Breast Issues for the Primary Care Physician

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Objectives

- Compare and contrast the (many) guidelines for breast cancer screening
- Review options assessment of breast cancer risk
- Discuss the controversy about breast density
## Screening Guidelines

<table>
<thead>
<tr>
<th>GROUP</th>
<th>FREQUENCY In years</th>
<th>40-49 YEARS</th>
<th>50-69 YEARS</th>
<th>≥70 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Preventive Services (2016)</td>
<td>Two</td>
<td>Individualize</td>
<td>Yes</td>
<td>Yes to age 74</td>
</tr>
<tr>
<td>Canadian Task Force (2011)</td>
<td>Two to three</td>
<td>Recommend against</td>
<td>Yes</td>
<td>Yes to age 74</td>
</tr>
<tr>
<td>ACP</td>
<td>One to two</td>
<td>Individualize</td>
<td>Yes</td>
<td>Yes to age 74</td>
</tr>
<tr>
<td>ACOG</td>
<td>One</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ACR</td>
<td>One</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Case 1

Karen presents to you for a well woman visit. She is 42 years old. She asks you if she should begin breast cancer screening. She has no family history of breast cancer and no prior history of breast biopsies. She is an average risk patient for breast cancer. What do you tell her given the wide variation in guidelines?
A Rational Approach

Oeffinger KC et al.

*Breast cancer screening for women at average risk 2015 guideline update from the American Cancer Society.*

JAMA. 2015; 314(15):1599-1614
Currently the guidelines for breast cancer screening vary among professional organizations causing women and providers much uncertainty about what to recommend.

In response to new evidence from long-term follow-up data of screening trials, the American Cancer Society (ACS) commissioned a systematic review of the breast cancer screening literature taking into account the quality of the evidence about the balance of benefits and harms.
Methods

- The ACS assembled an interdisciplinary group of experts and tasked them with developing guidelines for *average risk women*

- Guidelines were developed and graded:
  - A strong recommendation is meant to convey that benefits > harms
  - Qualified recommendations suggest that there is clear evidence of benefit but less certainty about either the balance of benefits and harms or about patients’ values and preferences (which, when considered, could lead to different decisions by different patients).
Critical outcomes were considered to be prevention of breast cancer deaths, quality of life years gained by screening, life expectancy, false positives, overdiagnosis, and overtreatment. Breast cancer characteristics at diagnosis and short and long term emotional effects such as anxiety and depression were considered important but not critical outcomes. A total of 10 RCTs, 22 cohort studies, and 13 case control studies were considered.
Recommendation 1: Screening Mammography Should Begin at Age 45 (Strong)

- This recommendation was based on analyzing breast cancer incidence and mortality in 5 year intervals for women between 40 and 50; previous screening trials had clustered outcomes in 10 year age increment.

- The five year risk of breast cancer among women 40 to 44 (0.6%) is less than that in women aged 45 to 49 (0.9%) and women aged 50 to 54 (1.1%).

- The risk of breast cancer mortality reduction is similarly different with a reduction of 18% in women 40 to 44 and 32% in women 45 to 49.

- They further qualify this recommendation by stating that all women should have the opportunity to begin screening at age 40 if they so desire.
Results: Breast Cancer Burden by Age at Diagnosis
Relative Reduction in Breast Cancer Mortality Associated with Screening

### 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>
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<tr>
<td>Broeders et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Meta-analysis of 7 studies; publication years, 2004-2012</td>
<td>18 842</td>
<td>40-79</td>
<td>1987-2008</td>
<td>Screening mammography</td>
<td>OR, 0.46 (0.4-0.54)</td>
</tr>
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<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>
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</tr>
<tr>
<td>Broeders et al&lt;sup&gt;29&lt;/sup&gt;</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>
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<tr>
<td><strong>Randomized Clinical Trials</strong></td>
<td></td>
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<tr>
<td>Gøtzsche and Jørgenson,&lt;sup&gt;30&lt;/sup&gt;</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>
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</tr>
<tr>
<td>Berry et al&lt;sup&gt;4&lt;/sup&gt;</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.
Recommendation 2: Women aged 45 to 54 should be screened annually (Qualified)

- Screening interval is important to reduce the diagnosis of interval cancers that appear clinically between screening examinations
  - Data reviewed suggested that in women greater than age 50 few interval cancers were detected; in contrast, in women in their 40s the rate of interval cancers was 40% of the control group incidence rate in the first 12 months after a normal screening examination.
  - It is unclear if this difference is age related or influenced by menopausal state and several studies have suggested that menopausal state is the more important factor.
Recommendation 3: After age 55 Biannual Mammography is Recommended (Qualified)

- The benefits of annual screening are reduced after the menopausal transition; most women will be post menopausal by age 55

- More frequent screening over a lifetime carries an increased risk of false positives

- Balancing risks and benefits 55 is the recommended age at which to transition to biannual screening
Recommendation 4: Women should continue screening mammography as long as they have a life expectancy of 10 years (Qualified)

- Breast cancer incidence continues to increase until age 80, and 26% of breast cancer deaths are attributed to a diagnosis after age 74

- For women who are healthy and have a life expectancy greater than 10 years, decisions should be individualized
Recommendation 5: The ACS does not recommend clinical breast examinations (CBE) for breast cancer screening (Qualified).

- The ACS based this recommendation on the fact that there were no studies demonstrating a benefit of CBE in addition to mammography.

- They also cited moderate quality evidence that CBE increases false positive examinations.
Limitations and Cautions

- Most of the screening trials began before 2000 and
  - Used only film mammography and
  - Had different breast cancer treatment regimens
- Thus the long term follow up information may not represent the impact of screening and breast cancer treatment today
- The ACS also included observational cohorts in its data analysis which the USPSTF does not include because of the inherent risk of bias in cohort studies
- Patient preferences may vary from individual to individual and the ACS recognizes that different patients may have a different weighing of risks and benefits
The new guidelines are helpful in offering an evidenced based review of newer literature and framing the benefits of screening in the context of harms. It must be remembered that these guidelines refer to women of average breast cancer risk and offer a rational approach to screening in this population of women.
Other Imaging Modalities

ULTRASOUND
- Not for screening
- Diagnostic imaging alone or in conjunction with diagnostic mammogram
- Guide for core biopsies
- Pregnant/lactating women

MRI
- Screening in conjunction with mammogram for high-risk patients (>20% lifetime risk, breast irradiation, BRCA)
- Breast implants
- Some new cancer diagnoses
Case 2

Marianne is a 60 year old woman who comes to you for advice. She received a letter from her radiologist telling her that she has increased breast density and that she should talk to her primary care physician to determine if any more testing is needed. What will you tell her?
Breast Density
Alone Should Not Drive Screening

Kerlikowske K et al. *Identifying women with dense breasts at high risk for interval cancer*. 2015: Annals of Internal Medicine. 163(10)
Breast cancer advocates in many states have lobbied for patient notification about increased breast density because

- It is a marker of increased risk
- The sensitivity of mammograms is decreased—false negative rate varies up to 10 fold across the categories of breast density
- 40% of women aged 40 to 74 years have dense breasts (defined as heterogeneously or extremely dense)
Different professional organizations have differing recommendations:

- ACOG: recommends against supplemental screening
- USPSTF and the ACS: state that there is insufficient information to recommend for or against supplemental screening
- American College of Radiology: suggests that supplemental ultrasound evaluation could be considered.

Despite the lack of data and absence of consensus, 24 states have now required that patients with increased breast density be notified of their increased risk and suggest that they discuss additional screening with their providers.
The goal of this study was to determine which patients with increased breast density are associated with high interval cancer rates and thus would benefit from supplemental screening.
Methods

- Data from the Breast Cancer Surveillance Consortium (BCSC) mammography registries
  - Women aged 40 to 74 years
  - Who underwent digital screening mammography
  - Between 2002 and 2011
- An interval cancer rate greater than 1 case per 1000 mammograms was considered to be unacceptable performance
- Interval cancer rates were analyzed with different predictive scenarios including: breast density alone, breast density modified by age, and breast density modified by 5 year calculated BCSC breast cancer risk
Methods

Digital screening mammography examinations performed from 2002 to 2011 among women aged 40 to 74 y with ≥12 mo of follow-up
Examinations: 905 882
Women: 399 815

Excluded women with history of breast cancer or implants, unilateral mammography, mammography examinations ≤9 mo apart, and first screening mammography examinations

Digital screening mammography examinations performed from 2002 to 2011 among women aged 40 to 74 y with ≥12 mo of follow-up
Examinations: 831 455
Women: 365 426

Mammography examinations without invasive cancer diagnosed within 12 mo
(n = 828 759)

Mammography examinations with invasive cancer diagnosed within 12 mo
(n = 2696)

Mammography examinations among women who did not develop cancer within 12 mo
Examinations: 825 586
Women: 362 730*

Mammography examinations not associated with cancer within 12 mo among women who went on to develop cancer within 12 mo of an examination
Examinations: 3173
Women: 1425 (of 2696)
### Table 3. Interval Cancer Rates, by BI-RADS Breast Density and Age or BCSC 5-y Risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval Cancer Cases (95% CI) per 1000 Mammography Examinations (by BI-RADS Breast Density), n*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Almost Entirely Fat</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>40-49 y</td>
<td>0.19 (0.04-0.56)</td>
</tr>
<tr>
<td>50-59 y</td>
<td>0.14 (0.05-0.34)</td>
</tr>
<tr>
<td>60-69 y</td>
<td>0.23 (0.10-0.45)</td>
</tr>
<tr>
<td>70-74 y</td>
<td>0.35 (0.10-0.90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BCSC 5-y risk†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0%–&lt;1.00%)</td>
<td>0.14 (0.06-0.26)</td>
</tr>
<tr>
<td>Average (1.00%–1.66%)</td>
<td>0.31 (0.13-0.65)</td>
</tr>
<tr>
<td>Intermediate (1.67%–2.49%)</td>
<td>0.48 (0.13-1.22)</td>
</tr>
<tr>
<td>High or very high (≥2.50%)</td>
<td>‡</td>
</tr>
</tbody>
</table>

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System.
* Boldface values are above the accepted cut point of 1 interval cancer case per 1000 examinations.
† Model includes age, race, family history of breast cancer, history of breast biopsy, and BI-RADS breast density.
‡ Too few cases to calculate a stable measure.
## Results

**Table 5. Projected Outcomes (per 100 000 Women With Dense Breasts) of Strategies to Identify Women Aged 40 to 74 y for Discussion of Supplemental Imaging**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Women Considered for Discussion of Supplemental Imaging, n (%)</th>
<th>Interval Cancer Cases for Potential Detection by Supplemental Imaging (95% CI), n</th>
<th>Ratio of Women Considered for Discussion of Supplemental Imaging to Interval Cancer Cases for Potential Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. All women with heterogeneously or extremely dense breasts</td>
<td>100 000 (100)</td>
<td>89 (80-98)</td>
<td>1124</td>
</tr>
<tr>
<td>2. All women with extremely dense breasts</td>
<td>16 956 (17)</td>
<td>19 (15-24)</td>
<td>892</td>
</tr>
<tr>
<td>3. Women aged 50-74 y with extremely dense breasts or aged 70-74 y with heterogeneously dense breasts*</td>
<td>13 470 (13)</td>
<td>16 (13-21)</td>
<td>842</td>
</tr>
<tr>
<td>4. Women with risk ≥1.67% and extremely dense breasts or risk ≥2.50% and heterogeneously dense breasts*</td>
<td>24 294 (24)</td>
<td>35 (30-42)</td>
<td>694</td>
</tr>
<tr>
<td>5. Women aged 40-74 y with extremely dense breasts or aged 40-49 y with heterogeneously dense breasts†</td>
<td>46 412 (46)</td>
<td>41 (35-49)</td>
<td>1132</td>
</tr>
<tr>
<td>6. Women with risk ≥1.67% and heterogeneously or extremely dense breasts‡</td>
<td>48 722 (49)</td>
<td>56 (49-64)</td>
<td>870</td>
</tr>
</tbody>
</table>

* Interval cancer rate >1 case per 1000 examinations.
† Sensitivity <75%.
‡ Interval rate of advanced-stage disease >0.4 case per 1000 examinations.
About half of women with heterogeneously dense breasts or extremely dense breasts were at low to average 5 year breast cancer risks (0% to 1.66%).

Interval cancer rates greater than 1 case per 1000 mammography examinations were observed in women:

- With extremely dense breasts and a 5 year cancer rate of $>1.67\%$
- With heterogeneously dense breasts and a 5 year cancer rate of $>2.5\%$

These two groups represented only 24% of women with dense breasts suggesting that the majority of women with dense breasts are not at risk for increased interval cancer detection.
Increased breast density alone should not prompt additional supplemental imaging. The most important prognostic factor identified to date to help determine which patients with increased breast density are at risk for interval cancers is the 5 year BCSC breast cancer risk.

Physicians should calculate individual breast cancer risks for all patients and use this information in counseling patients about decision making about alternative breast cancer screening strategies.
Case 3

Susan comes to your office for a routine visit. You take some time to update her family history. She tells you that her sister has been diagnosed with breast cancer at age 52.

“Should I be worried about getting breast cancer too?”
Goals of Breast Cancer Risk Assessment

- Assess for indications for genetic counseling/testing and/or referral
  - Appropriately managing women with BRCA1/2 mutations decreases breast cancer incidence by 80-95%
- Estimate overall risk and discuss risk reduction strategies
  - Enhanced screening, lifestyle changes, pharmacologic prevention, prophylactic surgery
Indications for Referral for Genetic Counseling

- BRCA 1/2 mutation in family
- Breast cancer before age 50 in affected relatives
- Bilateral breast cancer
- Family history of ovarian cancer
- ≥2 breast cancers same side of the family
- Male relatives with breast cancer
- Ashkenazi Jem and a family history of breast/ovarian cancer
Risk Assessment

NON MODIFIABLE
- Dense breasts
- First degree relative with breast cancer
- Hx of benign breast bx
- More estrogen exposure
- Nulliparous
- Chest radiation

MODIFIABLE
- Hormone Use
- Overweight/obesity
- Alcohol use
- Smoking
You determine, after obtaining a detailed family history, that your patient does not meet criteria for genetics counseling referral.

You find out:
- Susan is 50
- Her menarche was age 14
- Age at first birth was 28
- One first degree relative with breast cancer
- No hx of breast cancer or DCIS
- One breast biopsy in the past (fibroadenoma)
- Breast density is scattered fibroglandular disease
Breast Cancer Risk Assessment

Gail Model
- Age
- Age at start of menopause
- Age at first live birth
- 1st degree relative
- Breast cancer or DCIS
- Breast biopsy

BCSC
- Age
- 1st degree relatives
- Breast ca, DCIS, LCIS
- Breast biopsy
- Race
- Breast density

5 year risk: 2% (average 1.3%)
5 year risk: 2.16% (average 1.25%)
Case 3

“Is there anything I can do to decrease the likelihood that I will get cancer?”
Methods

- Double-blinded RCT comparing Tamoxifen vs. Raloxifene
- 19,747 women
  - Over 35 years old AND post-menopausal
  - 5 year Gail “at risk”
- Exclusion criteria
  - h/o thromboembolic event; h/o malignancy; uncontrolled Afib, HTN or DM; severe psych disease; recent hormone therapy
Methods

- Mean age 58.5 years
- Mean treatment duration was ~ 3 years
- Mean follow-up 3.9 years

- Primary endpoint: invasive breast cancer

- Secondary endpoints:
  - Endometrial cancer, In situ cancer, CHD, CVA/TIA, PE/DVT, osteoporotic fx, cataracts, death, and QOL
STAR Trial

No difference in rates of invasive breast cancer
- Tamoxifen 4.3 vs. Raloxifene 4.1 per 1000

Non-sig increased rates of noninvasive in those treated with Raloxifene vs. Tamoxifen
- RR 1.40
  (CI 0.98 – 2.00), p = 0.052
Non-sig decrease incidence of uterine cancer with Raloxifene vs. Tamoxifen
- RR 0.62
  (CI 0.35 – 1.08)

Significant decrease in thromboembolic events with Raloxifene
- RR 0.70
  (CI 0.54 – 0.91)

STAR Trial
Conclusion

- Raloxifene equivalent to Tamoxifen for prevention of invasive breast cancer, but has:
  - Lower rates of thromboembolic events
  - Trend toward decreased uterine cancer
- Tamoxifen showed a trend toward decreased rates of noninvasive breast cancer
Used data from 1992 Breast Cancer Prevention Trial and the STAR trial

Created benefit/risk index of chemoprevention for women with varying:
  • Age
  • Race
  • Gail risk
  • History of hysterectomy
Compared the estimated incidence for adverse events with and without chemoprophylaxis
  - Stratified by age and breast cancer risk

Divided adverse events into life threatening, severe, and other
  - Weighted the significance of these events accordingly
Benefit/Risk Assessment for Breast Cancer Chemoprevention With Raloxifene or Tamoxifen for Women Age 50 Years or Older

**Life threatening (1.0)**
- Invasive breast cancer
- Stroke
- Endometrial cancer
- PE
- Hip Fracture

**Severe (0.5)**
- In situ cancer
- DVT

**Other (0.0)**
- Colles’ fracture
- Spine fracture
- Cataracts
Using incidences and weighted values, calculated likelihood a patient of a given age/BC risk would benefit from chemoprophylaxis.

Evidence defined as:
- Strong: >90% chance of patient benefit
- Moderate: 60-89% chance of benefit
- Weak: <60% chance of benefit
Non Hispanic White Women with a uterus:

### Benefit/Risk Assessment for Breast Cancer Chemoprevention With Raloxifene or Tamoxifen for Women Age 50 Years or Older

<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></td>
<td>50-59</td>
<td>60-69</td>
</tr>
<tr>
<td>1.5</td>
<td>-133</td>
<td>-310</td>
</tr>
<tr>
<td>2.0</td>
<td>-105</td>
<td>-283</td>
</tr>
<tr>
<td>2.5</td>
<td>-78</td>
<td>-255</td>
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<tr>
<td>3.0</td>
<td>-51</td>
<td>-228</td>
</tr>
<tr>
<td>3.5</td>
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<td>-202</td>
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<td>4.0</td>
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<td>4.5</td>
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<td>-148</td>
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<tr>
<td>5.0</td>
<td>56</td>
<td>-121</td>
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<td>5.5</td>
<td>83</td>
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</tr>
<tr>
<td>6.0</td>
<td>109</td>
<td>-69</td>
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<td>6.5</td>
<td>135</td>
<td>-42</td>
</tr>
<tr>
<td>7.0</td>
<td>162</td>
<td>-15</td>
</tr>
</tbody>
</table>

Using BCPT data and WHI baseline rates
Combining RR from BCPT and STAR using WHI baseline rates

Strong evidence of benefits outweighing risks
Moderate evidence of benefits outweighing risks
Benefits do not outweigh risks

5-year projected risk of IBC is \( \geq 1.67\% \).
Non Hispanic White Women without a uterus:

<table>
<thead>
<tr>
<th>Risk of IBC (%)</th>
<th>Tamoxifen v Placebo (without uterus)</th>
<th>Raloxifene v Placebo (without uterus)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>50-59</td>
<td>60-69</td>
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<tr>
<td>1.5</td>
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<tr>
<td>2.0</td>
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<td>-53</td>
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<td>2.5</td>
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<td>7.0</td>
<td>244</td>
<td>189</td>
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<tr>
<td></td>
<td>270</td>
<td>215</td>
</tr>
</tbody>
</table>

5-year projected risk of IBC is ≥ 1.67%.

Using BCPT data and WHI baseline rates:
Combining RR from BCPT and STAR using WHI baseline rates:

- Strong evidence of benefits outweighing risks
- Moderate evidence of benefits outweighing risks
- Benefits do not outweigh risks
Take Home Messages

Screening for breast cancer requires:
- Risk assessment
- Navigating guidelines; consider ACS

Breast density alone should not prompt additional screening

Consider adding primary prevention to your repertoire