<td>408 (64)</td>
<td>391 (62)</td>
</tr>
<tr>
<td>Alive/Event-free</td>
<td>218(37)</td>
<td>226(36)</td>
<td>237(38)</td>
</tr>
</tbody>
</table>

Fisher et al. NEJM October 2002

Overall Survival (Panel A) and Disease-free Survival (Panel B) in the Two Groups

Breast Cancer: Primary Surgery Options / Outcomes
- Contraindications to MRM:
  - Multifocal / multicentric disease
  - Large lesion relative to breast: poor cosmetic outcome
  - Radiation therapy issues:
    - Active collagen vascular disorder
    - Logistical issues

RISK OF SYSTEMIC METASTASES
1. Lymph node metastases
2. Size primary lesion
3. Degree differentiation
4. Hormone receptor status
5. Her-2/neu expression
Adjuvant Therapy of Breast Cancer

- Risk of metastasis:
  - 1 cm ~ 12% risk
  - 1 LN ~ 6% risk

Therefore 2.5 cm ~ 30%
2 LN ~ 12%
Risk ~ 42%

BREAST CANCER
SYSTEMIC ADJUVANT THERAPY
1. All axillary node positive cases
2. Node negative at significant risk

BREAST CANCER
SYSTEMIC THERAPY
1. Hormonally based
2. Chemotherapy
3. Monoclonal antibody preparations

Simulation of Impact of Chemotherapy:
(Based on EBCTG Meta-Analysis)

Annual Odds of Recurrence:
- Nil ~ 15%/Yr
- CMF ~ 11.4%
  (Reduced by 24%)
- AC ~ 10%
  (Reduced by 12%)
- AC → T ~ 7.8%
  (Reduced by 22%)

BREAST CANCER
Hormonally Based Therapy
Estrogen acting as a growth factor in tumor cells which express hormone receptors
**BREAST CANCER**

**Hormonally Based Therapy**

Reduce estrogen action

1. Block with antagonist
   “selective estrogen receptor modulator”
2. Reduce production
   - pre-menopausal
   - post-menopausal

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**Estrogen Production in Premenopausal and Postmenopausal Patients**

- **Hypothalamus**
  - LHRH
  - PITUITARY
    - LUTEINIZING HORMONE
      - **OVARIES**
        - **ESTRADIOL**

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**Premenopausal Breast Cancer**

**Hormonally Based Therapy**

Reduce production

1. Surgical oophorectomy
2. Medical oophorectomy

**Selective Estrogen Receptor Modulator**

1. Tamoxifen

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**TAMOXIFEN: IMPROVEMENT IN DFS**

<table>
<thead>
<tr>
<th>Years</th>
<th>Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Yr. Tamoxifen</td>
<td>54.5%</td>
</tr>
<tr>
<td>5 Yr. Placebo</td>
<td>54.5%</td>
</tr>
<tr>
<td>10 Yr. Tamoxifen</td>
<td>68.2%</td>
</tr>
<tr>
<td>10 Yr. Placebo</td>
<td>68.2%</td>
</tr>
<tr>
<td>15 Yr. Tamoxifen</td>
<td>68.2%</td>
</tr>
<tr>
<td>15 Yr. Placebo</td>
<td>68.2%</td>
</tr>
</tbody>
</table>

Adapted with permission - Early Breast Cancer Trials' Group, 2000.
**Postmenopausal Women**

- Estrogen synthesis
  - Occurs in non-ovarian tissue
- Concentrations in breast tissue higher than in serum
  - Equivalent to premenopausal levels
- Tumor ER concentrations higher than in premenopausal patients
  - Increase with age

**Rationale for Aromatase Inhibitors for Breast Cancer Treatment**

- Selective inhibition of all estrogen biosynthesis
- No estrogenic effects (compared with antiestrogens, tamoxifen)
- Different mode of action from antiestrogens ie non-cross resistant with tamoxifen
- Few side effects

**Estrogen Production in Premenopausal and Postmenopausal Patients**

- Hypothalamus
- Gonadotropins (FSH + LH)
- Ovary
  - Estrogens
  - Progesterone
- Pituitary gland
  - Adrenocorticotropic hormone (ACTH)
- Adrenal gland
  - Cortisol
  - Adrenosterone
  - Pregnenolone
- Cholesterol
- Testosterone
- Estradiol
- Estrone
  - Androstenedione
- Aromatase inactivators and inhibitors

**Steroid Biosynthesis**

**Postmenopausal Breast Cancer Hormonally Based Therapy**

1) Selective estrogen receptor modulator ie tamoxifen
2) Reduce production by aromatase inhibition
   ie anastazole, letrozole, exemestane
Multiple steps involving P-450 enzymes and production of steroid intermediates:

- Androstenedione
- Estrone
- Estradiol
- Testosterone
- Cortisol
- Aldosterone
- Cholesterol

Selective Versus Nonselective Aromatase Inhibition:

**Selective Inhibitors**

**Nonselective Inhibitors**

Selective Inhibitors: Anastrozole

Nonselective Inhibitors: Tamoxifen

Probability of Recurrence in Receptor-positive Population:

<table>
<thead>
<tr>
<th>Time to event (months)</th>
<th>AN vs TAM</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>0</td>
<td>0.78</td>
<td>0.65–0.93</td>
<td>0.007</td>
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</table>

<table>
<thead>
<tr>
<th>No. of Pts. at risk</th>
<th>AN</th>
<th>TAM</th>
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<tr>
<td></td>
<td>2617</td>
<td>2598</td>
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<td></td>
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<tr>
<td></td>
<td>1258</td>
<td>1210</td>
</tr>
<tr>
<td></td>
<td>602</td>
<td>574</td>
</tr>
</tbody>
</table>

* Censoring non-BC deaths before recurrence

**BREAST CANCER**

Pathology

Her-2/Neu

1. Transmembrane protein
2. Epidermal growth factor receptor family
3. Activates a tyrosine kinase pathway
4. Over expressed in 25% cases

**HER2 Protein Overexpression Associated with Poor Prognosis and Shortened Survival**

- Approximately 25% of breast cancers are HER2-positive.
- In retrospective studies, HER2 was found to be associated with:
  - Shortened survival
  - More rapid tumor progression
  - Increased relapse rates
  - Shorter time to relapse
  - Poor responses to standard therapies

- Approximately 95% of breast cancers are HER2-positive.

- In retrospective studies, HER2 was found to be associated with:
  - Shortened survival
  - More rapid tumor progression
  - Increased relapse rates
  - Shorter time to relapse
  - Poor responses to standard therapies
**Trastuzumab (Herceptin): Humanized Anti-HER2 Antibody**

- Targets HER2 oncoprotein, which occurs in approximately 25% of patients with breast cancer.
- High affinity (Kd = 5 nM) and specificity.
- 95% human, 5% murine.
  - Less immunogenicity.
  - Increased recruitment of immune effector cells.

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**TRASTUZUMAB**

**Mechanism of Action**

1. Down regulation receptor.
2. Antibody dependent cell mediated cytotoxicity.
3. Prevents dimerization of receptors, decreasing signal transduction.

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**Disease-Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>B-31</th>
<th></th>
<th>N9831</th>
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<tbody>
<tr>
<td></td>
<td>AC-TH</td>
<td>AC-TH</td>
<td>AC-TH</td>
<td>AC-TH</td>
</tr>
<tr>
<td>Events</td>
<td>864</td>
<td>111</td>
<td>50</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>87%</td>
<td>77%</td>
<td>87%</td>
<td>77%</td>
</tr>
<tr>
<td>HR</td>
<td>0.45</td>
<td>2.4x10^-3</td>
<td>0.55</td>
<td>1.6x10^-4</td>
</tr>
</tbody>
</table>

**Questions?**

**Thank you!**