Breast Cancer screening in 2016

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Clinical Assistant Professor
Family Medicine Refresher Course
• No financial disclosures.
43 yo woman presents for health maintenance. She is nulliparous, premenopausal and had an aunt who was diagnosed with breast cancer at 67y. She would like to know when she should start screening mammograms and how often.
Aims:

• Review factors influencing breast cancer risk

• Discuss the evidence behind the most recent screening guidelines for mammography

• Describe other screening modalities, and their pros and cons

• Discuss recommendations for screening high risk women
BREAST CANCER RISK FACTORS
Risk Factors - SEX

Age-standardized rates (ASR) with the estimated annual percentage changes in the ASR for male and female breast cancer incidence rates.

Anderson W F et al. JCO 2010;28:232-239
Risk Factors - AGE

<table>
<thead>
<tr>
<th>If current age is..</th>
<th>10 yr risk (%)</th>
<th>Or 1 in...</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.6</td>
<td>1,760</td>
</tr>
<tr>
<td>30</td>
<td>0.44</td>
<td>229</td>
</tr>
<tr>
<td>40</td>
<td>1.45</td>
<td>69</td>
</tr>
<tr>
<td>50</td>
<td>2.31</td>
<td>42</td>
</tr>
<tr>
<td>60</td>
<td>3.49</td>
<td>29</td>
</tr>
<tr>
<td>70</td>
<td>3.84</td>
<td>27</td>
</tr>
<tr>
<td>80</td>
<td>3.0</td>
<td>33</td>
</tr>
<tr>
<td>lifetime</td>
<td>12.42</td>
<td>8</td>
</tr>
</tbody>
</table>

SEER Cancer Statistics Review 1975-2010
Age specific probability of developing invasive breast cancer
Risk factors - RACE

Female Breast Cancer
Incidence Rates* by Race and Ethnicity, U.S., 1999–2010
## Risk factors – HORMONAL/REPRODUCTIVE

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopause &gt; 55yrs</td>
<td>↑ by 2</td>
</tr>
<tr>
<td>First menstruation &lt; 12 yrs</td>
<td>↑ by 4</td>
</tr>
<tr>
<td>Never pregnant</td>
<td>↑ by half</td>
</tr>
<tr>
<td>Late first pregnancy</td>
<td>↑ by 2</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>↑ by 2</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>↓ by about 10%</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>↑ by 24%</td>
</tr>
</tbody>
</table>
## Risk Factors – LIFESTYLE/MEDICAL HISTORY

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Effect on risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal obesity</td>
<td>↑ by 2</td>
</tr>
<tr>
<td>Alcohol use (≥1 glass/dy)</td>
<td>↑ by about 30%</td>
</tr>
<tr>
<td>Personal history of breast cancer</td>
<td>↑ by 2-3</td>
</tr>
<tr>
<td>History of chest radiation at a young age</td>
<td>↑ by 10-15</td>
</tr>
<tr>
<td>Prior breast biopsies</td>
<td>Depends (2-8 fold increase)</td>
</tr>
<tr>
<td>Dense breasts on mammography</td>
<td>↑ by 2-5</td>
</tr>
</tbody>
</table>
Breast density

(Are you dense?)
Risk factors –

Family History

Only 20% of women with breast cancer have a family history; but women with a family history have a higher risk of breast cancer

- Mother/sister/daughter: risk $\uparrow \times 2$
- Mother and sister: risk $\uparrow \times 3.5$
- Aunt/cousin/grandma: risk $\uparrow$ by 50%

Risk is affected by number and age of relatives with cancer

About 2% of familial cancers are caused by a specific hereditary mutation

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BRCA 1 and 2 mutation

- 0.1% of the population have the mutation
- Breast cancer risk is 48-76% lifetime
- Genetic counseling indicated when there is a ≥10% probability of the mutation
- Testing cost $3400
  - Thresholds required to ensure insurance coverage
- Genetic Information Nondiscrimination Act (GINA) - 2008
Who should get testing?
NCCN guidelines

- Known family history of mutation
- Personal h/o breast cancer and:
  - Age <46yr
  - Bilateral breast cancer
  - Age <60 and triple negative breast cancer
  - Dx < 50y with 1 or more relatives with BC/OC
  - Dx any age with 2 or more relatives with BC/OC
  - Dx any age with 1 or more relative dx <50yrs
  - Dx any age with 2 or more relative with pancreatic/prostate
  - Dx any age with 1 or more relative with ovarian Ca
- Personal history of ovarian cancer
- Male breast cancer
- Pancreatic cancer or prostate cancer < 50y with ≥ 2 relatives with breast/ovarian/pancreatic cancer
- Family history only
  - 1\textsuperscript{st}/2\textsuperscript{nd} degree relative meeting any above criteria
  - Third degree relative with breast/ovarian with ≥ 2 close relatives with breast/ovarian (at least 1 under 50yrs)

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# Models for calculating risk

## Germline Mutation Risk Prediction Models
- BRCAPRO
- BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm)
- IBIS
- Myriad II
- Manchester
- Penn II

## Breast Cancer Risk Assessment Models
- Gail
- Claus
- Tyrer-Kuzik
- Jonker
Modified Gail model risk assessment tool
http://brca.nci.nih.gov/brc

6 breast cancer risk factors

- Age
- hormonal or reproductive history (age at menarche and age at first live birth)
- previous history of breast disease (number of breast biopsies and history of atypical hyperplasia)
- family history (number of first-degree relatives with breast cancer).

High risk ≥ 20% lifetime risk or ≥ 1.7% 5 yr risk
Limitations of risk prediction models

<table>
<thead>
<tr>
<th>Germline Mutation Risk Prediction Models</th>
<th>Breast Cancer Risk Assessment Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adoption, small family size</td>
<td>• Reliance on known risk factors (60% of breast cancers occur in the absence of known risk factors)</td>
</tr>
<tr>
<td>• Lack of information/ inaccurate information about family history</td>
<td>• Not all risk factors included</td>
</tr>
<tr>
<td>• Only includes 1st and 2nd degree relatives</td>
<td>• Less accurate for patient different from the source data population</td>
</tr>
<tr>
<td>• Other cancers not included</td>
<td></td>
</tr>
<tr>
<td>• Population specific details not included</td>
<td></td>
</tr>
</tbody>
</table>
RISK IS ASSESSED

NOW WHAT?

5 yr risk: 0.8%
Lifetime risk 10.8%
SCREENING IN 2016
All women should begin annual screening mammography at age 40yrs.
Screening recommendations galore

United States Preventative Task Force 2016

• Biannual screening
  • Start at age 50y
  • End at age 75y
• No self breast exam (2002)
• Screening before age 50y individual decision.
• Insufficient evidence to recommend for or against
  • Screening after 75y
  • Screening before age 50y
  • Clinical breast exam (2002)

American Cancer Society Recommendations 2015

• Annual screening from 45-55y, then biannual as long as 10yr life expectancy
• Women <45y should have the opportunity to screen
• Women >55y should have the opportunity to continue annual screening
• No clinical breast exam
The anatomy of a screening guideline

Benefits

Harms
Harms

• Anxiety and worry associated with a false positive diagnosis

• Discomfort and other adverse consequences of a negative biopsy

• Over diagnosis
## Age Specific Screening Outcomes

<table>
<thead>
<tr>
<th>Outcome: n per 1000 women screened</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive mammography</td>
<td>121.2</td>
<td>93.2</td>
<td>80.8</td>
<td>69.6</td>
</tr>
<tr>
<td>Additional imaging recommended</td>
<td>124.9</td>
<td>98.5</td>
<td>88.7</td>
<td>79.0</td>
</tr>
<tr>
<td>Biopsy recommended</td>
<td>16.4</td>
<td>15.9</td>
<td>16.5</td>
<td>17.5</td>
</tr>
<tr>
<td>Screen-detected invasive cancer</td>
<td>2.2</td>
<td>3.5</td>
<td>5.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Screen detected DCIS</td>
<td>1.6</td>
<td>1.8</td>
<td>2.1</td>
<td>2.3</td>
</tr>
</tbody>
</table>
10 yr probability of false positive mammography based on age

Risk of false positive recall:
- 16.5% at first mammogram
- 9.5% at subsequent mammogram

Risk of recommendation for false positive biopsy:
- 2.5% at first mammogram
- 1.5% at subsequent mammogram

63% of women felt that 500 false positives per life saved was acceptable.

37% felt that 10,000 false positives per life saved would be acceptable.

62% did not think that false positives should affect decision making about mammography.
Overdiagnosis

- The identification of a screen-detected cancer that would not have led to symptomatic breast cancer if undetected by screening.

- Associated with overtreatment
Key finding:
15% to 25% of cases of cancer are over diagnosed, translating to 6 to 10 women over diagnosed for every 2500 women invited.
## How much overdiagnosis?

<table>
<thead>
<tr>
<th>Type of study</th>
<th># of studies</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Proportion of new cancers representing diagnosis</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>Cochrane review (7 trials)</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>UK independent review (2 trials)</td>
<td>10.7-19%</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>18 studies, including 1 evaluating interval of mammogram</td>
<td>Range 0-54%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>1</td>
<td>Biennial less overdiagnosis than annual by “much less than half”</td>
</tr>
</tbody>
</table>

Wide variability in methodology and estimates
BENEFITS OF MAMMOGRAPHY MORTALITY
### Table 3. Estimated Relative Reduction in Breast Cancer Mortality Associated With Mammography Screening, by Study Design Among Pooled Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Sample Size or Population</th>
<th>Age Range, y</th>
<th>Period or Duration of Follow-up, y</th>
<th>Exposure or Intervention</th>
<th>Relative Mortality Reduction With Screening (95% CI or Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-Control Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broeders et al[^29]</td>
<td>Meta-analysis of 7 studies; publication years, 2004-2012</td>
<td>18 842</td>
<td>40-&gt;79</td>
<td>1987-2008</td>
<td>Screening mammography</td>
<td>OR, 0.46 (0.4-0.54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Screening mammography (corrected for self-selection)</td>
<td>OR, 0.52 (0.42-0.65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Invitation to screening mammography</td>
<td>OR, 0.69 (0.57-0.83)</td>
</tr>
<tr>
<td><strong>Incidence-Based Mortality Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broeders et al[^29]</td>
<td>Meta-analysis of 7 studies; publication years, 1997-2010</td>
<td>&gt;2 million</td>
<td>45-69</td>
<td>6-22 y</td>
<td>Screening mammography</td>
<td>RR, 0.62 (0.56-0.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Invitation to screening mammography</td>
<td>RR, 0.75 (0.69-0.81)</td>
</tr>
<tr>
<td><strong>Randomized Clinical Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gøtzsche and Jørgenson[^30]</td>
<td>Meta-analysis of 7 trials; publication years, 1963-1991</td>
<td>289 552 invited, 309 538 not invited</td>
<td>39-74</td>
<td>7 and 13 y</td>
<td>Screening mammography</td>
<td>RR, 0.81 (0.74-0.87)</td>
</tr>
<tr>
<td><strong>Model-Based Estimates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berry et al[^4]</td>
<td>7 models</td>
<td>30-79</td>
<td>NA</td>
<td></td>
<td>Screening mammography</td>
<td>Median, 15% (range, 7%-23%)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; OR, odds ratio; RR, relative risk.
AGE AT FIRST MAMMOGRAM
Efficacy by age

- Mammography is roughly equally effective, on a relative basis, in all age groups
  - 20% reduction in age-adjusted mortality rates based on randomized trials
  - 27-40% reduction based on modern day observational trials

- The balance of benefits and drawbacks is largely a function of the risk of breast cancer in each age group
Breast Cancer risk in younger women

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Incidence rate per 100,000</th>
<th>Probability of being diagnosed in the 1 yr interval</th>
<th>% of BC deaths by age at diagnosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>1 in N</td>
</tr>
<tr>
<td>35</td>
<td>44.9</td>
<td>0.0%</td>
<td>2,212</td>
</tr>
<tr>
<td>36</td>
<td>51.9</td>
<td>0.1%</td>
<td>1,943</td>
</tr>
<tr>
<td>37</td>
<td>61.6</td>
<td>0.1%</td>
<td>1,713</td>
</tr>
<tr>
<td>38</td>
<td>65.9</td>
<td>0.1%</td>
<td>1,440</td>
</tr>
<tr>
<td>39</td>
<td>79</td>
<td>0.1%</td>
<td>1,232</td>
</tr>
<tr>
<td>40</td>
<td>106.3</td>
<td>0.1%</td>
<td>1,076</td>
</tr>
<tr>
<td>41</td>
<td>109.8</td>
<td>0.1%</td>
<td>954</td>
</tr>
<tr>
<td>42</td>
<td>120.9</td>
<td>0.1%</td>
<td>857</td>
</tr>
<tr>
<td>43</td>
<td>130.6</td>
<td>0.1%</td>
<td>774</td>
</tr>
<tr>
<td>44</td>
<td>148.3</td>
<td>0.1%</td>
<td>706</td>
</tr>
<tr>
<td>45</td>
<td>165.9</td>
<td>0.2%</td>
<td>648</td>
</tr>
</tbody>
</table>

Risk between ages 40-41 is 9 in 10,000.

The recall rate is 1,600-2,000 per 10,000 (about 1 in 5).

a. Delay adjusted incidence rates, SEER18, 2008-2012
Table 4. Distribution of Female Population Size, 5-Year Absolute Breast Cancer Risk, and Age-Specific Breast Cancer Incidence Rates by Age

<table>
<thead>
<tr>
<th>Age, y</th>
<th>2011 Population Size (in 1000s)</th>
<th>5-Year Absolute Breast Cancer Risk, 2009-2011, %</th>
<th>Breast Cancer Incidence Rate per 100,000 Population, 2007-2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-34</td>
<td>72,049</td>
<td>0.2</td>
<td>5.3</td>
</tr>
<tr>
<td>35-39</td>
<td>9837</td>
<td>0.3</td>
<td>59.5</td>
</tr>
<tr>
<td>40-44</td>
<td>10,576</td>
<td>0.6</td>
<td>122.5</td>
</tr>
<tr>
<td>45-49</td>
<td>11,121</td>
<td>0.9</td>
<td>188.6</td>
</tr>
<tr>
<td>50-54</td>
<td>11,499</td>
<td>1.1</td>
<td>224.0</td>
</tr>
<tr>
<td>55-59</td>
<td>10,444</td>
<td>1.3</td>
<td>266.4</td>
</tr>
<tr>
<td>60-64</td>
<td>9,271</td>
<td>1.6</td>
<td>346.7</td>
</tr>
<tr>
<td>65-69</td>
<td>6,806</td>
<td>2.0</td>
<td>420.2</td>
</tr>
<tr>
<td>70-74</td>
<td>5,204</td>
<td>2.1</td>
<td>433.8</td>
</tr>
<tr>
<td>75-79</td>
<td>4,155</td>
<td>2.0</td>
<td>443.3</td>
</tr>
<tr>
<td>80-84</td>
<td>3,444</td>
<td>1.9</td>
<td>420.6</td>
</tr>
<tr>
<td>≥85</td>
<td>3,826</td>
<td>2.5</td>
<td>354.4</td>
</tr>
</tbody>
</table>
Breast Cancer Burden by Age at Diagnosis for the Period 2007-2011

A) Distribution of breast cancer cases by age at diagnosis

Age at diagnosis, y
- 20-24
- 25-29
- 30-34
- 35-39
- 40-44
- 45-49
- 50-54
- 55-59
- 60-64
- 65-69
- 70-74
- 75-79
- 80-84
- ≥85

Percentage
- 0
- 5
- 10
- 15
- 20

6% 10% 12% 12% 12% 13% 12% 12% 12%

B) Distribution of breast cancer deaths by age at diagnosis

Age at diagnosis, y
- 20-24
- 25-29
- 30-34
- 35-39
- 40-44
- 45-49
- 50-54
- 55-59
- 60-64
- 65-69
- 70-74
- 75-79
- 80-84
- ≥85

Percentage
- 0
- 5
- 10
- 15
- 20

7% 10% 11% 11% 11% 9%

C) Distribution of person-years of life lost due to breast cancer by age at diagnosis

Age at diagnosis, y
- 20-24
- 25-29
- 30-34
- 35-39
- 40-44
- 45-49
- 50-54
- 55-59
- 60-64
- 65-69
- 70-74
- 75-79
- 80-84
- ≥85

Percentage
- 0
- 5
- 10
- 15
- 20

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SCREENING INTERVAL
What determines screening interval?

• Screening interval is NOT a function of risk

• Screening interval should be determined by the rate of progression of cancer or pre-cancer

• Many screening intervals have been widening (Pap smear, PSA)
10 yr probability of false positive mammography based on age

Risk of false positive recall:
- 16.5% at first mammogram
- 9.5% at subsequent mammogram

Risk of recommendation for false positive biopsy:
- 2.5% at first mammogram
- 1.5% at subsequent mammogram

Supplemental Analysis of Screening Interval from NCI-Funded Breast Cancer Surveillance Consortium

Breast Tumor Prognostic Characteristics and Biennial vs Annual Mammography, Age, and Menopausal Status.


- prospective cohort of 15,440 women ages 40 to 85 years from 1996 to 2012

- Patients had breast cancer diagnosed within 1 year of an annual or within 2 years of a biennial screening mammogram.
Supplemental Analysis of Screening Interval from NCI-Funded Breast Cancer Surveillance Consortium

**Premenopausal women**

Biennial screening associated with

- More advanced stage disease (RR 1.28)
- Larger tumors (RR 1.21)
- Less favorable prognostic characteristics (RR 1.11)

**Postmenopausal women**

- No difference in tumor size, stage or characteristics between annual and biennial mammography.

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BREAST EXAM
Clinical breast exam

- Trials of clinical breast exam and mammography did not show benefit compared to mammography alone.

- ASC concluded “CBE not effective for screening” in the settings where mammography is available.

- Retrospective studies of clinician detected breast masses find that only 30-50% of these have an anatomic correlate, the majority of which are not cancer.
Breast Self-Examination

- BSE has been removed from guidelines for routine breast cancer screening (USPSTF, NCI)
- Based on 3 major studies:
  - large RCT from **Shanghai, China** - no difference in breast cancer mortality after 11 years in factory workers randomly assigned to BSE and follow-up versus a control group
  - **UK** group – 16 yrs of followup
  - **World Health Organization/Russia** trial – BSE taught at work, no difference at 11 yrs f/u
- NCI concluded a higher biopsy rate with no improvement of survival; however, compliance in all studies was low.
Screening in high risk patients

- ACS recommendation for ‘for all women without genetic mutation or previous chest radiation at a young age.’

- No differentiation of risk by prior h/o atypia, family history, mammographically dense breasts
Surveillance of high risk women
ACR guidelines - Mammography

- **BRCA1 or BRCA2 mutation carriers**: by age 30, but not before age 25

- Women with **1st degree relative with pre-menopausal BC**: by age 30 but not before age 25, or 10 years earlier than the age of diagnosis of relative, whichever is later

- Women with **≥20% lifetime risk for breast cancer by FH**: yearly starting by age 30 but not before age 25, or 10 years earlier than the age of diagnosis of the youngest affected relative, whichever is later

- Women with histories of **mantle radiation b/w 10-30yrs**: beginning 8 years after the radiation therapy but not before age 25

- Women with biopsy-proven **lobular neoplasia, ADH, DCIS, invasive breast cancer, or ovarian cancer** regardless of age
Tomosynthesis

- 3D mammography
- Improved detection of cancers in dense breasts
- Decreased call backs for more images
• 281, 187 digital mammograms (DM) compared to 173,663 digital mammograms + tomosynthesis (DMT) in 13 breast centers

• Recall rate 107 vs 91 / 1000 screens with DM vs DMT

• Cancer detection 4.2 vs 5.2 / 1000

• Invasive cancer detection 2.9 vs 4.1 / 1000

• Positive predictive value for recall 4.3% vs 6.4%

Friedewald et al. JAMA 2014
Who should have screening MRI?:

ACR Recommendations

1) Women with BRCA mutation
   - Annually starting by age 30

2) Untested first-degree relatives of women with BRCA mutations
   - Annually starting by age 30

3) Women with >20% lifetime risk for breast cancer
   - Annually starting by age 30

4) Women with histories of chest irradiation before 30yrs
   - Annually starting 8 years after the radiation therapy
Automated Whole Breast Ultrasound

- Useful for intermediate risk women with heterogeneously or very dense breasts, or high risk women unable or unwilling to have MRI
- ACRIN study – 4.3 additional invasive BC/1000 women (dense breasts)
- NOT meant to replace mammography as a screening tool
24 studies from 7 countries; only 6 ‘good quality’

Looked at performance of screening breast US, MRI and digital breast tomosynthesis

**Ultrasound**: Sensitivity of US for women with negative mammos 75-100%, specificity 86-94%

Additional cancer detection by US = 4.4/1000 exams, recall rates 14%

**MRI**: 3.6 to 28.6 additional cancer/1000 exams; recall rates 14-24%

**Tomosynthesis**: 1.4-2.5 additional cancers/1000 exams; lower recall rates than digital mammo
Where to next?
Questions?