Breast Cancer

“A buffet of breast cancer topics”

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• Disclosures:
  – none

Not related to anything presented in this lecture

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<table>
<thead>
<tr>
<th>Cancer incidence</th>
<th>Cancer cases</th>
<th>Cancer deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td></td>
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<tr>
<td>Cancer site</td>
<td>2012</td>
<td>2013</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>106,660</td>
<td>106,660</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>70,240</td>
<td>70,240</td>
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<tr>
<td>Uterine corpus</td>
<td>47,180</td>
<td>47,180</td>
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<tr>
<td>Thyroid</td>
<td>43,270</td>
<td>43,270</td>
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<tr>
<td>Melanoma of the skin</td>
<td>22,890</td>
<td>22,890</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>31,910</td>
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<tr>
<td>Acute &amp; chronic myeloproliferative disorders</td>
<td>20,630</td>
<td>20,630</td>
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<tr>
<td>Ovary</td>
<td>22,290</td>
<td>22,290</td>
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<tr>
<td>Pancreas</td>
<td>21,630</td>
<td>21,630</td>
</tr>
<tr>
<td>All sites</td>
<td>336,140</td>
<td>336,140</td>
</tr>
</tbody>
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Established breast cancer risk factors

- Age
- Overweight
- Alcohol use
- Physical activity
- Postmenopausal hormone use
- Late age at first birth (> 30 y.o.)
- Early age at menarche
- Late age at menopause
- BRCA1/2 and Family history
Menopausal hormone therapy

Women's Health Initiative

- Federally funded study of dietary modification, calcium/vitamin D, and postmenopausal hormones for heart disease and cancer prevention
  - 10,739 women without uterus – 0.625 mg conjugated equine estrogen vs placebo
  - 16,608 women with uterus – 0.625 mg CEE + 2.5 mg medroxyprogesterone vs placebo
  - 40% intervention group and 60% control

Women's Health Initiative – E+P

- Mean f/u 5.6 yrs
- 42% stopped study meds
- ↑↑ abnormal mammograms
- Risk drops quickly after stopping

Women's Health Initiative – CEE

- Stopped at 7.1 yrs mean f/u due to ↑ stroke and ? Overall benefit
  - HR 0.77 (95% CI 0.62-0.95) with 11.8 yrs f/u

Alcohol

Alcohol Intake and Breast Cancer
Alcohol and estrogen levels

Onland-Mouret 2006, J Clin Endocrinol Metab

Body mass index

P for trend = 0.001
P for trend = 0.03

Body mass index

- ↑↑ Postmenopausal breast cancer risk
  - 20-30% higher with BMI > 30
  - No increase in premenopausal breast cancer
- Main source of estrogen after menopause = fat tissue which converts androgens into estrogens

Body mass index and sex steroid levels

Body mass index and sex steroid levels

Family History/Genetics

Family History

Risk for Patient is Greater if:

- Women affected are first degree relatives
- Women in family affected at younger age
- Women in family have bilateral breast cancer
BRCA 1 & 2

- Germ-line genetic mutations ↑↑ risk of breast and ovarian cancer
  - BRCA1: 50-70% breast, 40-50% ovarian ca
  - BRCA2: 40-60% breast, 10-25% ovarian ca
  - ↑↑ male breast cancer with BRCA2
- Only explains 5-10% of all breast cancers

Prevention

Tamoxifen vs Raloxifene vs Aromatase Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen</th>
<th>Raloxifene</th>
<th>Aromatase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flashes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Bone Effect</td>
<td>positive</td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>Uterine stim</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Premenop OK</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
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</table>

Randomized placebo controlled prevention trials

- Tamoxifen, raloxifene, Aromatase – 40-60% ↓↓ breast ca risk
- Only prevents ER+ breast cancer
- No survival benefit seen

Why isn't breast cancer chemoprevention done more?
Absolute risk of breast cancer low
Side effects
Screening available for breast cancer

Screening mammography

To screen or not to screen

US Preventive Services Task Force controversy

- November 2009: “Recommends against routine screening mammography in women aged 40-49 years”
US Preventive Services Task Force controversy

- November 2009: “Recommends against routine screening mammography in women aged 40-49 years”
- December 2009: “The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient’s values regarding specific benefits and harms.”

What we know about screening

Women aged 50-74 should get routine screening mammogram

- Randomized controlled trials and meta-analyses => 20-30% ↓↓ mortality
- Recommended screening interval 1-2 years

When should we start screening?

Arguments against screening women aged 40-49

- Large randomized trials (100,000+) =>15-25% ↓↓ mortality but not statistically significant
- Breast cancer less common before age 50 so absolute benefits smaller
- Although screening began in 40’s, benefits generally not seen until women in 50’s
- More false positives among younger women

When should we start screening?

Arguments for screening women aged 40-49

- Although most individual trials not significant, meta-analyses => 7-23% significant ↓↓ mortality
- USPTF meta-analysis RR 0.85 (95% CI 0.75-0.96)
- Relative benefits similar to women 50+
- Many older negative studies used outdated techniques (e.g. single rather than double view)
- “Intention to treat” analyses, but some crossover between groups

False-positive mammograms – provider perspective

Definition varies: additional mammo to biopsy

- 20-50% estimated risk over 10 mammograms
- More common in women < age 50

Chances of Malignancy by Age and Type of Mammographic Finding

<table>
<thead>
<tr>
<th>Age</th>
<th>Mass Lesion</th>
<th>Calcifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>19/225 (8%)</td>
<td>21/66 (32%)</td>
</tr>
<tr>
<td>40-49</td>
<td>53/449 (12%)</td>
<td>62/201 (31%)</td>
</tr>
<tr>
<td>50-59</td>
<td>73/254 (29%)</td>
<td>35/175 (20%)</td>
</tr>
<tr>
<td>60-69</td>
<td>64/149 (43%)</td>
<td>29/120 (24%)</td>
</tr>
<tr>
<td>&gt;69</td>
<td>70/125 (56%)</td>
<td>18/72 (25%)</td>
</tr>
</tbody>
</table>

• Total 279/1202 (23%) 165/634 (26%)

Meyer, JAMA, 1999:281:1638
False-positive mammograms – patient perspective

Ductal Carcinoma In-Situ (DCIS)
- Rare before screening mammography
  - 57,650 cases in 2010
  - ~30% of all mammographically detected masses
- Uncertainty re: natural history of DCIS
  - 14-40% estimated to recur if untreated
  - Largest study had 80 women (Eusebi 1994)
  - Cannot identify those that will recur so all treated equally
  - Mastectomy or lumpectomy + RT +/-tamoxifen
  - Is it really cancer? Confusing nomenclature
  - Cancer cells similar to invasive disease, but no invasion of basement membrane

Lobular Carcinoma in Situ (LCIS)
- Often incidental finding
- ↑ risk of invasive carcinoma bilaterally without predictable location - ~1%/yr
  - Generally does not need surgical excision
- Management options
  - observation
  - tamoxifen
  - prophylactic bilateral mastectomy

Breast MRI
- More sensitive – especially in young women
  - May miss DCIS – does not replace mammograms
  - Many more false positives
- Current indications for MRI – ACS
  - Recommended for:
    - BRCA1/2, Li-Fraumeni, Cowden’s
    - Radiation to chest between age 10 and 30
    - Lifetime risk of >20-25%
  - Insufficient evidence for or against”
    - Personal history of breast cancer
    - Dense breasts on mammography
  = >Never been shown to reduce mortality!

Breast Cancer Treatment

Management of Primary Invasive Breast Cancer
- Disease confined to the breast +/- axillary lymph nodes
- Local tumor control
  - Lumpectomy/Radiation vs Mastectomy
- Systemic disease prevention
  - Adjuvant chemotherapy +/- hormonal therapy
Primary breast cancer – local control

Mastectomy vs lumpectomy + RT

- Mortality for patients with breast cancer:
  - Mastectomy: 100% 5-year survival
  - Lumpectomy + radiation: 90% 5-year survival

decision for adjuvant treatment based on:
- Likelihood of developing metastatic disease
- Overall life expectancy

Risk factors for development of metastatic breast cancer
- Tumor size and grade
- Axillary lymph node involvement
- Estrogen receptor status
- HER2/neu status

Breast Cancer is More than 1 Disease
1. Estrogen receptor positive – HER2 negative
   - Sensitive to hormonal therapy
2. Estrogen receptor positive – HER2 positive
   - Sensitive to hormones and trastuzumab
3. Estrogen receptor negative - HER2 positive
   - Sensitive to trastuzumab
4. Triple negative (basaloid)
   - No targeted therapies

Gene expression profiling of tumor

OncotypeDX®

For ER positive tumors and mainly node negative

Patients with a Recurrence Score of 25 in the clinical validation study had an Average Rate of Distant Recurrence at 10-years of 17.7% (compared to 30.4%)

Higher scores are indicative of a higher risk of recurrence, meaning patients with a high score are more likely to benefit from adjuvant chemotherapy.

Source: PNAS, 2004

Paik, MJ, 2004
Primary Breast Cancer –Adjuvant Rx

- Chemotherapy +/- Trastuzumab
- Hormonal Therapy
  - Tamoxifen
  - Aromatase Inhibitors
  - Ovarian suppression/ablation

Chemotherapy Improves Cure Rate for Patients with Primary Breast Cancer

Patients with node-positive breast cancer

Modified Radical Mastectomy

C – cyclophosphamide, d1-14
M – methotrexate days 1 & 8
F – 5-FU days 1 & 8
No Post-op treatment

Bonadonna, NEJM 1976;294:405 & 1995;332:301

Milan CMF Trial for Node + Disease

1976

1995

Flavors of Adjuvant Chemotherapy

- CMF –cyclophosphamide +methotrexate +5-FU
- CA –cyclophosphamide + doxorubicin
- CA - T - Taxane (paclitaxel or docetaxel)
- TAC - docetaxel + AC
- TC – doctaxel + cyclophosphamide
- CAF – AC + 5-FU

HER2/neu and Trastuzumab

- HER2/neu (c-erbB2) proto-oncogene - 185-kd transmembrane, glycoprotein growth factor receptor without known ligand
- Trastuzumab - Humanized monoclonal anti-p185HER
  - Can cause congestive heart failure
  - No administered with or after an anthracycline
- 20-25% of breast cancers overexpress HER2
- HER2+ tumors have worse prognosis, if not treated with trastuzumab

HER2neu pathway

Drugs include trastuzumab, lapatinib, pertuzumab

Hudis, NEJM, 2007
### Intergroup Adjuvant Trial N9831

- Cyclophosphamide/Doxorubicin x 4 q 3 wks
  - 2700 pts
- Paclitaxel q wk x 12
- Trastuzumab x 52

Perez, NEJM, 2005

### Adjuvant AC-T With and Without Trastuzumab: Combined Analysis of NASBP B-31 and N9831

- 50% Reduction in Recurrence

Perez, NEJM, 2005

### Adjuvant Hormonal therapy

- 1st targeted therapy!
  - ↓↓ breast cancer mortality by 1/3
- Tamoxifen – selective estrogen receptor modulator
  - No data for raloxifene in adjuvant setting
- Aromatase inhibitors
  - Only postmenopausal women
  - Anastrozole, letrozole, exemestane

### Metastatic Breast Cancer

### Metastatic Breast Cancer – Hormonal Rx

- 1st line except for visceral crisis
  - AI for postmenopausal
  - Tamoxifen + ovarian suppression for premenopausal
- Aromatase inhibitor
  - Anastrozole + letrozole – non-steroidal reversible AI
  - Exemstane – steroidal irreversible AI
  - Both equally effective
- Fulvestrant – pure estrogen receptor antagonist
- High dose progesterone /estrogens rarely used
Active Chemotherapeutic Agents in Metastatic Breast Cancer

- Doxorubicin
- Paclitaxel
- Docetaxel
- Cyclophosphamide
- Methotrexate
- Eribulin
- 5-fluorouracil
- Capecitabine
- Vinorelbine
- Gemcitabine
- Liposomal doxorubicin
- Ixabepilone

Principles of chemotherapy for metastatic breast cancer

- Different chemotherapy regimens have shown only modest improvements in overall survival
- Main goal of treatment is symptom prevention/palliation
- Single agent chemotherapy less toxic than doublet chemotherapy with similar effectiveness

Trastuzumab and Chemotherapy

Metastatic Breast Cancer

- Chemotherapy Alone
- Chemotherapy + Trastuzumab
- Chemotherapy + T

Slamon, NEJM 2001;344:783

Breast Cancer Summary

- Epidemiology – E+P HT, overweight, and alcohol use increase breast ca risk
- Prevention – Tamoxifen, raloxifene, and AI reduce breast ca risk, but no effect on mortality
- Screening – Mammography remains a mainstay for early diagnosis of breast ca – small benefit does exist for women in 40’s
- Primary, non-metastatic, breast cancer – Biologic subtypes of breast cancer drive appropriate therapy
- Metastatic breast cancer – New biologic agents offer hope for better survival

Bisphosphonates for bone metastases

- 70-75% of women with metastatic breast cancer have bone mets
- Complications of poorly controlled bone metastases
  - Pain
  - Hypercalcemia
  - Pathologic fracture
  - Cord/nerve compression
- Routine bisphosphonate use for bone metastases has significantly improved quality of life for metastatic pts
Question 1
Which of these statements are true about mammography?

1. Mammograms do not reduce mortality for women 40-49 years of age
2. MRI reduce breast cancer mortality more than mammograms do
3. 45% of abnormalities found on screening mammography turn out to be cancer
4. Mammographically detected lesions can be safely evaluated by core needle biopsy

Question 2
The following is true about metastatic breast cancer

1. Many women with metastatic breast cancer are cured of their disease
2. Hormone therapy is not effective for patients with liver metastases
3. Therapy for patients with metastatic breast cancer is determined by the biologic characteristics of their cancer
4. Chemotherapy has substantially extended life for patients with metastatic breast cancer

References