Chemoprevention of Breast Cancer: Who, What, When?

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Risk management prescription
- Quantitative risk assessment
- [Genetic counseling]
- [Genetic testing]
- Re-evaluation of risk over time
- Chemoprevention
- Imaging strategies or protocols
- Prophylactic surgery
- Regular follow-up visits for screening, monitoring and education

NSABP Breast Cancer Prevention Trial Design

Eligible Women at High Risk (5-yr risk ≥ 1.66%)

Randomization
n = 13,388

Tamoxifen
5 Years
n = 6681

Placebo
5 Years
n = 6707


BCPT Results: Cumulative Rate of Invasive Breast Cancer

Cumulative rates per 1000 women of invasive and non-invasive breast cancers in NSABP P-1 participants by treatment group


Summary of accrual and follow-up information

NSABP STAR Trial
- Total accrual = 19,747 women
- 3 women not at risk (bilateral mastectomy)
- Without follow-up n = 254
- Included in the analysis (through March 31, 2009) n = 19,490
- Average follow-up = 76.8 months
- Total woman-years of follow-up = 124,673

NSABP STAR Trial through March 31, 2009
Comparison of Predicted and Observed Invasive Breast Cancer Cases

- Tamoxifen: Predicted 500, Observed 247 (51.6% reduction)
- Raloxifene: Predicted 510, Observed 310 (39.9% reduction)

Average Annual Rate and Number of Uterine Cancers

- Tamoxifen: Average Annual Rate per 1000 = 65, 95% CI: 0.36 to 0.83
- Raloxifene: Average Annual Rate per 1000 = 37

Cumulative Incidence of Thromboembolic Events

- Tamoxifen: At Risk by Year 0 6 8 Events at 8 yrs. P-value
- Raloxifene: At Risk by Year 0 6 8 Events at 8 yrs. P-value

Average Annual Rate and Number of Invasive Breast Cancers in the NSABP STAR Trial

- Gail Model Projection: Av Ann Rate per 1000 = 312
- TAM: Av Ann Rate per 1000 = 163
- Raloxifene: Av Ann Rate per 1000 = 168

Vogel VG et al. JAMA 295(23):2727-2741, 2006
Noninvasive Breast Cancer or Atypia Present at Randomization in the NSABP STAR Trial

<table>
<thead>
<tr>
<th>Atypical LCIS</th>
<th>Hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number</td>
<td>1,789</td>
</tr>
<tr>
<td>% of Randomized</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Vogel VG et al. JAMA 295(23):2727-2741, 2006

In situ breast cancer cases in the NSABP STAR Trial

<table>
<thead>
<tr>
<th>Tamoxifen</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>As reported</td>
<td>57</td>
</tr>
<tr>
<td>Eliminating those with baseline LCIS</td>
<td>28</td>
</tr>
<tr>
<td>Eliminating LCIS or DCIS within the first year</td>
<td>18</td>
</tr>
</tbody>
</table>


NSABP STAR Trial
Average Annual Rate And Number of Non-invasive (In Situ) Cancers

Relative risk = 1.40
95% Confidence Interval: 0.98 to 2.00

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th># of Events</th>
<th>Rate per 1000</th>
<th>Risk Ratio</th>
<th>RR 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS</td>
<td>30</td>
<td>0.79</td>
<td>1.16</td>
<td>1.46</td>
</tr>
<tr>
<td>LCIS</td>
<td>21</td>
<td>0.56</td>
<td>0.76</td>
<td>1.37</td>
</tr>
<tr>
<td>Mixed</td>
<td>6</td>
<td>0.16</td>
<td>0.18</td>
<td>1.16</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>1.51</td>
<td>2.11</td>
<td>1.40</td>
</tr>
</tbody>
</table>

Vogel VG et al. JAMA 295(23):2727-2741, 2006
**STAR Trial DCIS cases by history of atypical hyperplasia**

- Treated with tamoxifen: 16, 14 (n = 30)
- Treated with raloxifene: 29, 15 (n = 44)

**Average Annual Rate and Number of Invasive Breast Cancers by History of Atypical Hyperplasia and Lobular Carcinoma in Situ**

- Atypical hyperplasia treated with tamoxifen: 0, 3
- Atypical hyperplasia treated with raloxifene: 3, 6
- LCIS: Tamoxifen 33, Raloxifene 41
- Atypical Hyperplasia: Tamoxifen 33, Raloxifene 46

**Cumulative incidence of invasive breast cancer in the NSABP STAR Trial 81-month update**

- Cumulative incidence for tamoxifen and raloxifene with P=0.01

**Meta-analysis summary**

- Meta-analysis indicates that the relative risk for estrogen receptor (ER)-positive invasive breast cancer is:
  - 0.55 for tamoxifen and
  - 0.43 for raloxifene

  which is a 45% reduction in risk of ER-positive breast cancer for tamoxifen and 57% for raloxifene, respectively
Risks and benefits
Tamoxifen Raloxifene

Ratio of beneficial to adverse effects for tamoxifen and raloxifene

Events in 1000 women over 7 years

- Invasive and non-invasive breast cancers prevented
- Endometrial cancers and thrombotic events

Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk for invasive breast cancer

- Tamoxifen
- Raloxifene

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Women in whom SERMs should be considered (1)
- History of lobular carcinoma in situ (LCIS)
- History of ductal carcinoma in situ (DCIS)
- History of atypical ductal or lobular hyperplasia
Atypia and tamoxifen use in the STAR Trial

- Half of women who submitted risk assessments were eligible for the trial
  BUT only 20% of eligible women enrolled
- Women with a diagnosis of atypical lobular or ductal hyperplasia in STAR were 70% more likely to agree to undertake SERM therapy than were women without these lesions, probably reflecting their more positive risk/benefit profiles


Women in whom SERMs should be considered (2)

- Women with mutations in either the BRCA1 or BRCA2 genes
  (other predisposing genetic mutations?)
- Women with Gail model
  5-year probability of breast cancer ≥ 1.66% and significant benefit:risk profile

Women in whom caution should be used when considering the use of SERMs

- History of stroke, transient ischemic attack, deep vein thrombosis, pulmonary embolus
- History of cataracts or cataract surgery
- Current use of hormone replacement therapy

Numbers of prescriptions for tamoxifen and raloxifene in the United States from 1995 to 2008
Guidelines for Breast Cancer Chemoprevention

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendation</th>
<th>Criteria</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF 2000</td>
<td>High risk should be counseled about chemoprevention</td>
<td>Gail Model</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Canadian Task Force on Preventive Health Care, 2001</td>
<td>High risk should be counseled about chemoprevention</td>
<td>Gail Model</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>ASCO, 2009</td>
<td>High risk may be offered chemoprevention</td>
<td>Gail Model or LCIS</td>
<td>Tamoxifen, Raloxifene</td>
</tr>
<tr>
<td>NCCN, 2012</td>
<td>High risk may be offered chemoprevention</td>
<td>Gail Model or LCIS</td>
<td>Tamoxifen, Raloxifene, Exemestane</td>
</tr>
</tbody>
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Atypical Breast Lesions and Chemoprevention

- Review of 76,333 path reports from 1987-2010 in 3 Boston hospitals
- 2,460 women with atypical breast lesions, 1999-2010
- Chart review for use of tamoxifen, raloxifene or aromatase inhibitor
- 18% of patients received chemoprevention

Breast Cancer at 10 years

<table>
<thead>
<tr>
<th></th>
<th>Chemoprevention YES</th>
<th>Chemoprevention NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>8.5%</td>
<td>19.9</td>
</tr>
<tr>
<td>ALH</td>
<td>8.5%</td>
<td>18.7%</td>
</tr>
<tr>
<td>LCIS</td>
<td>10.3%</td>
<td>32.4%</td>
</tr>
<tr>
<td>DCIS/ADH</td>
<td>2.1%</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

Coopey et al. SABCS, 2011

MAP3 trial

- A randomized, placebo-controlled, double-blind trial of exemestane designed to detect a 65% relative reduction in invasive breast cancer
- Eligible postmenopausal women 35 years of age or older had at least one of the following risk factors:
  - 60 years of age or older; Gail 5-year risk score greater than 1.66% (chances in 100 of invasive breast cancer developing within 5 years);
  - prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ;
  - ductal carcinoma in situ with mastectomy.

Cumulative Incidence of Invasive Breast Cancer

Because the risk of clotting increases with age, and because both stroke and pulmonary embolism are potentially life-threatening consequences of tamoxifen therapy, careful consideration must be given to risks versus benefits in older postmenopausal women who are considering tamoxifen for risk reduction.

Chemoprevention with a SERM may be particularly beneficial to women with atypical hyperplasia, a 5-year Gail model risk of more than 5%, lobular carcinoma in situ, or two or more first-degree relatives with breast cancer.
Recommendations for raloxifene, Visvanathan K et al, 2009

- May be offered to reduce the risk of ER-positive invasive BC in postmenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS
- Impact on breast cancer mortality is unknown
- May be used longer than 5 years in women with osteoporosis, in whom breast cancer risk reduction is a secondary benefit
- Should not be used for breast cancer risk reduction in premenopausal women (there are no data)
- Not recommended for use in women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack
- Weigh risks and benefits in decision making