Breast Cancer in Young Women

**Objectives**
- Discuss the epidemiology and biology of early onset breast cancer
- Discuss local therapy considerations and the role of CPM
- Discuss fertility concerns and preservation options

**Disclosures**
- No disclosures

**Breast Cancer Risk as a Function of Age**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>1 in x</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1,523</td>
</tr>
<tr>
<td>40</td>
<td>173</td>
</tr>
<tr>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>60</td>
<td>21</td>
</tr>
<tr>
<td>70</td>
<td>12</td>
</tr>
<tr>
<td>80</td>
<td>8</td>
</tr>
</tbody>
</table>
Breast Cancer Incidence & Mortality

<table>
<thead>
<tr>
<th>Age</th>
<th>In Situ Cases</th>
<th>Invasive Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>1,900</td>
<td>10,980</td>
<td>1,020</td>
</tr>
<tr>
<td>&lt;50</td>
<td>15,650</td>
<td>48,910</td>
<td>4,780</td>
</tr>
<tr>
<td>50-64</td>
<td>26,770</td>
<td>84,210</td>
<td>11,970</td>
</tr>
<tr>
<td>65+</td>
<td>22,220</td>
<td>99,220</td>
<td>22,870</td>
</tr>
<tr>
<td>All Ages</td>
<td>64,640</td>
<td>232,340</td>
<td>39,620</td>
</tr>
</tbody>
</table>

Breast Cancer Facts and Figures 2013-2014

Breast Cancer Incidence by Age
SEER 18 2003-2012. All Races, Females

Risk Factors: Young vs Old
- Family History
- Race
- BMI/Obesity
- Hormonal
- Other
  - History of mantle radiation
  - Heavy alcohol consumption
  - High intake of red meat

Breast Cancer Trends

SEER 9
1975-2000

SEER 17
2000-2004

Anders, Semin Oncol 2009;36(3):237-249

SEER Stat Facts
Genetic predisposition is a stronger risk factor
Suggests a familial cancer syndrome
- BRCA
- P53
- PTEN
50% of women diagnosed with breast cancer ≤ 30 and a family history of breast or ovarian cancer had a mutation in one of these genes, whereas only 8% of women with early onset breast cancer without a family history.

Eur J Cancer 2006;42:1143-1150

More common in white women over 45
African American women < 35
  2x the incidence
  3x the mortality

Breast Cancer Facts & Figures

Discrepancy in mortality is seen mainly in Stage I & II

Race – POSH study
- Prospective observational study
- Women with breast cancer ≤ 40
- Diagnosed and treated in UK 2000-2008
- N=2915

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Black</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median tumor diameter</td>
<td>22mm</td>
<td>26mm</td>
<td>.01</td>
</tr>
<tr>
<td>Multifocality</td>
<td>29%</td>
<td>43%</td>
<td>.002</td>
</tr>
<tr>
<td>Grade 3</td>
<td>60%</td>
<td>68%</td>
<td>NS</td>
</tr>
<tr>
<td>Nodal positivity</td>
<td>51%</td>
<td>56%</td>
<td>NS</td>
</tr>
<tr>
<td>TN breast cancer</td>
<td>19%</td>
<td>26%</td>
<td>.04</td>
</tr>
</tbody>
</table>

No difference in receipt of chemotherapy
Copson, Br J Cancer 2014;110 (1): 230-241
African American women had significantly worse OS & DFS.

**Race – POSH study**

MVA: Black ethnicity was an independent risk factor for DRFS in ER+ disease independent of BMI, tumor size, grade, or nodal status (HR 1.5)

**Relative Risk of breast cancer incidence according to BMI**

<table>
<thead>
<tr>
<th>BMI Kg/m²</th>
<th>Premenopausal (n=1179)</th>
<th>Postmenopausal (n=5629)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 22.5</td>
<td>0.96 (0.85-1.08)</td>
<td>0.85 (0.80-0.91)</td>
</tr>
<tr>
<td>22.5-24.9</td>
<td>1.00 (0.93-1.07)</td>
<td>1.00 (0.95-1.06)</td>
</tr>
<tr>
<td>25-27.4</td>
<td>0.98 (0.82-1.15)</td>
<td>1.10 (1.04-1.16)</td>
</tr>
<tr>
<td>27.5-29.5</td>
<td>0.99 (0.84-1.16)</td>
<td>1.21 (1.13-1.29)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>0.79 (0.68-0.93)</td>
<td>1.29 (1.22-1.36)</td>
</tr>
</tbody>
</table>

Trend per 10 units: 0.86 (0.73-1.00) 1.4 (1.31-1.49)

**Breast Cancer Incidence & Mortality According to BMI**

Reeves, BMJ 2007; 336(7630): 1134-1145

**Obesity**

- Postmenopausal
  - ↑ risk
- Premenopausal
  - ↓ risk
**Obesity**

- Meta-analysis
  - 9 cohort, 22 case control studies
  - the association between body weight and ER/PR defined breast cancer risk
- Risk for ER/PR + tumors
  - 20% lower among premenopausal women
  - 82% higher among postmenopausal women
- Each 5 unit ↑ in BMI
  - 33% ↑ risk among postmenopausal women
  - 10% ↓ risk among premenopausal women
- No association with ER-/PR- tumors


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**Obesity and Survival – Meta-analysis**

- 82 studies
- N= 213,075 women
- Summary RRs of total mortality for obese women
  - Premenopausal: 1.75 (95% CI: 1.26-2.41)
  - Postmenopausal: 1.34 (95% CI: 1.18-1.53)

Obesity is associated with a poorer overall and breast cancer survival in pre- and postmenopausal breast cancer

*Lifestyle modifications can improve OS*


---

**Obesity and Prognosis – POSH study**

Women < 40 with Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Healthy weight (BMI &lt; 25)</th>
<th>Overweight (BMI &gt; 25 to &lt; 30)</th>
<th>Obese (BMI &gt; 30)</th>
<th>P value (healthy vs obese)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>1526 (54%)</td>
<td>784 (27%)</td>
<td>533 (19%)</td>
<td></td>
</tr>
<tr>
<td>Median tumor size</td>
<td>20 mm</td>
<td>24 mm</td>
<td>26 mm</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grade 3 tumors</td>
<td>59%</td>
<td>64%</td>
<td>64%</td>
<td>.05</td>
</tr>
<tr>
<td>Node positive</td>
<td>49%</td>
<td>54%</td>
<td>55%</td>
<td>NS</td>
</tr>
<tr>
<td>ER neg</td>
<td>32%</td>
<td>40%</td>
<td>40%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Triple neg</td>
<td>18%</td>
<td>19%</td>
<td>25%</td>
<td>.001</td>
</tr>
</tbody>
</table>


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**Survival Outcomes**

SEER 17 2000-2005

<table>
<thead>
<tr>
<th>Survival (%)</th>
<th>10 yr relative survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 40: 72-80%</td>
</tr>
<tr>
<td></td>
<td>&gt; 40: 84-86%</td>
</tr>
</tbody>
</table>

Biology

• Young patients have more aggressive phenotype
  – Larger tumor size
  – More grade 3
  – Higher proliferation rates
  – More HER2+ tumors
  – Absence of ER/PR expression
  – More lymph node positive

DCIS: Randomized Trials

Lumpectomy +/- radiation

• NSABP B-17
• EORTC 10853
• SweDCIS
• UK/ANZ

Younger women tend to have a ↑ risk of in breast tumor recurrence
*Radiation was beneficial in all age groups and significantly beneficial in older patients

Incidence of DCIS

23,810 cases from the Florida Cancer Data System

Local Therapy Considerations

• DCIS: Should age impact treatment decisions?
• Invasive Breast Cancer: Age and molecular subtype
  • Is BCT safe or is mastectomy better?
• The role of contralateral prophylactic mastectomy (CPM)
  • Is there a survival advantage to CPM in young women?

SEER 9 data

Lumpectomy +/- radiation

DCIS Age-Adjusted Incidence

2001
2000
1999
1998
1997
1996
1995
1994
1993
1992
1991
1990
Incidence No. per 100,000
80
60
40
20
0
Year of Diagnosis
Age 50+
Age 40-
Age 60+
Age 50


Desantis, JNCI 2011;61:409-411
Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event

Irrespective of:
- Age at diagnosis
- Extent of breast conserving surgery
- Use of tamoxifen
- Method of DCIS detection
- Margin status
- Exfoliation
- Grade
- Comedonecrosis
- Architecture
- Tumor size

XRT halved the rate of ipsilateral breast events

JNCI 2010;41:162-77
Tamoxifen for DCIS by age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>NSABP B-24</th>
<th>UK/A/NZ</th>
<th>EBCTCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 yrs</td>
<td>60%</td>
<td>9.3%</td>
<td>17.9%</td>
</tr>
<tr>
<td>50-59 yrs</td>
<td>38%</td>
<td>27% over all (ipsilateral/contral)</td>
<td></td>
</tr>
<tr>
<td>60-69 yrs</td>
<td>22%</td>
<td>40% in those getting XRT *</td>
<td></td>
</tr>
<tr>
<td>&gt;70 yrs</td>
<td>40%</td>
<td>37%</td>
<td>34%</td>
</tr>
</tbody>
</table>

*No effect of age on tamoxifen efficacy; only XRT and tumor grade influenced efficacy

The benefit of tamoxifen is better for women younger to older than 50. However, XRT is beneficial in all age groups.

Tamoxifen is uniformly beneficial in all recurrences. XRT is beneficial to all women, but less beneficial in younger women.

Petrelli, Radiother Oncol 2011; 195-9

DCIS: What about mastectomy?

- **BCS + XRT**
  - LR 8.9%
  - Avg f/u = 62 months

- **Mastectomy**
  - LR 1.4%
  - Average f/u = 80 months

Boyages, Cancer 1999;85:616-28

**IBIS-II DCIS**
- Randomize postmenopausal women with DCIS to tamoxifen vs anastrozole x 5 years

**NSABP B-35**
- Anastrozole vs tamoxifen in postmenopausal patient with DCIS treated with lumpectomy + XRT

**DCIS and AIs**
- Not appropriate in premenopausal women
- Postmenopausal younger women

**The Real Question:**
Do breast surgery treatment options truly confer the same survival in young women?

**Local recurrence is higher in younger women**
- XRT is less effective in younger women
- The Oxford Overview (EBCTCG) found that LR and survival are linked (4:1)
Survival for DCIS

Despite recurrence, survival remains outstanding

DCIS: Overall Survival

93% 3 yr OS
NCDB Data
N=211,645 DCIS, n=30,263

85% 10 yr OS
SEER Data
N=2,819
1993-1998

Solin, Cancer 2005;103(6):1137-1146

DCIS: DSS

Long-term outcome after BCS with XRT for mammographically detected DCIS

Retrospective series
1,003 women
98% DSS at 15 yrs

Soeteman, JNCI 2013;105:774-781

DCIS treatment options and outcome

Death from breast cancer for the different treatment strategies

- 3 million simulated women aged 45 yrs
- 8-17, 8-24, UK/A/NZ

Sectman, JNCI 2013;105:774-781
**DCIS: Age is Significant**

<table>
<thead>
<tr>
<th>Solin (n=1,003)</th>
<th>Kerlikowske (n=1,036)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P-value LR</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.00062</td>
</tr>
<tr>
<td>Margins</td>
<td>0.024</td>
</tr>
<tr>
<td>Institution</td>
<td>NS</td>
</tr>
<tr>
<td>Date of Tx</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor location</td>
<td>NS</td>
</tr>
<tr>
<td>PET scan</td>
<td>NS</td>
</tr>
<tr>
<td>MMG findings</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical T size</td>
<td>NS</td>
</tr>
<tr>
<td>Volume excised</td>
<td>NS</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td></td>
</tr>
<tr>
<td>Any LR</td>
<td>1.4 (0.6-2.4)</td>
</tr>
<tr>
<td>Age (40-49 v &gt; 50)</td>
<td>3.5 (0.9-2.4)</td>
</tr>
<tr>
<td>Malignant</td>
<td>3.0 (1.4-6.7)</td>
</tr>
<tr>
<td>&lt;1.0 mm</td>
<td>2.3 (1.1-4.9)</td>
</tr>
<tr>
<td>1-1.9 mm</td>
<td>3.1 (1.1-9.0)</td>
</tr>
<tr>
<td>≥10 mm</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Nuclear grade</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>4.6 (2.2-9.8)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.1 (1.1-4.2)</td>
</tr>
<tr>
<td>Low</td>
<td>1.0 (referent)</td>
</tr>
</tbody>
</table>

The importance of age may, in part, depend on what confounding factors you adjust for (or don’t).
**Biology of DCIS**

**Age: DCIS and MF/MC**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;40</th>
<th>40-70</th>
<th>&gt;70</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicentric (%)</td>
<td>29.3</td>
<td>17.7</td>
<td>13.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Multifocality (%)</td>
<td>30.1</td>
<td>17.5</td>
<td>13.0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Alvarado, Ann Surg Oncol 2012

**7,271 Mastectomy Patients with DCIS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Unifocal N=6,884</th>
<th>Multifocal/Multicentric N=887</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I (%)</td>
<td>4.7</td>
<td>9.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Grade II/III (%)</td>
<td>95.3</td>
<td>90.2</td>
<td>87.9</td>
</tr>
</tbody>
</table>

Yerushalmi, Ann Oncol 2012

**DCIS: Age and Comedonecrosis**

**403 Cases of DCIS**

<table>
<thead>
<tr>
<th>Size</th>
<th>Difference by age*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comedonecrosis</td>
<td>Absent = older*</td>
<td>Present = younger*</td>
</tr>
</tbody>
</table>

0.003

*Specifics not given

Perez, Diag Pathol 2014:9:227

**AGE: DCIS and Grade**

**4,037 cases of DCIS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>&lt;40 (n=129)</th>
<th>40-70 (n=1,669)</th>
<th>&gt;70 (n=314)</th>
<th>&lt;40 vs &gt;70</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I (%)</td>
<td>6.7</td>
<td>9.6</td>
<td>13.0</td>
<td>0.029</td>
<td>0.049</td>
</tr>
<tr>
<td>Grade II/III (%)</td>
<td>93.3</td>
<td>90.4</td>
<td>87.0</td>
<td>0.049</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Alvarado, Ann Surg Oncol 2012

**403 cases of DCIS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mean age (y, range)</th>
<th>Low grade = 58.4</th>
<th>High grade = 53.0</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y, range)</td>
<td>Low grade = 58.4</td>
<td>High grade = 53.0</td>
<td>0.027</td>
<td></td>
</tr>
</tbody>
</table>

Perez, Diag Pathol 2014

Age is a surrogate for biology

Should we be looking at DCIS another way???
**DCIS: Phenotypes (All women)**

<table>
<thead>
<tr>
<th>Estimated Phenotype</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2</th>
<th>Basal-like</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>ER or PR+, HER2-</td>
<td>ER or PR+, HER2+</td>
<td>ER, PR, &amp; HER2+, CK5,6+, and EGFR+</td>
<td>ER, PR, &amp; HER2+, CK5,6+, and EGFR+</td>
<td>ER, PR, &amp; HER2+, CK5,6+, and EGFR+</td>
</tr>
<tr>
<td>n (%)</td>
<td>170 (62.5)</td>
<td>36 (13.2)</td>
<td>37 (13.6)</td>
<td>21 (7.7)</td>
<td>8 (2.9)</td>
</tr>
</tbody>
</table>

* IHC

Tamimi, Breast Cancer Res 2008;10:404

---

**DCIS: Phenotypes and LR**

- 314 women (median age 57.7 y)

<table>
<thead>
<tr>
<th>Estimated Phenotype</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2</th>
<th>Triple Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>ER or PR+, HER2-</td>
<td>ER or PR+, HER2+</td>
<td>ER and PR, HER2+</td>
<td>ERPR and HER2+</td>
</tr>
<tr>
<td>LR, all types (10yr)</td>
<td>7.6%</td>
<td>41.5%</td>
<td>47.7%</td>
<td>34.3%</td>
</tr>
</tbody>
</table>

Adjusted HR for LR
Referent | 5.14 (2.04-13.0) | 6.46 (2.40-17.3) | 3.27 (1.13-9.44)

*Adjusted for age, tumor size, grade, Ki67, microinvasion present, surgery type, margin status

<<Age may be just a number and a surrogate for biology>>

Williams, Ann Oncol 2015;26(5):1019

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**DCIS: Phenotypes (Young women <40)**

<table>
<thead>
<tr>
<th>Estimated Phenotype</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>ER or PR+, HER2-</td>
<td>ER or PR+, HER2+</td>
<td>ER, PR, &amp; HER2+, CK5,6+, and EGFR+</td>
<td>ER, PR, &amp; HER2+, CK5,6+, and EGFR+</td>
</tr>
<tr>
<td>n (%)</td>
<td>19 (63.3%)</td>
<td>7 (22.6%)</td>
<td>4 (13.3%)</td>
<td>3 (13.3%)</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>37.2</td>
<td>36.3</td>
<td>30.8</td>
<td>35</td>
</tr>
</tbody>
</table>

* High grade DCIS (73.2%)
* Intermediate grade DCIS (26.8%)
* Tissue microarrays

VandenBusche, Hum Pathol 2013;44(11):2487-93

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**Invasive Breast Cancer: Local Therapy Considerations**

- Rates of local recurrence by age following breast conservation
- Is mastectomy better than breast conservation for young women
- The impact of biology on LR and its interaction with age
Invasive Breast Cancer: Local Therapy

- 6 RCTs have proven that BCT and mastectomy are equal in OS
- 12-23% of women were < 40 y

<table>
<thead>
<tr>
<th>Author</th>
<th>Study years</th>
<th>Breast RT</th>
<th>Systemic Therapy</th>
<th>Age groups (y)</th>
<th>5 yr LR</th>
<th>10 yr LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voogd</td>
<td>1980-1989</td>
<td>All</td>
<td>Node+</td>
<td>&lt; 35, 36-40, 41-50, 51-60, &gt;60</td>
<td>35%</td>
<td>9%</td>
</tr>
<tr>
<td>Cabrasulo</td>
<td>1970-1986</td>
<td>85%</td>
<td>Chemo 30%, Endocrine 25%</td>
<td>&lt;35, 35-65, &gt;60</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Martin</td>
<td>1989-1998</td>
<td>Randomized</td>
<td>Chemo 80%</td>
<td>30-50, 51-60, &gt;60</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Kromer</td>
<td>1982-1998</td>
<td>NA</td>
<td>High risk (42%)</td>
<td>&lt; 35, &gt;40</td>
<td>15%</td>
<td>2%</td>
</tr>
<tr>
<td>Bland</td>
<td>1992-1998</td>
<td>Routine</td>
<td></td>
<td>25-50, 51-60, &gt;60</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Arnott</td>
<td>1997-2006</td>
<td>Routine</td>
<td></td>
<td>20-50, 51-60, &gt;50</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

van Loos, European Journal of Cancer 2013;(49):3093

*1143 women ≤ 40

Changes in Surgical Trends in Young Women

Surgical Operation by year in women < 45 y (Stage 0-II)
Can bigger surgery or mastectomy improve local control in young women?

**LR in young women: Mastectomy vs BCT**
- Population based cancer registry in the Netherlands
- 1,451 women ≤40 treated for Stage I-II IBC from 1988-2005
- 889 treated with BCT vs 562 treated with mastectomy

**Local Control & Survival by surgery type**
- Multivariate analysis:
  - Number of + nodes
  - LVI
  - Margin status
  - Use of chemotherapy
  - NOT TYPE OF LOCAL THERAPY

<<<Young age alone is not a contraindication to BCT>>>

*van der Sangen, Breast Cancer Res Treat 2011;127:207-215*

*Cao, Int J Radiation Oncol Biol Phys 2014;90(3):509-517*
Survival differs by biologic subtype

Survival differs by biologic subtype

Biologic Subtype by Age

Younger women present with higher rates of poor prognostic subtypes

Age appears to confer the same risk in each subtype except for Triple Negative

• Meta-analysis of 12,592 women
• 7,174: BCT
• 5,418: mastectomy

LRR differs by biologic subtype

Kim, World J Surg 2011;35:124

Lowery, Breast Cancer Res Treat 2012;133(3):831-841


Azile et al. (2012) subtypes defined by gene expression profiling

Azile et al. (2011) subtypes defined by flow cytometry

Azile et al. (2012) subtypes defined by flow cytometry

Azile et al. (2011) subtypes defined by gene expression profiling

Breast Cancer subtypes according to age determined by gene expression profiling

Breast Cancer subtypes according to age determined by gene expression profiling
### Interaction of Age, Subtype, and Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recurrence Free Survival</th>
<th>Breast Cancer Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 35 yr (vs. &gt; 35 yr)</td>
<td>1.62</td>
<td>1.79</td>
</tr>
<tr>
<td>HR+/HER2+ vs HR+/HER2-</td>
<td>1.61</td>
<td>3.37</td>
</tr>
<tr>
<td>TN vs HR-/HER2-</td>
<td>2.15</td>
<td>3.49</td>
</tr>
<tr>
<td>HR-/HER2+ vs HR-/HER2-</td>
<td>2.25</td>
<td>3.63</td>
</tr>
<tr>
<td>Mastectomy vs BCS</td>
<td>1.04</td>
<td>NA</td>
</tr>
</tbody>
</table>

Type of surgery not a significant predictor of outcome

Kim, World J Surg 2017;35:124

### Trends in CPM for Unilateral Cancer

A Report from the National Cancer Data Base, 1998-2007

---

### Contra

### laterial P

### rophylactic M

### astectomy

- Trends in CPM in young women
- Risk of contralateral breast cancer (CBC) in young women
- Is there a survival advantage from CPM in young women

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### Changing Surgical Trends in Young Patients

National Cancer Data Base 2003-2010

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### Figure 2

Graph showing percentage trends in the American Joint Committee on Cancer stages.
The risk of CBC is low and has decreased over time
- SEER, 1973-1996
- Incidence of CBC at 5 years: 3%
- Incidence of CBC at 10 years: 6%
- Incidence of CBC at 20 years: 12%
- Both age and receptor status have been shown to be associated with CBC risk


Are we seeing this trend?
What is the risk of contralateral breast cancer (CBC)?

- The risk of CBC is low and has decreased over time
- Incidence of CBC at 5 years: 3%
- Incidence of CBC at 10 years: 6%
- Incidence of CBC at 20 years: 12%
- Both age and receptor status have been shown to be associated with CBC risk


Is there a Survival Advantage to CPM in Young Women?

- Only if it reduces the risk of a fatal CBC
- Studies looking at survival advantage of CPM report conflicting results.
- Cochrane review: insufficient evidence to show CPM has survival advantage*

Lostumbo, Cochrane Database Syst Rev. 2010


DCIS: CPM Rates by Age


CPM is effective
- Reduces risk of CBC by about 90%
The Problem

- Chemotherapy is gonadotoxic
- Fertility wanes with age
- Tamoxifen is teratogenic

Solutions

- Early referral to a reproductive endocrinologist
- Some stop tamoxifen early to try and conceive
Treatment | Age <30 | Age 30-40 | Age >40
--- | --- | --- | ---
None | 0 | <5 | 20-28
CMF x 6 | 19 | 31-38 | 76-96

Partridge, Breast 2007

<table>
<thead>
<tr>
<th>Fertility Preservation Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCO Recommendations for Fertility Preservation</td>
</tr>
<tr>
<td>- Assessment of risk for infertility</td>
</tr>
<tr>
<td>- Communication with patient</td>
</tr>
<tr>
<td>- Patient at risk for treatment induced infertility</td>
</tr>
<tr>
<td>- Patient interested in fertility preservation options</td>
</tr>
<tr>
<td>- Refer to specialist with expertise in fertility preservation</td>
</tr>
</tbody>
</table>

Eligible for proven fertility preservation method |
- Testicular sperm extraction |
- Embryo cryopreservation |
- Oocyte cryopreservation |
- Conservative gynecologic surgery |
- Investigational fertility preservation techniques |
- Cryopreservation of ovarian tissue |
- Ovarian suppression |
- Clinical or natural pregnancy encouraged |

Fertility Concerns in Young Women

N = 620 women ≤ 40 at dx
- 51% were concerned about becoming infertile after treatment
- 68% recalled discussing fertility issues with their physician before treatment
- 10% pursued fertility preservation techniques
  - 7% underwent embryo cryopreservation
  - 1% underwent oocyte cryopreservation
  - 3% received gonadotropin-releasing hormone agonist

Ruddy, JCO, 2014

Embryo vs Oocyte Cryopreservation

- Both require controlled ovarian hyperstimulation
- Both require same amount of time 2-3 weeks
- Key difference: Whether or not oocytes are fertilized prior to freezing
- In experienced centers, approximately equally effective
- More centers are experienced with embryo cryopreservation and long-term outcomes are better studied

Ruddy, JCO, 2014
Does suppressing the ovaries during chemotherapy help protect future fertility?

- GnRH agonists are most often used
  - Induce ovarian quiescence and temporary menopause
- Some studies reported menses in > 90% of women after chemotherapy
- Criticisms
  - Most studies are small
  - Return of menses ≠ fertility
  - Reproductive outcomes poor
  - Low rates of pregnancy

**GnRH as Fertility Preservation Meta-Analysis**

<table>
<thead>
<tr>
<th>Author, location of study</th>
<th>No. with ovarian function (%)</th>
<th>No. with ovarian function (%)</th>
<th>No. with ovarian function (%)</th>
<th>No. with ovarian function (%)</th>
<th>IVF success (% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bentwich et al 2005, Israel</td>
<td>75 (70-82)</td>
<td>38 (46-54)</td>
<td>12 (20-23)</td>
<td>2.01 (1.58-2.50)</td>
<td></td>
</tr>
<tr>
<td>Bentwich et al 2005, Israel</td>
<td>8 (8-10)</td>
<td>9 (4-44)</td>
<td>2 (3-23)</td>
<td>2.29 (1.94-2.76)</td>
<td></td>
</tr>
<tr>
<td>Cohen-Falk et al 2007, Spain</td>
<td>50 (27-93)</td>
<td>9 (6-23)</td>
<td>2 (3-23)</td>
<td>3.91 (1.91-7.99)</td>
<td></td>
</tr>
<tr>
<td>Cohn et al 2008, Israel</td>
<td>7 (7-10)</td>
<td>6 (5-83)</td>
<td>1 (2.15-4.62)</td>
<td>1.31 (1.16-1.48)</td>
<td></td>
</tr>
<tr>
<td>Loporcaro et al 2007, Italy</td>
<td>14 (14-100)</td>
<td>15 (7-47)</td>
<td>1 (2.14-3.73)</td>
<td>2.14 (1.18-3.73)</td>
<td></td>
</tr>
<tr>
<td>Pinsky &amp; Neumann et al 2007, Argentina</td>
<td>12 (12-100)</td>
<td>17 (11-65)</td>
<td>1.41 (1.87-2.3)</td>
<td>1.41 (1.87-2.3)</td>
<td></td>
</tr>
<tr>
<td>Pinto et al 2004, John-Hopkins</td>
<td>4 (4-100)</td>
<td>12 (20-67)</td>
<td>1 (2.14-3.73)</td>
<td>2.14 (1.18-3.73)</td>
<td></td>
</tr>
<tr>
<td>Siu Y et al 2006, University of Michigan</td>
<td>20 (19-95)</td>
<td>30 (14-70)</td>
<td>2 (3.36-5.19)</td>
<td>2.29 (1.94-2.76)</td>
<td></td>
</tr>
<tr>
<td>Weitman et al 1997, U.K. Summary RR</td>
<td>8 (4-50)</td>
<td>9 (6-67)</td>
<td>1 (2.14-3.73)</td>
<td>2.14 (1.18-3.73)</td>
<td></td>
</tr>
</tbody>
</table>

GnRH agonists associated with a 68% ↑ in ovarian function
22% vs 14% achieved pregnancy

**POEMS results**

- Important caveats
  - Study closed early due to funding issues
  - Loss to f/u and incomplete menstrual and FSH data collection
  - More pregnancy attempts in goserelin arm

- No perfect study
- Most suggest some benefit
- Potential benefit may outweigh the risks 1° in ER- tumors
- Can use after cryopreservation of oocytes or embryos

Moore, NEJM 2015;372:923-32
Conclusion: Breast Cancer in Young Women

- Different incidence
- Different risk factors
- Different biology
- Different mortality

Conclusions: Breast Cancer in Young Women - Invasive

- Young age is associated with higher rates of local failure
- LR for BCT > mastectomy, but no survival advantage
- LRR & survival differ by biologic subtype
- Young women present with more aggressive biology
- Age continues to impact outcome in HR+ tumors, less impact on outcome in TN tumors
- Bigger surgery does not overcome bad biology

Conclusion: Breast Cancer in Young Women - DCIS

- LR is higher in younger women
- LR for BCT > mastectomy in younger women, OS appears =
- XRT is less effective in younger women, but still provides a benefit
- Tamoxifen is equally effective across age groups for DCIS
- DCIS has an outstanding outcome
- Age is a surrogate for biology and that surrogacy needs to be better defined
- Phenotypes do exist in DCIS and may be a better method of characterization

Conclusions: CPM

- 25-30% of young women with early stage breast cancer are undergoing CPM
- CPM ↓ CBC by about 90%
- Risk of a CBC is low and has ↓ over time
- CBC are smaller and less aggressive