Breast Cancer: Risk Assessment and Prevention

Nadine M. Tung, MD
Beth Israel Deaconess Medical Center
Cancer Risk

Risk Assessment
- Genetic testing referral? (BRCA1/2)
- If no inherited mutation - use models (e.g., Gail)

Risk Management
- Screening
- Prevention medications
- Prophylactic surgery
- Lifestyle strategies
How Much Breast and Ovarian Cancer Is Hereditary?

Breast Cancer
- 15%-20% Hereditary
- 5-10% Sporadic
- Family clusters

Ovarian Cancer
- ~15-20% Hereditary
Mutations are Found Throughout the BRCA1 and BRCA2 Genes
Autosomal Dominant Inheritance

Father with mutation on one chromosome

Each child has a 50% chance of inheriting an autosomal dominant disorder
BRCA1-2 Mutations Increase the Risk of Early-Onset Breast Cancer

By age 40
Population Risk: 0.5%
Hereditary Risk: 10% - 20%

By age 50
Population Risk: 2%
Hereditary Risk: 33% - 50%

By age 70
Population Risk: 7%
Hereditary Risk: 56% - 87%
BRCA1-2 Mutations Increase the Risk of Ovarian Cancer

By age 70

Population Risk
Hereditary Risk

< 2%
28% - 59% (BRCA1)
16% - 27% (BRCA2)

Ovarian cancer/ fallopian tube cancer/ primary peritoneal cancer
Risks of Other Cancers: BRCA1/2

- Male Breast Cancer (BRCA2 > BRCA1)
  - 7-8% by age 70 (≤ 1% in general population)

- Prostate Cancer (BRCA2/BRCA1)
  - ~ 23% by age 80 (10% in general population)

- Pancreatic Cancer (BRCA2 > BRCA1)
  - 2-8% by age 80 (< 1% in general population)

- Melanoma (BRCA2 > BRCA1)
  - 5% (ocular as well)

Thompson, JNCI 2002, 94:1358
Liede, JCO 2004, 22:735
Features that Indicate an Increased Likelihood of *BRCA* mutation

- Ovarian, Pancr Cancer, Metast Prostate Cancer (any age)
- Young breast cancer (≤ 45 years; ≤ 50 if small family)
- Multiple cases of breast cancer in family (≥ 3 or ≥ 2 if one ≤ age 50)
- Two breast cancers in the same woman, first ≤ 50 yrs
- Ashkenazi Jewish heritage & breast cancer
- Male breast cancer
- Triple Negative Breast Cancer ≤ age 60
- 3 relatives same side of family: Breast Cancer (any age), +/or Prostate Cancer
- Known BRCA mutation in the family
How Much Breast and Ovarian Cancer Is Hereditary?

Breast Cancer

15%-20%

5-10%

Sporadic
Family clusters
Hereditary
## Gene Mutations Associated with a Hereditary Predisposition to Breast Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Breast Cancer Risk (by age 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High penetrance (RR &gt; 5; Lifetime Risk &gt; 40%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>Breast-ovarian</td>
<td>57-87%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Breast-ovarian</td>
<td>57-87%</td>
</tr>
<tr>
<td>TP53</td>
<td>Li-Fraumeni</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden Syndrome</td>
<td>25-50%</td>
</tr>
<tr>
<td>STK11/LKB1</td>
<td>Peutz-Jeghers</td>
<td>45-54%</td>
</tr>
<tr>
<td>CDH1</td>
<td>Diffuse gastric cancer</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Moderate penetrance (RR 2-5; Lifetime risk 20-40%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>Pancreatic cancer</td>
<td>NA</td>
</tr>
<tr>
<td>ATM</td>
<td>Ataxia-telangectasia</td>
<td>NA</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Li-Fraumeni variant</td>
<td>NA</td>
</tr>
</tbody>
</table>

# Breast/Ovarian Cancer Risks with Novel Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALB2</td>
<td>Y (OR 5.3)</td>
</tr>
<tr>
<td>ATM</td>
<td>Y (OR 2.8)</td>
</tr>
<tr>
<td>CHEK2 (truncating)</td>
<td>Y (OR 3.0)</td>
</tr>
<tr>
<td>NBN</td>
<td>Y (OR 2.7)</td>
</tr>
<tr>
<td>NF1</td>
<td>Y (OR 2.6)</td>
</tr>
<tr>
<td>BRIP1</td>
<td></td>
</tr>
</tbody>
</table>

Easton et al NEJM 2015
Next-Gen sequencing: gene panels

1. Allow simultaneous analysis of multiple genes...for similar cost

2. Several different companies- with different genes in their panels

3. Generally, include genes at least 2X risk of cancer

4. Approaches to multi-gene panels
   - All cancer risk genes in one panel vs one type cancer
   - High risk genes only vs high and mod risk genes
Hereditary Multigene Panels

---

**Hereditary Cancer Next-Gen Panels by Gene**

<table>
<thead>
<tr>
<th>GENES</th>
<th>BreastNext</th>
<th>OvaNext</th>
<th>ColoNext</th>
<th>CancerNext</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BARD1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRE11A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRS3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUTYH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPCAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMPRIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMAD4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **ALL CANCERS**
- **COLON**
- **BREAST**
- **BREAST + OVARY**

(COPYRIGHT)
For patients who previously had negative BRCA 1/2 testing

- Consider referral back to genetics if:
  - Tested before 2007: need updated BRCA testing
  - Tested before 2014: did not get multi-gene testing

- Remember
  - Family history changes - retake every year
    - Patient who previously did not meet testing criteria, may now
Cancer Risk

- Risk Assessment
  - Genetic testing referral? (BRCA, etc)
  - If no inherited mutation - use models (e.g., Gail)

- Risk Management
  - Screening
  - Prevention medications
  - Prophylactic surgery
  - Lifestyle strategies
## Established Risk Factors for Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (<em>≥</em> 50 vs &lt; 50)</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Familial/Hereditary factors</strong></td>
<td></td>
</tr>
<tr>
<td>First degree relative</td>
<td>2 (1.4-13.6)</td>
</tr>
<tr>
<td>BRCA mutation</td>
<td>6-14</td>
</tr>
<tr>
<td><strong>Reproductive and Hormonal</strong></td>
<td></td>
</tr>
<tr>
<td>Menarche &lt; 12 or menopause ≥ 55</td>
<td>~ 1.5</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2.0</td>
</tr>
<tr>
<td>Age of FLB &gt;30</td>
<td>1.3 – 2.2</td>
</tr>
<tr>
<td>Hormone replacement therapy (E + P)</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td><strong>Benign breast lesions</strong></td>
<td>Absolute risk 1-2%/ year</td>
</tr>
<tr>
<td>LCIS</td>
<td>4.0 - 4.4</td>
</tr>
<tr>
<td>atypical hyperplasia</td>
<td></td>
</tr>
<tr>
<td><strong>Exposure to ionizing radiation</strong> (&lt;30 yo)</td>
<td>1.4 (related to age)</td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong> (12g/d vs none)</td>
<td>1.1 - 4.0</td>
</tr>
<tr>
<td><strong>Increased body mass index</strong> (post-men)</td>
<td>1.3 - 2.5</td>
</tr>
</tbody>
</table>
## Risk of Breast Cancer with benign findings on breast biopsy

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Risk of breast cancer (RR)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-proliferative</td>
<td>none</td>
<td>- simple fibroadenoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- fibrocyctic changes</td>
</tr>
<tr>
<td>Proliferative Without Atypia</td>
<td>1.5-2.0</td>
<td>- usual ductal hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- complex fibroadenoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Sclerosing adenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- papilloma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- radial scar</td>
</tr>
<tr>
<td>Proliferative With Atypia</td>
<td>&gt; 2.0</td>
<td>- <strong>Atypical hyperplasia:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ductal (ADH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- lobular (ALH)</td>
</tr>
</tbody>
</table>
## Breast Pathology and Risk of Breast Cancer

<table>
<thead>
<tr>
<th>Normal</th>
<th>Atypical Hyperplasia (AH)</th>
<th>Carcinoma in-situ (CIS)</th>
<th>Invasive Cancer (IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal</td>
<td>ADH</td>
<td>DCIS</td>
<td>IDC</td>
</tr>
<tr>
<td>Lobular</td>
<td>ALH</td>
<td>LCIS</td>
<td>ILC</td>
</tr>
</tbody>
</table>

Normal cells

[Image of normal cells]

ADH

[Image of atypical ductal hyperplasia]

DCIS

[Image of ductal carcinoma in situ]

IDC

[Image of invasive ductal carcinoma]

ALH

[Image of atypical lobular hyperplasia]

LCIS

[Image of lobular carcinoma in situ]

ILC

[Image of lobular carcinoma]
Carcinoma In-situ (CIS)
Pre-invasive breast cancer: cannot metastasize

- **DCIS (ductal carcinoma in-situ):**
  - Usually dx by calcifications on mammogram
  - Usually involves one duct system of the breast
  - Treated like breast cancer with mastectomy or lumpectomy and radiation

- **LCIS (lobular carcinoma in-situ):**
  - Dx incidentally on biopsy for other reason
  - Presumed to exist throughout both breasts
  - Therefore surgical treatment would have to be bilateral mastectomies

- **Both:** associated with ~ 1-2%/year risk of invasive breast cancer if not resected
### Breast pathology and Risk of Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Atypical Hyperplasia (AH)</th>
<th>Carcinoma in-situ (CIS)</th>
<th>Invasive Cancer (IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ductal</strong> ADH</td>
<td></td>
<td>DCIS</td>
<td>IDC</td>
</tr>
<tr>
<td></td>
<td>4x ↑ risk</td>
<td>Considered “cancer”</td>
<td></td>
</tr>
<tr>
<td><strong>Lobular</strong> ALH</td>
<td></td>
<td>LCIS</td>
<td>ILC</td>
</tr>
<tr>
<td></td>
<td>4x ↑ risk</td>
<td>1.3% risk/yr invasive cancer</td>
<td></td>
</tr>
</tbody>
</table>
Breast Cancer Risk

- **Risk Assessment**
  - Genetic testing referral? (BRCA1/2)
  - If no inherited mutation - use models (e.g., Gail)

- **Risk Management**
  - Screening
  - Prevention medications
  - Prophylactic surgery
  - Lifestyle strategies
Models:

Breast Cancer Risk Assessment

- **Gail** (BCRAT): online
- **Claus**: app (iphone, ipad)
- **Tyrer-Cuzick** (IBIS): online
Gail model (BCRAT)
http://www.cancer.gov/bcrisktool/

- age
- family history
- reproductive history
  - age menses
  - age at FLB
- previous breast biopsies
- Atypical hyperplasia?
- Ethnicity

Calculates 5-yr and LTR invasive breast cancer
Gail Model Shortcomings
( limited family history )

- Only includes info about FDR
- No paternal history
- No 2\textsuperscript{nd} degree relatives
- Does not ask age of breast cancer
Claus Model

Claus et al. Cancer 1994
Tyrer-Cuzick model (IBIS)

www.ems-trials.org/riskevaluator/

In addition to including the most family history, includes:

- BMI (height/weight)
- Age at menopause
- HRT use
- LCIS
- Breast density
- Genetic testing results

NOT in Gail Model
Risk Assessment Models

- **Gail (BCRAT)**
  - +: family hx and other risk factors
  - +: Most validated
  - -: Limited fam hx; not include breast density

- **Claus**
  - +: quick
  - -: Only family hx

- **Tyrer-Cuzick**
  - +: Family hx and other risk factors
  - -: not user friendly
Risk Assessment Models

- **Gail (BCRAT)**
  - + : family hx and other risk factors
  - +: Most validated
  - - : Limited family hx

If strong family history-
refer for genetic testing and more extensive risk assessment (other models)
Breast Density
Mammographic Density and the Risk and Detection of Breast Cancer

Mammographic Breast Density

The diagram shows the relative risk associated with different categories of breast density. The categories are:

- None
- <10%
- 10–25%
- 25–50%
- 50–75%
- >75%

The relative risk is represented by the height of the bars, with the highest risk being 5.3. The images above the graph illustrate the appearance of breasts with different density levels.
| A- fatty (10%) |
| B- scattered fibroglandular (40%) |
| C- heterogeneously dense (40%) |
| D- extremely dense (10%) |

50% women have “dense breasts”
Not reproducible
Only increases accuracy of models slightly
What constitutes an increased risk of breast cancer?

- 5 year risk: ≥ 1.7% (by any model)
  - Used as criteria for participation in breast cancer prevention medication trials

- Lifetime risk (by any model): used to determine MRI
  - 15-25%: moderate risk
  - > 25%: high risk
Breast Cancer Risk

- **Risk Assessment**
  - Genetic testing referral? (BRCA, etc)
  - If no inherited mutation - use models (e.g., Gail)

- **Risk Management**
  - Screening
  - Prevention medications
  - Prophylactic surgery
  - Lifestyle strategies
Mammography
Odds Ratio for breast cancer death
8 randomized trials: 13 yr F/U

Mammograms: 20% decrease in breast cancer deaths

Adapted from Cochrane review 2011
# Mammography Guidelines in the US

## “Average Risk Woman”

<table>
<thead>
<tr>
<th>Organization</th>
<th>Start Screening at age, y</th>
<th>Stop Screening at age, y</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF</td>
<td>50</td>
<td>74</td>
<td>Every 2 yrs (avg risk)</td>
</tr>
<tr>
<td>ACS</td>
<td>45</td>
<td>As appropriate based on life expectancy</td>
<td>45-54: annual ≥ 55: biennial</td>
</tr>
<tr>
<td>ACR, ACOG</td>
<td>40</td>
<td></td>
<td>annual</td>
</tr>
</tbody>
</table>
What’s the controversy for women in their 40’s?
**USPSTF: Benefit of Mammography by Age**

*Table 1. Pooled RRs for Breast Cancer Mortality From Mammography Screening Trials for All Ages*

<table>
<thead>
<tr>
<th>Age</th>
<th>Trials Included, n</th>
<th>RR for Breast Cancer Mortality (95% CrI)</th>
<th>NNI to Prevent 1 Breast Cancer Death (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39–49 y</td>
<td>8*</td>
<td>0.85 (0.75–0.96)</td>
<td>1904 (929–6378)</td>
</tr>
<tr>
<td>50–59 y</td>
<td>6†</td>
<td>0.86 (0.75–0.99)</td>
<td>1339 (322–7455)</td>
</tr>
<tr>
<td>60–69 y</td>
<td>2‡</td>
<td>0.68 (0.54–0.87)</td>
<td>377 (230–1050)</td>
</tr>
<tr>
<td>70–74 y</td>
<td>1§</td>
<td>1.12 (0.73–1.72)</td>
<td>Not available</td>
</tr>
</tbody>
</table>

*Ann Intern Med. 2009;151:727-737*
Benefit of Mammography: Radiologists Argue

However:

- Better results with modern technology?
  - Not all studies used digital mammography (some used single view)

- Better results if analyze just those who screened?
  - Screening compliance only 70%
In order to save one breast cancer death...

<table>
<thead>
<tr>
<th>Age</th>
<th>↓ in Breast Cancer Death</th>
<th># Women Needed to be Invited to Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>39-49</td>
<td>15%</td>
<td>1904</td>
</tr>
<tr>
<td>50-59</td>
<td>15%</td>
<td>1339</td>
</tr>
<tr>
<td>60-69</td>
<td>32%</td>
<td>377</td>
</tr>
<tr>
<td>70-74</td>
<td>------</td>
<td>------</td>
</tr>
</tbody>
</table>

What are the possible “harms” of mammography?

- False + (call back, anxiety, biopsy)
- Overdiagnosis (DCIS, indolent invasive cancers)
Which women age 40-49 have risk = woman > age 50

- Family hx
  - 9% have FDR with breast cancer

- Prior breast biopsy
  - Atypical hyperplasia, LCIS etc.

*Annals Int Med, 2012; 157: 597-8*
Women at increased risk of breast cancer: When to start mammograms?

- “5-10 years earlier than the youngest breast cancer in the family”

- No mammograms until > age 30?
  - Lack of sensitivity of mammograms in very young women
  - Radiation exposure in developing breast

JCO 29: 2011 (suppl; abstr 1526)
American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography

- Lifetime risk of breast cancer > 20-25%

Saslow et al. CA Cancer J Clin 2007; 57:75-89
Higher Sensitivity for Detecting Breast Cancer at Earlier Stage if MRI + Mammography

<table>
<thead>
<tr>
<th></th>
<th>MRI + mammo</th>
<th>mammo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 cm</td>
<td>43%</td>
<td>12%</td>
</tr>
<tr>
<td>Negative nodes</td>
<td>79%</td>
<td>44%</td>
</tr>
</tbody>
</table>
MRI vs mammogram:
women at increased risk of breast cancer

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>mammogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity</td>
<td>95%</td>
<td>36%</td>
</tr>
<tr>
<td>specificity</td>
<td>77% - 95% *</td>
<td>99.8%</td>
</tr>
</tbody>
</table>

* Specificity of MRI extremely operator (radiologist) dependent

Drawbacks of Breast MRI

- Specificity lower than mammography: false positives (unnecessary biopsies)
- More difficult: claustrophobic; injection; longer
- Expensive
- No contrast if renal disease
Who should have MRI screening?

- BRCA+
- Hx of chest radiation (e.g., Hodgkins disease)
- > 20-25% lifetime risk of breast cancer?
  - if willing to accept false +
  - Especially if dense breasts on mammogram
MRI: more controversial

- LCIS
- Atypical hyperplasia
- Dense breasts on mammo
- LTR 15-20%
- Personal history breast cancer

Saslow et al. CA Cancer J Clin 2007; 57:75-89
MRI and mammogram

- MRI does not replace mammography
- Alternate annual mammogram and MRI every 6 months?
3D mammogram
(digital mammography + tomosynthesis)
2D vs 3D mammo

- 454,850 patients at 13 sites
- Not randomized

Cancer Detection:
- 2D mammo: 4.2 / 1000
- 3D mammo: 5.4 / 1000 (+1 invasive cancer)

Recall rate:
- 2D: 10.7%
- 3D: 9.1%

3D: more radiation (negligible)

Friedewald et al. JAMA 2014; 311: 2499-2507
Marinovich et al. JNCI 2018- meta-analysis
Sensitivity: 1000 women screened

# breast cancers detected

- Mammo 8
- Mammo + US 11 + 3
- Mammo + MRI 26 +15
- Mammo + MRI + US 26 +15

One Approach

- Average Risk (< 15% LTR): Not Dense
  - 2D or 3D mammography
- Average Risk (< 15% LTR): Dense
  - 2D or 3D mammography.....plus US?
- High Risk (ACS guidelines): > 20-25% LTR
  - Mammography & Breast MRI
    ------Coming soon------
- Intermediate risk (15-20% LTR): Dense
  - mammography & Abbreviated MRI (q 2 yrs?)
  - contrast enhanced mammography
Management of Breast Cancer Risk

- Screening
- Prevention medication
  - tamoxifen
  - raloxifene
  - aromatase inhibitor (e.g., exemestane)
- Preventative (Prophylactic) Surgery
- Lifestyle strategies
Breast Cancer Prevention Meds

- **Tamoxifen and Raloxifene (SERMS)**
  - Competitive antagonists of the estrogen receptor in breast tissue
  - *tamoxifen*: effective in *pre-* and *postmenopausal*
  - *raloxifene*: only studied in *postmen women* (osteoporosis)

- **Aromatase inhibitors (exemestane, anastrozole)**
  - Prevent estrogen production in *postmenopausal* women: block conversion of androgens to estrogen

- **Rationale**: tamoxifen and aromatase inhibitors- less contralateral breast cancer
Randomized Control Trials (RCT) for Breast Cancer Prevention

- “Women at increased risk”

- Eligibility varied
  - 5 year risk breast cancer $\geq 1.7\%$ (Gail, IBIS/Tyrer-Cuzick models)
  - LCIS
  - Strong family history
## Select Randomized Chemoprevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Meds</th>
<th>Pop</th>
<th>invasive breast cancer (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP P-1</td>
<td>13,175</td>
<td>Tamoxifen vs placebo</td>
<td>Premen &amp; Postmen</td>
<td>0.51 (0.39-0.66)</td>
</tr>
<tr>
<td>IBIS-I</td>
<td>7,154</td>
<td></td>
<td></td>
<td>0.74 (0.58–0.94)</td>
</tr>
<tr>
<td>STAR</td>
<td>19,471</td>
<td>Raloxifene vs tamoxifen</td>
<td>Postmen</td>
<td>1.24 (tam better) (1.05–1.47)</td>
</tr>
<tr>
<td>MAP.3</td>
<td>4,560</td>
<td>Aromatase vs placebo</td>
<td>Postmen</td>
<td>0.35 (0.18–0.70)</td>
</tr>
<tr>
<td>IBIS-II</td>
<td>3,864</td>
<td></td>
<td></td>
<td>0.50 (0.32–0.76)</td>
</tr>
</tbody>
</table>

Fisher JNCI 1998  
Goss NEJM 2011  
Cuzick JNCI 2007  
Cuzick Lancet 2014  
Vogel Cancer Prev Res 2010
Benefit of Prevention Meds

- Tamoxifen: ~ 50% decrease in breast cancer
- Raloxifene: 75% as effective as tamoxifene = 37.5% decrease in breast cancer
- Aromatase inhibitors: 65% decrease in breast cancer

NSABP P-1
STAR trial
IBIS-II
MAP.3
How Long do the benefits of tamoxifen last?
IBIS-1 Trial

- European breast cancer prevention trial: tamoxifen x 5 yrs vs placebo
- The breast cancer risk reduction was constant for 10 years
- Most of the side effects only lasted while on tamoxifen

Side effects of tamoxifen

- **Side effects:**
  - **Serious:**
    - Blood clot ($\leq 1\%$)
    - **Uterine cancer** (additional 1%)
    - **Cataracts** (20% relative increase)
  - **Nuisance**
    - **Menopausal**: Hot flashes etc
    - Non-cancerous vaginal bleeding
    - Others
Weighing risks/benefits of tamoxifen chemoprevention

Best therapeutic ratio for tamoxifen:

< age 50 or

> age 50 with hysterectomy

Fisher et al. JNCI 2005; 97:1652
1. Raloxifene: 75% as effective as tamoxifen

2. But Raloxifene safer:
   raloxifene (compared to tamoxifen)
   - Endometrial cancer: no increase with raloxifene
   - DVT/PE: ↓ RR = 0.75 (CI: 0.60-0.93)
   - Cataracts: ↓ RR = 0.80 (CI: 0.72-0.89)

3. Both meds increase bone density equally

Vogel et al. JAMA 2006; 295:2727-2741
Risks/Benefits:
tamoxifen/raloxifene chemoprevention
STAR trial

Aromatase inhibitors

- Main Side effects:
  - Arthralgias/Myalgias: reversible
  - Decrease bone density

- Bones: increase in age-related bone loss
  - T-score loss at 2 years:
    - additional -1.2 (hip) -1.9 (spine)

Lancet Oncol 2012; 13: 275–84
USPSTF 2013/2019 and ASCO 2013 Guidelines for Breast Cancer Prevention Medication Use

- Discuss with women ≥ age 35 with 5 years risk (absolute) ≥ 1.7 (includes LCIS) (≥ 3% better)

- Pre-menopausal: tamoxifen

- Post-menopausal:
  - Tamoxifen- 20 mg/day
  - Raloxifene- 60 mg/day
  - Exemestane- 25 mg/day (Anastrazole 1.0 mg/day)

- Discuss Benefits vs Risks

Visvanathan et al. JCO 2013; 31: 2942-2962
JAMA. 2019;322(9):857-867
Management of Breast Cancer Risk

- Screening
- Prevention medication
- Preventative (Prophylactic) Surgery
- Lifestyle strategies
Prophylactic Mastectomy

Simple (total) mastectomy

Lifetime risk of breast cancer decreased by 90%

Meijers-Heijboer et al. NEJM 2001;345:159
Rebbeck et al. JCO 2004; 22:1055
Breast Reconstruction (DIEP FLAP) after Prophylactic Mastectomies

BEFORE

AFTER
Other possible prevention strategies:

**lifestyle and supplements**

- Exercise – yes
- Limit alcohol consumption- yes
- Maintain optimal weight- yes (especially post-menopausal)

- Soy ?
- Diet- probably no
- Vitamin D?
- Aspirin- no
Hormonal Contraception and Breast Cancer Risk

- 1.8 million Danish women: 15-49 yo
- Current/recent users: RR 1.2 (1.12-1.26)
- Increased risk with longer duration
  - < 1 yr (RR 1.09); > 10 yrs RR 1.38
- Risk ↓ after cessation, except for those who used > 5 yrs (still risk at 5 yrs after stopping)
- No difference for various combinations or for progestins (even Mirena)
- ↑ risk if start < age 20 ??

Morch et al NEJM 2017
Nadine Tung
ntung@bidmc.harvard.edu