Early Detection, Risk Reduction and Primary Care Support of Breast Cancer

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3 November 2008

2008 Breast Cancer Estimates

182,460 NEW CASES
- 4% Melanoma of Skin
- 4% Thyroid
- 26% Breast
- 14% Lung & Bronchus
- 3% Leukemia
- 10% Colon & Rectum
- 3% Ovary
- 6% Uterus
- 3% Urinary
- 4% Non-Hodgkin’s Lymphoma
- 23% All Other Sites

40,480 DEATHS
- 2% Brain
- 15% Breast
- 26% Lung & Bronchus
- 6% Pancreas
- 9% Colon & Rectum
- 6% Ovary
- 3% Uterus
- 2% Urinary
- 2% Liver and biliary
- 3% Non-Hodgkin’s Lymphoma
- 3% Leukemia
- 23% All Other Sites
49 yo Woman Presents with a Breast Mass that She Found on Self Exam

- What history do you want?
  - How long has she known about it?
  - How has she been feeling in general?
    - Fatigue, pain anywhere, shortness of breath, nausea, headache
  - How has her general health been?
    - Diabetes, heart disease, hypertension, renal, pulmonary or liver problems, tobacco, alcohol
  - Does she have known risk factors for breast cancer?
  - Last menstrual period
Breast Cancer Risk Factors

- Age
- Family history including age and bilaterality
- Age at menarch
- Age at first live birth
- Prior breast biopsies
  - Atypia

How did these get to be known as risk factors?

The Breast Cancer Detection Demonstration Project

- Took place from 1973-1980
- 29 mammography centers funded by the NIH to provide free breast exams and mammograms in order to increase the use of mammography
- 283,222 women screened
- 4,275 breast cancers detected (9% by exam alone)
- Participants filled out health questionnaires and answers were correlated with diagnosis of breast cancer

In 1989, these risk factors were weighted and combined in a statistical model by Mitchell Gail to estimate a woman’s five-year and lifetime risk of breast cancer
Are There Other Risk Factors?

• Alcohol use—linear correlation in several cohort studies
• Hormone replacement therapy with estrogen + progesterone combination (not with estrogen alone in women who have had prior hysterectomy)—Women’s Health Initiative study
• Oral contraceptives—long time, current users
• Prior mid-range dose breast irradiation

Breast Cancer Incidence by Age

Ravdin P, et al. 2007, NEJM
Breast Cancer Incidence and HRT Usage

Ravdin P, et al. 2007, NEJM

Question

• What is the most important thing to know about risk factors for breast cancer?
**Answer**

Most women who get breast cancer have

No Risk Factors!

**What Other History is Important?**

- Family history of breast/ovarian cancer
  - BRCA1 and BRCA2
- Pre-menopausal breast cancer, childhood sarcoma, brain tumors, adrenal cancers, acute leukemia (Li-Fraumeni syndrome)
- Breast cancer, thyroid cancer, multiple hamartomas (Cowden’s syndrome)
American Cancer Society Guidelines for Breast Cancer Screening Using MRI

Recommend Annual MRI Screening (Based on Evidence)
• BRCA mutation
• First-degree relative of BRCA carrier but untested
• Lifetime risk ~20–25% or greater as defined by BRCAPRO or other models that are largely dependent on family history

Recommend Annual MRI Screening (Based on Expert Consensus Opinion)
• Radiation to chest between age 10 and 30 years
• Li-Fraumeni syndrome and first-degree relatives
• Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives


American Cancer Society Guidelines for Breast Cancer Screening Using MRI

Insufficient Evidence to Recommend for or Against MRI Screening
• Lifetime risk 15–20%, as defined by BRCAPRO or other models that are largely dependent on family history
• Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)
• Atypical ductal hyperplasia (ADH)
• Heterogeneously or extremely dense breast on mammography
• Women with a personal history of breast cancer including ductal carcinoma in situ (DCIS)

Recommend Against MRI Screening (Based on Expert Consensus Opinion)
• Women at 15% lifetime risk

Physical Exam: What Do You Document?

- Tumor size
- Location in the breast (quadrant)—draw a picture
- Skin fixation, edema, erythema
- Chest wall fixation
- Nodes: ipsilateral, contralateral, supraclavicular, infraclavicular, cervical. Also matted or fixed and size
- Contralateral breast exam
- Cardiac, lung and abdominal exams

NSABP Protocol B-07

Relation of management of the breast to disease free survival and survival

Total M. | Segmental M. | Segmental M. + Breast Radiation
---|---|---
713 | 719 | 731
“The secret of the care of the patient is in caring for the patient.”

Francis W. Peabody
“The Care of the Patient”
Lecture to Harvard Medical School Students
1927

Breast Cancer Risk Reduction

The Breast Cancer Prevention Trial (BCPT) and The Study of Tamoxifen and Raloxifene (STAR)
NSABP B-14 Study in Node negative, ER+ Pts

Design

Randomized

Placebo

Tamoxifen

Basis for BCPT: NSABP B-14 Trial

Second Cancer in Opposite Breast

<table>
<thead>
<tr>
<th></th>
<th>PLAC</th>
<th>TAM</th>
</tr>
</thead>
<tbody>
<tr>
<td># Cancers</td>
<td>55</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>1424 pts.</td>
<td>1419 pts.</td>
</tr>
</tbody>
</table>

p=0.001
ELIGIBLE PARTICIPANTS

RANDOMIZATION (n=13,388)

TAMOXIFEN 5 YEARS (n= 6681)

PLACEBO 5 YEARS (n = 6707)

BCPT Design: Selection Criteria

- Age $\geq$ 60 years
- Lobular neoplasia on breast biopsy
- Age 35-59 with elevated risk ($\geq$ 1.66% 5-yr risk)
- Modified Gail model incorporated the following variables
  - Number of affected 1st degree female relatives
  - Number of previous breast biopsies
  - Atypical hyperplasia
  - Menarche age
  - Nulliparity or age of first live birth
  - Race

Cumulative Rate of Invasive Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>175</td>
<td>43.4</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>89</td>
<td>22.0</td>
</tr>
</tbody>
</table>

P < 0.00001

www.breastcancerprevention.org
ER Status

<table>
<thead>
<tr>
<th>Rate/1000</th>
<th>Negative</th>
<th>Positive</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31</td>
<td>41</td>
<td>14</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* # of events


BCPT Results: Invasive Breast Cancer Cases in All Age Groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total</th>
<th>35-49</th>
<th>50-59</th>
<th>60+</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>175</td>
<td>68</td>
<td>50</td>
<td>57</td>
</tr>
<tr>
<td>20</td>
<td>89</td>
<td>38</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>140</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>160</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BCPT Results: Annual Breast Cancer Cases**

![Bar chart showing annual breast cancer cases for Placebo and Tamoxifen groups over 6 years of follow-up.]

- Year 1: Placebo 24, Tamoxifen 6
- Year 2: Placebo 46, Tamoxifen 21
- Year 3: Placebo 39, Tamoxifen 24
- Year 4: Placebo 31, Tamoxifen 16
- Year 5: Placebo 28, Tamoxifen 8
- Year 6: Placebo 24, Tamoxifen 4


**BCPT Results: Fracture Events**

<table>
<thead>
<tr>
<th>Fracture Site</th>
<th>Placebo</th>
<th>Tamoxifen</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>137</td>
<td>111</td>
<td>0.81</td>
<td>0.63-1.05</td>
</tr>
<tr>
<td>Hip</td>
<td>22</td>
<td>12</td>
<td>0.55</td>
<td>0.25-1.15</td>
</tr>
<tr>
<td>Colles’</td>
<td>23</td>
<td>14</td>
<td>0.61</td>
<td>0.29-1.23</td>
</tr>
</tbody>
</table>

### BCPT

**Invasive Endometrial Cancers by FIGO Stage**

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>%</td>
</tr>
<tr>
<td>I</td>
<td>14</td>
<td>93</td>
</tr>
<tr>
<td>II &amp; III</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

### BCPT

**Endometrial Cancers by Age**

<table>
<thead>
<tr>
<th>Age</th>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 49</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>≥ 50</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>15</td>
<td>36</td>
</tr>
</tbody>
</table>
ACOG Recommendations for Monitoring Women on Tamoxifen

• Alert patients to the signs of endometrial pathology
• Instruct patients to report abnormal vaginal bleeding
• Annual gynecologic evaluation
• Gynecologic evaluation and endometrial sampling in the presence of abnormal vaginal bleeding
• Routine biopsy and ultrasound *not* necessary in absence of symptoms

ACOG Committee on Gynecologic Practice. February 1996.

BCPT Results: Vascular Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>DVT</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>CVA</td>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>TIA</td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

PE = pulmonary embolism; DVT = deep vein thrombosis; CVA = cerebral vascular accident (stroke); TIA = transient ischemic attack

### BCPT Vascular Events by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 49</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>≥ 50</td>
<td>60</td>
<td>91</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>110</td>
</tr>
</tbody>
</table>

### BCPT Quality of Life Data

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Tamoxifen</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal discharge</td>
<td>55</td>
<td>34</td>
<td>1.60</td>
</tr>
<tr>
<td>Cold sweats</td>
<td>21</td>
<td>15</td>
<td>1.45</td>
</tr>
<tr>
<td>Genital itching</td>
<td>47</td>
<td>38</td>
<td>1.23</td>
</tr>
<tr>
<td>Night sweats</td>
<td>67</td>
<td>55</td>
<td>1.22</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>78</td>
<td>65</td>
<td>1.19</td>
</tr>
<tr>
<td>Pain with intercourse</td>
<td>28</td>
<td>24</td>
<td>1.17</td>
</tr>
</tbody>
</table>
BCPT Quality of Life Data (cont’d)

- Symptoms NOT associated with tamoxifen
  - Depression
  - Nausea
  - Vaginal dryness
  - Weight gain
  - Irregular menses
  - Fluid retention

Management of “Bothersome” Tamoxifen Side Effects

Before Starting Therapy

- Take baseline history, especially noting menopausal symptoms that already exist
- Inform patient of potential side effects
- Assure patient that interventions are available to deal with side effects
Management of “Bothersome” Tamoxifen Side Effects (cont’d)

During Therapy

- Initiate discussions with patient at follow-up visits regarding any symptoms
- Do not minimize or dismiss any symptom
- Monitor intervention efficacy and, if symptoms do not abate, try a different intervention
- Consider a “drug holiday” if side effects become intolerable

Symptom Management for Hot Flushes

- Vitamin E: 1000-1200 IU/day (unproven)
- *SSRIs: venlafaxine or citalopram
- Gabapentin (increase to 300 mg t.i.d.)
- Clonidine (patch)

* Other SSRIs block CYP2D6 enzyme responsible for activation of tamoxifen to endoxifin
NSABP P-1
Breast Cancer Prevention Trial
Summary

• Randomized, Double-Blind Study, Tamoxifen vs. Placebo
• 13,388 participants at increased risk for breast cancer
• 49% reduction in invasive breast cancer (P=0.00001)
• First randomized trial to demonstrate that the incidence of breast cancer can be reduced

Chemical Structure

Tamoxifen

Raloxifene
MORE Study

Postmenopausal women with osteoporosis

- Placebo
- Raloxifene 60 mg/d
- Raloxifene 120 mg/d

MORE Trial Subjects

- 7,705 postmenopausal women < age 80 at 180 sites in 25 countries
- Osteoporosis
  - Prevent vertebral fracture and/or
  - Hip or spine bone density T-score ≤ –2.5
- Exclusions
  - Prior breast or endometrial cancer
  - Abnormal uterine bleeding
Raloxifene Reduced the Risk of Invasive Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>2,576</td>
<td>5,129</td>
</tr>
<tr>
<td>Breast cancer cases</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>Woman-yrs of follow-up</td>
<td>7,484</td>
<td>15,007</td>
</tr>
<tr>
<td>Rate (per 1,000 pt.-yrs)</td>
<td>3.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Raloxifene RR (95% CI) = 0.24 (0.13, 0.44)  P<0.0001

Cummings et al; JAMA 1999

Venous Thromboembolism

<table>
<thead>
<tr>
<th></th>
<th>BCPT</th>
<th>Placebo</th>
<th>Tamoxifen</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DVT</td>
<td>22</td>
<td>35</td>
<td>1.6 (0.9, 2.9)</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>6</td>
<td>18</td>
<td>3.0 (1.2, 9.3)</td>
</tr>
</tbody>
</table>

MORE

<table>
<thead>
<tr>
<th></th>
<th>DVT or PE</th>
<th>Placebo</th>
<th>Raloxifene</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>49</td>
<td></td>
<td>3.1 (1.5, 6.2)</td>
</tr>
</tbody>
</table>

Cummings et al; JAMA 1999
Raloxifene and Endometrial Cancer

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects*</td>
<td>1,999</td>
<td>3,958</td>
</tr>
<tr>
<td>Endometrial cancer cases</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Rate (per 1,000 pt.-yrs)</td>
<td>0.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Raloxifene RR (95% CI) = 0.8 (0.21, 2.67)

* Based on 5,957 women without hysterectomy

Cummings et al; JAMA 1999

NSABP STAR Schema

Risk-Eligible Postmenopausal Women

STRATIFICATION
- Age
- Gail Model Risk
- Race
- History of LCIS

TAMOXIFEN
- 20 mg/day
- x 5 years

RALOXIFENE
- 60 mg/day
- x 5 years
STAR Trial Objectives

Primary objective:

Evaluate the effect of raloxifene vs. tamoxifen in reducing the incidence of

• Invasive breast cancer

STAR Trial Objectives

Secondary objectives:

• Noninvasive breast cancer
• Endometrial cancer
• Ischemic Heart Disease
• Fractures
  – Hip
  – Spine
  – Wrist (Colles')
NSABP STAR

Eligibility

• 35 years of age or older
  – Postmenopausal
  – Risk eligible

NSABP P-2

STAR Summary of Screening, Accrual and Follow-Up Information

Women screened for breast cancer risk 184,460
Women who were breast cancer risk eligible 96,368
Women randomly assigned treatment 19,747
Total person-years of follow-up 76,828
Average follow-up (months) 47.3
P-2 STAR

Prior Hysterectomy 51.5%
(10,027)

Cumulative Incidence of Invasive Breast Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk by Year</th>
<th># of Events</th>
<th>Rate/1000 at 6 yrs.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>9726 6653 809</td>
<td>163</td>
<td>25.1</td>
<td>0.83</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>9745 6703 833</td>
<td>168</td>
<td>24.8</td>
<td></td>
</tr>
</tbody>
</table>
P-2 STAR
Average Annual Rate and Number of Uterine Cancers

RR = 0.62, 95% CI: 0.35 to 1.08

<table>
<thead>
<tr>
<th></th>
<th>TAM</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia</td>
<td>84</td>
<td>14</td>
</tr>
<tr>
<td>with Atypia</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>w/o Atypia</td>
<td>72</td>
<td>13</td>
</tr>
</tbody>
</table>

* # of events
# of Hysterectomies for Non-Cancer Reasons

<table>
<thead>
<tr>
<th></th>
<th>TAM</th>
<th>RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>244</td>
<td>111</td>
</tr>
</tbody>
</table>

P-2 STAR
Cumulative Incidence of Thromboembolic Events

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk by Year</th>
<th># of Events</th>
<th>Rate/1000 at 6 yrs.</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>9726 6682 814</td>
<td>141</td>
<td>21.0</td>
<td>0.70</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>9745 6764 836</td>
<td>100</td>
<td>16.0</td>
<td></td>
</tr>
</tbody>
</table>

P-value= 0.01
P-2 STAR
Average Annual Rate and Number of Strokes

<table>
<thead>
<tr>
<th></th>
<th>TAM</th>
<th>Raloxifene</th>
<th>Av Ann Rate per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Osteoporotic Fractures by Site and Treatment Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of event</td>
<td>Tamoxifen #</td>
<td>Raloxifene #</td>
<td>Risk Ratio (RR)</td>
</tr>
<tr>
<td>Hip</td>
<td>26</td>
<td>23</td>
<td>0.88</td>
</tr>
<tr>
<td>Spine</td>
<td>53</td>
<td>52</td>
<td>0.98</td>
</tr>
<tr>
<td>Radius (Colles’)</td>
<td>27</td>
<td>23</td>
<td>0.85</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>98</td>
<td>0.92</td>
</tr>
</tbody>
</table>

* # of events
P-2 STAR

Summary

• In post-menopausal women raloxifene is as effective as tamoxifen in the prevention of primary invasive breast cancer
• Compared to tamoxifen, raloxifene use results in
  – Fewer thromboembolic events
  – Fewer endometrial cancers
  – Fewer cataracts