Breast density: imaging, risks and recommendations

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Disclosures

- Dr. Maureen Baxter has no relevant disclosures
- Dr. Alison Conlin has no relevant disclosures
Objectives

- Explain the risks and prevalence of dense breast tissue
- Discuss the various screening options
- Provide a framework for screening patients with dense breast tissue
- Understand breast cancer risk factors, risk calculators and their limits
- Understand how breast cancer risk is calculated in women with a history of breast cancer

Your mammogram shows that your breast tissue is dense. Dense breast tissue is common and is not abnormal. However, dense breast tissue can make it harder to evaluate the results of your mammogram and may also be associated with an increased risk of breast cancer. This information about the results of your mammogram is given to you to raise your awareness and to promote discussion with your health care provider. Together, you can decide if you may benefit from further screening. A report of your results was sent to your health care provider.
Legislation and Regulations

- 31 States require breast density notification
- There is no standard on what patients are told or how they are informed
- 6 states require insurance coverage, but not all women are covered, and national providers may be exempt
Breast Density

- Ratio of fat to fibroglandular tissue in the breast.

- The American College of Radiology has four grades of breast composition to describe the breast density of all patients using the following patterns:
  - Type 1: fatty (<25% glandular tissue)
  - Type 2: scattered (25-50% scattered fibroglandular tissue)
  - Type 3: heterogeneously dense (51-75% fibroglandular)
  - Type 4: dense (>75% fibroglandular)
1. Masking

Surrounding breast tissue obscures a cancer.

Implications of Breast Density - Masking

Effectiveness of Screening Mammography
- All Women:
  - Sensitivity 85%
  - Proven mortality reduction
- Women with Dense Breasts
  - Sensitivity 48-65%
  - More than 1/3 of breast cancers not visible in women with dense breasts


2. Increased Risk of Breast Cancer

- 1.2 - 2 times (4.7 times when compared to fatty)
- Dense breast tissue increases the risk of developing breast cancer more than family history, postmenopausal weight gain, or late childbearing

Mammography

Mammography is the only method of screening for breast cancer shown to decrease mortality.
Failure Analysis

- 609 breast cancer deaths; median age 49 yr at dx
- 29% cancer deaths were among women screened
  - 19% screen detected
  - 10% interval cancers
  - 71% deaths among unscreened women

Interval Cancer

- Cancer dx by clinical symptoms in interval between recommended screenings
- Worse prognosis and worse outcome
### Interval Cancers and Breast Density

<table>
<thead>
<tr>
<th>Density</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10%</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>10-24%</td>
<td>2.1</td>
<td>(0.9, 5.2)</td>
</tr>
<tr>
<td>25-49%</td>
<td>3.6</td>
<td>(1.5, 8.7)</td>
</tr>
<tr>
<td>50-74%</td>
<td>5.6</td>
<td>(2.1, 15.3)</td>
</tr>
<tr>
<td>≥ 75%</td>
<td>17.8</td>
<td>(4.8, 65.9)</td>
</tr>
</tbody>
</table>

\[ p < .001 \]


### Possible tests to add to mammography

<table>
<thead>
<tr>
<th>Modality vs. Mammography alone</th>
<th>Absolute (^1) Cancer Detection per 1000 screens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical breast exam</td>
<td>0.3</td>
</tr>
<tr>
<td>Double Read or CAD</td>
<td>1</td>
</tr>
<tr>
<td>Tomosynthesis</td>
<td>1-2</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>3-4</td>
</tr>
<tr>
<td>Molecular Breast Imaging, CEDM</td>
<td>7-8</td>
</tr>
<tr>
<td>MRI</td>
<td>10</td>
</tr>
</tbody>
</table>

\(^1\) Copyright Wendle Berg, MD, PhD
Screening MRI

- MRI not affected by breast density
- High sensitivity
  - Combination of mammography and MRI in high risk population has the highest sensitivity: 92.7%
- No radiation
- Expensive
- Requires contrast injection
EVA Trial: Screening Patients with Increased Risk of Breast Cancer

- Evaluated different modalities, used alone or in combination

![Graph: Cancer yield of the different imaging methods, used alone or in combination.](image)

Kuhl C et al. JCO 2010;28:1450-1457

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**Future?**

Abbreviated Breast Magnetic Resonance Imaging (MRI): First Postcontrast Subtracted Images and Maximum-Intensity Projection—A Novel Approach to Breast Cancer Screening With MRI [Christiane K. Kuhl](#)

- MRI acquisition time 3 minutes
- Radiologist read time of 3 seconds for MIP and 30 seconds for full exam
- 18.2 additional cancer/1000 compared to those screened with mammography and US.

### Relative Cost

**National Medicare Global 2007**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>76094 Bilateral Breast MRI</td>
<td>$1,144</td>
</tr>
<tr>
<td>76092 Screening Mammogram</td>
<td>$92</td>
</tr>
<tr>
<td>76091 Diagnostic Mammogram</td>
<td>$109</td>
</tr>
<tr>
<td>76445 Breast Ultrasound</td>
<td>$85</td>
</tr>
<tr>
<td>Screening Ultrasound</td>
<td>~$300</td>
</tr>
</tbody>
</table>
High Risk Factors for Breast Cancer (American Cancer Society)

- Patients with a known BRCA mutation
- First degree relatives of a BRCA carrier (parent, sibling, offspring), but untested
- Patients with >20% lifetime risk
- Patients with radiation to chest between ages 10-30 yrs

Imaging Guidelines for High Risk Patients (ACS)

- Annual screening digital mammography
- Annual screening MRI (usually covered by insurance)
- May alternate every 6 months or may be done at same time
- Begin at age 30 and continue for as long as patient is in good health
- If patient can’t or doesn’t want MRI, then screening US
  - Claustrophobia, pacemaker, inadequate insurance
Screening Breast Ultrasound

- No radiation
- Not limited by dense tissue
- No contrast injection
- Cost
ACRIN 6666 Trial

- 2637 HIGH RISK patients with dense breasts
- Single screening US in addition to mammography
- 4.2 additional cancers/1000 high risk women
  - IDC (11/12)
  - Mean size 1.0 cm
  - Almost all node negative (96%)
- Inferior to MRI and BSGI

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False Positives Over 3 Years

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>Mammo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall Rate</td>
<td>515 (10.7%)</td>
<td>453 (9.4%)</td>
<td>.03</td>
</tr>
<tr>
<td>Biopsy Rate</td>
<td>266 (5.5%)</td>
<td>97 (2.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PPV Biopsies</td>
<td>31/266 (11.7%)</td>
<td>37/97 (38.1%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Berg WA et al JNCI 2016; 108, epub 12/18/15
Average time to perform bilateral US:

19 Minutes

Since Enactment of the Legislation in Connecticut

- Weigert and Steenbergen:
  - 8647 screening US on women with dense breasts in CT
  - 3.25 additional cancers/1000

- Hooley et al
  - 935 screening US on women with dense breasts in CT
  - 3.2 additional cancers/1000
  - PPV of BI-RADS 4 masses = 6.5%

- Parrish, Wakefield, and Frimmer
  - 5519 screening US
  - 2 additional cancers/1000
Automated Breast Ultrasound

- Image acquisition is uncoupled from interpretation
- Interpreted by radiologist
- Minimizes operator dependence
- Patients must be recalled for further evaluation, increasing the recall rate from 4.2% to 9.6% in one study (Kelly et al)
Digital Breast Tomosynthesis

- Increases detection of cancer by 35%
- Decreases callbacks by 15-30%
- Increased false positives for ultrasound compared to decreased false positives for tomosynthesis
- Ionizing radiation

Ultrasound vs. Tomosynthesis [ASTOUND]

- First study to compare the modalities in *Journal of Clinical Oncology*
  Tagliafico AS et al JCO 2016;epub 3/9/16
- 3231 women with negative 2D mammogram were screened with US and tomosynthesis
- 13 additional cancers detected by tomo (4/1000)
  - 1 detected only by tomo
- 23 detected by US (7/1000)
  - 11 detected only by US
False Positives ASTOUND

- For any testing
  - 1.7% for tomosynthesis
  - 2.0% for US
- For biopsy
  - 0.7% for both
- However:
  - Most had priors for comparison
  - 6 month follow-ups were not considered a test positive

Conclusion

The Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts' interim analysis shows that ultrasound has better incremental BC detection than tomosynthesis in mammography-negative dense breasts at a similar FP-recall rate. However, future application of adjunct screening should consider that tomosynthesis detected more than 50% of the additional BCs in these women and could potentially be the primary screening modality.
Cost

- US - $425 (not covered by insurance)

Where Does that Leave Us?
Proposed Approach

- Women with dense breast tissue should receive a 3D mammogram if possible and convenient
- Reassurance
- Very concerned patients may elect screening US
- High risk patients should get an MRI
Who is at risk?

- Gender
- Age
- Race
- Personal history
- Family history

Clemons et al, 2001 NEJM

Family history as a risk factor

- Prior chest radiation
- Lifestyle factors
  - obesity, alcohol use
- Reproductive and menstrual history
  - Longer menses=higher risk

Breast cancer risk

- Sporadic
- Familial
- Genetic

15%
10%
Breast Cancer Risk with atypical hyperplasia

Educate patients and providers about cancer risk
Determine if genetic testing is indicated
Decide when screening mammogram should be started
Identify high risk patients for whom other screening or prevention measures can be offered
Risk Models

- Breast Cancer Risk Assessment Tool (GAIL)
- Claus
- Tyrer-Cuzick (IBIS)
- BRCAPRO
- BOADICEA
- Decurion French Model
- BPC3 Model

Example Case: Family Z

Age 40 now
Menarche age 12
First birth age 25
No biopsies
GAIL Model Assessment

Pros

- Free and accessible
- Easy to use and quick
- Takes into account relatives and some personal factors
- Good for atypia

Cons

- Does not take into account 2\textsuperscript{nd}/3\textsuperscript{rd} degree relatives
- Cannot use in women <35
- Does not take into account ages of diagnosis
- Underestimates risks for some ethnicities
CLAUS MODEL

Claus risk for breast cancer

- Claus table for two second-degree relatives
- Probability to age 79 = 20.9%
  - To age 39 = 2.4%
  - To age 49 = 6.1%
  - To age 59 = 11.4%
  - To age 69 = 16.9%

CLAUS MODEL

Pros
- Takes into account 1st AND 2nd degree relatives
- Takes into account ages of breast cancer diagnoses
- Can be used to calculate risk for MRI

Cons
- Physical Tables
- Need to enter pedigree so takes longer
- Does not take into account any personal factors like biopsy or reproductive factors
**IBIS MODEL**

**Pros**
- Takes into account age, personal factors, use of HRT, height and weight.
- Takes into account ovarian cancer risks
- Risk goes up to age 85
- Runs a BRCApro

**Cons**
- Need to enter pedigree and risk factors
- Need the program
- Tends to be highest risks/overestimates risk

**OTHER MODELS**

**BRCAPRO**
- Statistical model to help determine risk of carrying a gremlin BRCA 1 or BRCA 2 mutation

**BOADICEA**
- Decruion French Model

**BPC3 Model**
- Newer model incorporating SNPs and personal risk factors, awaits validation
Breast cancer prevention

- So called ‘chemoprevention’
- Women who are at higher than average risk can reduce their risk by 50-70% by taking tamoxifen for 5yrs
- Evidence for exemestane and anastrozole in post-menopausal women with 60% reduction for 5 years


Thank you!