Breast Cancer: Risk Assessment and Prevention

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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
Breast/Ovarian Cancer Genetics
How Much Breast and Ovarian Cancer Is Hereditary?

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

Ovarian Cancer:
- Sporadic
- Family clusters: 10-15%
- Hereditary: ~20-25%

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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: < 2%
Hereditary Risk: 28% - 59% (BRCA1), 16% - 27% (BRCA2)
Risks of Other Cancers: \textit{BRCA1/2}

- Male Breast Cancer (\textit{BRCA2} > \textit{BRCA1})
  - 7-8\% by age 70 (\textless 1\% in general population)

- Prostate Cancer (\textit{BRCA2/BRCA1})
  - 33-39\% by age 70 (7\% in general population)

- Pancreatic Cancer (\textit{BRCA2} > \textit{BRCA1})
  - 2-8\% by age 80 (\textless 1\% in general population)

- Melanoma (\textit{BRCA2} > \textit{BRCA1})
  - 5\% (ocular as well)

Thompson, JNCI 2002, 94:1358;
Liede, JCO 2004, 22:735
1. **Pre-test and post-test counseling** by “health care professional” trained to counsel and interpret results

2. Several **models** to determine sufficient risk
   (insufficient data to recommend one vs another)
   - Based on family hx
   - Statistical models based on family hx ( > 10% ?)
Features that Indicate an Increased Likelihood of BRCA mutation

- Ovarian cancer (any age) (fallopian tube and PPC)
- 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: Breast Cancer +/or Pancreatic Cancer +/or Prostate Cancer (> Gleason 7)
Has patient received the most “up-to-date” BRCA testing?

- **BRCA test changes**
  - 2006: large rearrangement analysis began
  - Since 2013: routinely included in BRCA testing
How Much Breast and Ovarian Cancer Is Hereditary?

Breast Cancer

- Sporadic
- Family clusters
- Hereditary

10-15%
15%-20%
# 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>Low-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>
<tr>
<td>BRIP1</td>
<td>Fancomi’s anemia</td>
<td>NA</td>
</tr>
</tbody>
</table>

Hereditary Cancer Risk Panels

- Next generation (next-gen) sequencing panel
- Simultaneously analyze 14 - 25 (or more) genes that are associated with inherited cancer
- Generally, include genes at least 2X risk of cancer
- For breast cancer, ~ 4% of women who test negative for BRCA1/2 will have another mutation

Kurian et al. JCO 2014; 32: 2001
Tung et al. 2015;121:25-33.
Gene-Panel Sequencing and the Prediction of Breast-Cancer Risk

Douglas F. Easton, Ph.D., Paul D.P. Pharoah, Ph.D., Antonis C. Antoniou, Ph.D., Marc Tischkowitz, M.D., Ph.D., Sean V. Tavtigian, Ph.D., Katherine L. Nathanson, M.D., Peter Devilee, Ph.D., Alfons Meindl, Ph.D., Fergus J. Couch, Ph.D., Melissa Southey, Ph.D., David E. Goldgar, Ph.D., D. Gareth R. Evans, M.D., Georgia Chenevix-Trench, Ph.D., Nazneen Rahman, M.D., Ph.D., Mark Robson, M.D., Susan M. Domchek, M.D., and William D. Foulkes, M.B., B.S., Ph.D.
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
# 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>
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<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>PMS2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>APC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMPR1A</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>

**Breast**

**Ovarian**

**Colon**

**All Cancers**
Next-Gen hereditary gene panels

- But:
  - Who should test? All BRCA-negative?
  - What genes should be in the panel?
  - What is the risk of breast cancer (and other cancers) with mutations in other genes?
  - VUS (Variants of Uncertain Significance): nonpathogenic or deleterious mutation?
  - Surprise findings
For patients who previously had negative BRCA 1/2 testing

- Consider referral back to genetics if:
  - Tested before 2006 (BART)
  - Strong family history of cancer
  - Diagnosed at young age
  - Diagnosed with multiple cancers

- May need:
  - Updated BRCA testing
  - Panel testing for other cancer susceptibility genes
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> (≥ 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> (risk for either breast)</td>
<td></td>
</tr>
<tr>
<td>LCIS</td>
<td>Absolute risk 1-2%/ year</td>
</tr>
<tr>
<td>atypical hyperplasia</td>
<td>4.0 - 4.4</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>▪ fibrocystic 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>▪ radal scar</td>
</tr>
<tr>
<td>Proliferative With Atypia</td>
<td>&gt; 2.0</td>
<td>▪ Atypical hyperplasia:</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></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></td>
<td>ADH</td>
<td>DCIS</td>
<td>IDC</td>
</tr>
<tr>
<td><img src="#" alt="Normal cells" /></td>
<td><img src="#" alt="ADH" /></td>
<td><img src="#" alt="DCIS" /></td>
<td><img src="#" alt="IDC" /></td>
</tr>
<tr>
<td><strong>Lobular</strong></td>
<td>ALH</td>
<td>LCIS</td>
<td>ILC</td>
</tr>
<tr>
<td><img src="#" alt="Normal cells" /></td>
<td><img src="#" alt="ALH" /></td>
<td><img src="#" alt="LCIS" /></td>
<td><img src="#" alt="ILC" /></td>
</tr>
</tbody>
</table>
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
<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></td>
<td>ADH 4x ↑ risk</td>
<td>DCIS Considered “cancer”</td>
<td>IDC</td>
</tr>
<tr>
<td><strong>Lobular</strong></td>
<td>ALH 4x ↑ risk</td>
<td>LCIS 1-2 % risk invasive cancer/year</td>
<td>ILC</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)
- Tyret-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
(family history questions)

- Includes limited fam hx (only FDR)
- No paternal history
- No extended family - does NOT ask about 2nd degree relatives
- Does not ask age of breast cancer in relatives
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

NOT in Gail Model
Risk Assessment Models

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

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

- **Tyrer-Cuzick**
  - +: Family hx and other risk factors
  - -: Time consuming
What other risk factors are not in the models?

- Breast Density
- SNPs
Mammographic Density and the Risk and Detection of Breast Cancer

Mammographic Breast Density

![Diagram showing mammograms and relative risk for different categories of breast density.](image)

- **None**: Relative Risk 1
- **<10%**: Relative Risk 1.2
- **10 - 25%**: Relative Risk 2.2
- **25 - 50%**: Relative Risk 2.4
- **50 - 75%**: Relative Risk 3.4
- **>75%**: Relative Risk 5.3

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Mammographic Breast Density

- 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
SNPs: Single nucleotide polymorphisms

= Single base pair changes in genes
Breast Cancer Susceptibility Genes

Clinical

>5x
High

2-5x
Moderate

< 2x
Moderate: GWAS

Foulkes, NEJM 2008
Polygenic Risk Score

- ~ 80 SNPs identified that increase risk of breast cancer
- Each RR < 1.5
- Multiply them together = polygenic risk score
- Not included in risk models or clinical testing for inherited cancer risk genes
What constitutes an increased risk of breast cancer?

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

- **Lifetime risk** (by any model):
  - 15-30%: moderate risk
  - > 30%: high risk
Breast Cancer Risk

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Mammography
Odds Ratio for breast cancer death
8 randomized trials: 13 yr F/U

Adapted from Cochrane review 2011
Odds Ratio for breast cancer death

8 randomized trials: 13 yr F/U

Adapted from Cochrane review 2011
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
What’s the controversy for women in their 40’s?
US Preventive Services Task Force (USPSTF): 2009 update on mammogram recommendations: avg risk

- Age 40-49: does not recommend routine screening
  - Except BRCA+ or hx of chest radiation (Hodgkins disease)

- Age 50-74: biennial screening

- > Age 75: insufficient data to make recommendation
# Recommendations for Mammography

## Average Risk Woman

<table>
<thead>
<tr>
<th>USPSTF</th>
<th>ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age 50-74: q 2 yrs</td>
<td>- Age 45-54: annual</td>
</tr>
<tr>
<td></td>
<td>- ≥ 55: q 2 years</td>
</tr>
<tr>
<td></td>
<td>- &gt; 70 if healthy</td>
</tr>
</tbody>
</table>
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% Crl)</th>
<th>NNI to Prevent 1 Breast Cancer Death (95% Crl)</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>
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>
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<tbody>
<tr>
<td>39-49</td>
<td>15%</td>
<td>1904</td>
<td>726</td>
</tr>
<tr>
<td>50-59</td>
<td>15%</td>
<td>1339</td>
<td>260</td>
</tr>
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<td>198</td>
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What are the possible “harms” of mammography?

- False + (call back, anxiety, biopsy)
- Overdiagnosis (DCIS, indolent invasive cancers)
**Recommendations for Mammography**

**Average Risk Woman**

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<tr>
<td></td>
<td>&gt; 55: q 2 years</td>
</tr>
</tbody>
</table>

**Caveat: Patient’s Values**

- **< age 45:** can **still have mammogram** if willing to accept harms (F+ and overdx)
- **> age 55:** can **have annual** mammogram if willing to accept harms (F+ and overdx)
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.

- **Wisdom study** (using Gail model, mammography density and SNPs)

*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
Breast Cancers Detected with MRI: Smaller and More Often Node Negative

<table>
<thead>
<tr>
<th></th>
<th>With MRI</th>
<th>Without MRI</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>

NEJM 2004; Vol 351:427
## MRI vs Mammogram in High Risk Women: Increased Sensitivity, Decreased Specificity

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>Mammogram</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>95%</td>
<td>36%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>95% *</td>
<td>99.8%</td>
</tr>
</tbody>
</table>

* Specificity of MRI extremely operator (radiologist) dependent

Warner et al. JAMA 2004; 292:1317
Drawbacks of Breast MRI

- Specificity lower than mammography: false positives (unnecessary biopsies)
- More difficult: claustrophobic; injection; longer
- Expensive
- IV contrast (gadolinium) required
- 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? (fam hx)
  - If willing to accept false +
  - Especially if dense breasts on mammogram
MRI and mammogram

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

<table>
<thead>
<tr>
<th></th>
<th>digital</th>
<th>tomosynthesis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per 1000 screens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer dx</td>
<td>4.2</td>
<td>5.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>--invasive</td>
<td>2.9</td>
<td>4.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>--DCIS</td>
<td>1.4</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Call back</td>
<td>107 (11%)</td>
<td>91 (9%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Friedewald et al. JAMA 2014; 311: 2499-2507
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: no endometrial cancer
    - Only studied in postmen women (osteoporosis)

- Aromatase inhibitors (exemestane, anastrazole)
  - 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 ≥ 1.7% (Gail, IBIS 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  
Vogel Cancer Prev Res 2010
Benefit of Prevention Meds

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

Limitations of prevention meds

- Only estrogen-receptor positive (ER+) breast cancers decreased
- No survival benefit demonstrated
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
Raloxifene: STAR trial

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**

<table>
<thead>
<tr>
<th>5-Year Projected Risk of IBC (%)</th>
<th>Tamoxifen vs Placebo (with uterus)</th>
<th>Raloxifene vs Placebo (with uterus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0</td>
<td>50-59: 3, 60-69: -175, 70-79: -190</td>
<td>50-59: 128, 60-69: 97, 70-79: 93</td>
</tr>
</tbody>
</table>

*Freedman et al. J Clin Oncol 2011; 29:2327-2333*
Aromatase inhibitors

- Main Side effects:
  - Arthritis/ 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 2009 and ASCO 2013 Guidelines for Breast Cancer Prevention Medication Use

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

- 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
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
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