Detection to Prediction: Imaging Markers of Breast Cancer Risk

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Disclosure

• Per agreement between Mayo Clinic and Gamma Medica, I receive royalties for licensed MBI technologies.
Cancer Care Continuum

Prevention
- Diet
- Physical Activity
- Tobacco use
- Alcohol use
- Environment
- Immunization
- Chemoprevention

Screening
- Imaging
- Screening tests
- Genetic testing

Diagnosis
- Imaging
- Biopsy
- Pathology
- Staging
- Biomarkers
- Molecular profile

Treatment
- Imaging
- Systemic therapy
- Surgery
- Radiation

Survivorship
- Imaging
- Surveillance for recurrence
- Screening for related cancers

End of Life Care

Adapted from National Academies Press, 2013
Screening Guidelines

Mammography for “Average Risk” Women:

<table>
<thead>
<tr>
<th></th>
<th>ACOG</th>
<th>ACR, SBI</th>
<th>ACS</th>
<th>AMA</th>
<th>NCCN</th>
<th>USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age to start</td>
<td>40</td>
<td>40</td>
<td>45</td>
<td>40</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Age to stop</td>
<td>Cont. as long as in good health</td>
<td>When life expectancy &lt; 5-7 yrs</td>
<td>When life expectancy &lt; 10 yrs</td>
<td>When life expectancy &lt; 10 yrs</td>
<td>No limit</td>
<td>74</td>
</tr>
<tr>
<td>Frequency</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual 45-54; 1-2 years 55+</td>
<td>Annual</td>
<td>Annual</td>
<td>Every 2 yrs</td>
</tr>
</tbody>
</table>

Annual screening MRI for Women at “Increased Risk”

Saslow, CA Cancer J Clin 2007
Risk models

- IBIS (Tyrer-Cuzick model)
- Claus Model

{ Familial models to be used for determining appropriateness of MRI screening (> 20% lifetime)

- NCI Breast Cancer Risk Assessment Tool (Gail model)
  - FDA guideline: chemoprevention if 5-year-risk >1.67%
- Breast Cancer Surveillance Consortium model
  - Only model to include breast density
Mammographic Density

“The breasts are almost entirely fatty. …mammography is highly sensitive in this setting”

“The breasts are extremely dense, which lowers the sensitivity of mammography”

Breast composition categories, ACR BI-RADS 5th edition
Density masks breast cancer
What is the sensitivity of mammography in dense breasts?

- Studies only including mammography
  - 1 year of follow-up, until next screening mammogram
  - Estimate sensitivity of ~80%

<table>
<thead>
<tr>
<th>Density</th>
<th>Sensitivity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost entirely fat</td>
<td>78.3 (59.4–89.9)</td>
</tr>
<tr>
<td>Scattered fibroglandular densities</td>
<td>86.6 (80.3–91.1)</td>
</tr>
<tr>
<td>Heterogeneously dense</td>
<td>82.1 (76.6–86.6)</td>
</tr>
<tr>
<td>Extremely dense</td>
<td>83.6 (69.7–91.9)</td>
</tr>
</tbody>
</table>

Kerlikowske, Ann Intern Med, 2011
What is the sensitivity of mammography in dense breasts?

• Supplemental screening in dense breasts
  • Cancers revealed that otherwise were not counted in mammography audit
  • Estimate sensitivity of 20-40%

<table>
<thead>
<tr>
<th>Supplemental Screening Method</th>
<th>Sensitivity of Mammo alone</th>
<th>Sensitivity of Mammo + supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated whole-breast US (Kelly et al)</td>
<td>40%</td>
<td>81%</td>
</tr>
<tr>
<td>ACRIN 6666 – 3 yrs of radiologist-performed US (Berg et al)</td>
<td>52%</td>
<td>76%</td>
</tr>
<tr>
<td>ACRIN 6666 – MRI after 3 yrs mammo+US (Berg et al)</td>
<td>31%</td>
<td>100%</td>
</tr>
<tr>
<td>Molecular breast imaging (Rhodes et al)</td>
<td>24%</td>
<td>91%</td>
</tr>
</tbody>
</table>

Kelly et al Eur Radiol 2011; Berg et al, JAMA 2012; Rhodes et al, AJR 2015
Dual-risk of Density

1. Masking prevalent cancers (present at the time)
2. Greater likelihood of incident cancers (will develop later)
   • Mechanism linking density and cancer is unclear
     • Hypothesis that more glandular tissue, more likely to develop cancer
     • Extremely dense vs. fatty, RR of 4 to 6
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 or BRCA2 mutation</td>
<td>10.0–32.0</td>
</tr>
<tr>
<td>Family history of cancer (no known mutation)†</td>
<td></td>
</tr>
<tr>
<td>1 first-degree relative</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>2 first-degree relatives</td>
<td>3.0</td>
</tr>
<tr>
<td>3 or more first-degree relatives</td>
<td>4.0</td>
</tr>
<tr>
<td>1 second-degree relative</td>
<td>1.2–1.5</td>
</tr>
<tr>
<td>Therapeutic radiation to chest at &lt;30 yr of age‡</td>
<td>7.0–17.0</td>
</tr>
<tr>
<td>Hormonal factors</td>
<td></td>
</tr>
<tr>
<td>Late (age &gt;30 yr) parity or nulliparity</td>
<td>1.2–1.7</td>
</tr>
<tr>
<td>Early (age &lt;12 yr) menarche or late menopause (age &gt;55 yr)</td>
<td>1.2–1.3</td>
</tr>
<tr>
<td>Combined hormone-replacement therapy (e.g., for 10 or more yr)</td>
<td>1.5</td>
</tr>
<tr>
<td>Breast density (very dense vs. mainly fatty)</td>
<td>5.0</td>
</tr>
<tr>
<td>Atypical ductal or lobular hyperplasia or lobular carcinoma in situ on previous breast biopsy</td>
<td>4.0</td>
</tr>
</tbody>
</table>
Factors that impact density

- Age
- Menopause
- Hormone use
- BMI
- Anti-estrogen drugs
- Parity
- Genetics

Density by Age

Sprague et al, JNCI 2014
Density to predict risk

- Density alone does not have discriminatory accuracy to be a useful risk predictor
- 40-50% of women have dense breasts
- Should all be considered at “elevated risk”?
- Should all receive supplemental screening?

“Risk stratification will be an essential tool in determining the best screening plan for each woman.”

Slanetz, Freer, and Birdwell, NEJM 2015
Molecular breast imaging (MBI)

-Performed with injection of Tc-99m sestamibi and dedicated gamma camera
  - Dual-head CZT-based system capable of low-dose imaging

-Mayo experience
  - >5000 MBI exams since ~2004
  - Recommends MBI for supplemental screening
    - Women with dense breasts, intermediate risk
    - MR recommended, cannot be performed

-In dense breasts, MBI finds an additional 8 to 9 cancers per 1000 screened.

Rhodes et al, AJR 2015
Typical Negative MBI Screening Exam

Mammogram (Tomosynthesis C-view)
Variability in fibroglandular uptake

Lack of uptake: Photopenia

Marked uptake
Masking cancer
49 yr old with extremely dense breasts, hx of multiple breast cysts

Extremely dense parenchyma with “innumerable large nodules”

MBI: “background activity makes the study non-diagnostic”

MRI: “small masses could be obscured”

Right breast: Scattered foci of DCIS throughout all 4 quadrants

Left breast: Exuberant proliferative fibrocystic changes with multiple sclerosing papillary lesions and foci of ADH
Change our thinking about background

• Instead of just an occasional annoyance…
  • Should document consistently - potential to mask cancers
  • Termed “background parenchymal uptake (BPU)”

• What is the etiology of BPU?
  • Tc-99m sestamibi uptake in the breast is poorly understood
  • In cancer: related to angiogenesis, and sequestered in mitochondria

• Hypothesize that BPU could signify a tissue environment primed for breast cancer development
MBI Lexicon includes BPU Categories

- Inter-reader agreement: $\kappa = 0.84$
- Intra-reader agreement: $\kappa = 0.87$ to $0.94$

Prevalence of BPU categories in dense breasts

Conners et al, AJR 2012; Hruska et al, AJR 2015
Association of BPU with clinical factors

- Women with high background (moderate/marked) more likely to be
  - Younger (mean age 50 vs. 58)
  - Pre or perimenopausal
  - If postmenopausal, more likely using hormone therapy
Hormone therapy can influence BPU
Menstrual cycle can influence BPU

- BPU changes with cycle observed in about 30% of premenopausal women studied
  - Higher in luteal phase vs. follicular
  - Scheduling MBI in follicular phase (days 7-10) can minimize BPU
Menstrual cycle can influence BPU

• Dramatic increase at luteal phase
Menstrual cycle not influencing BPU

- Photopenic BPU at both phases
Hormonal effects on BPU

- Some patients show imaging changes with hormonal changes, others do not
- May reflect variability in hormone responsiveness of breast tissue
- May be differentiator in determining breast cancer risk?
  - Particularly important in guiding decisions to use hormone therapy
Beyond hormonal influence

4 different postmenopausal women, no exogenous hormones.

Mammograms
Similar density

Corresponding MBI Exams
BPU prevalence varies across density categories

<table>
<thead>
<tr>
<th>Density Category</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photopenic</td>
<td>N= 85</td>
<td></td>
</tr>
<tr>
<td>Photopenic</td>
<td>N= 164</td>
<td>(34%)</td>
</tr>
<tr>
<td>Photopenic</td>
<td>N= 900</td>
<td>(22%)</td>
</tr>
<tr>
<td>Minimal to mild</td>
<td>55 of 164</td>
<td>(34%)</td>
</tr>
<tr>
<td>Minimal to mild</td>
<td>72 of 164</td>
<td>(44%)</td>
</tr>
<tr>
<td>Moderate or Marked</td>
<td>37 of 164</td>
<td>(22%)</td>
</tr>
</tbody>
</table>
Case-Control Study

• Purpose: To investigate whether BPU on MBI is a risk factor for incident breast cancer
Case-Control Study

• Reviewed institutional MBI database
  • >3000 women with screening MBI performed between 2005-2014
  • Earliest (index) MBI used for analysis

• Excluded
  • Prevalent breast cancer cases
  • Women with breast implants

• Participants followed for breast cancer through
  • Review of medical records
  • Linkage to Mayo Clinic Tumor Registry
Cases and Controls

- 62 incident breast cancer cases
  - 45 (73%) were invasive and 17 (27%) were DCIS
  - Median time to diagnosis: 3.3 years (range 0.5 to 8.8 years) after index MBI.

- 179 controls randomly selected
  - Matched on
    - Age (within 5 yrs)
    - Menopausal status
    - MBI year
  - Required to be followed at least as long as matched case

- Two breast radiologists read all MBIs independently
  - Blinded to case status
Case-Control Study Results

- Women with high BPU more likely to develop breast cancer than women with low BPU.

<table>
<thead>
<tr>
<th>BPU as dichotomous variable</th>
<th>Odds Ratio†, adjusted for BMI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td></td>
</tr>
<tr>
<td>Photopenic or Minimal-mild</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate or Marked</td>
<td><strong>3.4 (1.6, 7.3)</strong></td>
</tr>
<tr>
<td>P-value</td>
<td>0.002</td>
</tr>
<tr>
<td>Reader 2</td>
<td></td>
</tr>
<tr>
<td>Photopenic or Minimal-mild</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate or Marked</td>
<td><strong>4.8 (2.1, 10.8)</strong></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.001</td>
</tr>
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</table>

†Numbers in parentheses are 95% confidence intervals
Case-Control Study Results

- Association remained with adjustment for density

<table>
<thead>
<tr>
<th>BPU as dichotomous variable</th>
<th>Odds Ratio†, adjusted for BMI†</th>
<th>Odds Ratio†, adjusted for BMI and BI-RADS density</th>
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<td>3.3 (1.6, 7.2)</td>
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<tr>
<td>P-value</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Reader 2</strong></td>
<td></td>
<td></td>
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<tr>
<td>Photopenic or Minimal-mild</td>
<td>1.0</td>
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Case-Control Study Results

- Association remained with adjustment for postmenopausal HT

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<th>Odds Ratio†, adjusted for BMI†</th>
<th>Odds Ratio†, adjusted for BMI and BI-RADS density</th>
<th>Odds Ratio†, adjusted for BMI and postmenopausal HT</th>
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<td>Reader 1</td>
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<td></td>
</tr>
<tr>
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<td>1.0</td>
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</tr>
<tr>
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<td><strong>3.4 (1.6, 7.3)</strong></td>
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<td><strong>3.6 (1.7, 7.7)</strong></td>
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<td>P-value</td>
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<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
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<td></td>
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<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate or Marked</td>
<td><strong>4.8 (2.1, 10.8)</strong></td>
<td><strong>4.6 (2.1, 10.5)</strong></td>
<td><strong>5.0 (2.2, 11.4)</strong></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
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†Numbers in parentheses are 95% confidence intervals
Screening mammogram
Negative, Extremely dense

2 years later,
Presented with clinical symptoms
(nipple retraction)

MRI performed:
Right breast: atypia
Left breast: Grade I, 0.9 cm invasive ductal carcinoma, node negative

Case example: 41 yr old woman with strong family hx
Case-control study Conclusions

• BPU on MBI is an imaging biomarker associated with breast cancer risk; OR 3.4 to 4.8

• Associations remained
  • With adjustment for mammographic density
  • With adjustment for hormone therapy use
  • When limited to postmenopausal women only
    • Suggests risk factor is not just cyclic effect artifact
  • When limited to invasive cancer cases only
Background parenchymal enhancement (BPE) at breast MR imaging

• Associated with hormonal influences
  • Menopausal status (King, Eur Radiol 2012; Hegensheid, Eur Radiol 2012)
  • Menstrual cycle phase (Kuhl, Radiology 1997; Delille, Breast J 2005)
  • Hormone therapy use (Delille, Radiology 2005)
  • Tamoxifen and AI use (King, Radiology 2012)

• Variable background among women with similar
  • Mammographic density (Kuhl et al, JMRI 2014)
  • MR-depicted fibroglandular tissue (King et al, Radiology 2011)
MRI background parenchymal enhancement (BPE)

Post-contrast maximum intensity projections

Per ACR BI-RADS:
“visually estimated enhancement of fibroglandular tissue of the breasts”
Refers to the volume and intensity of enhancement
MRI BPE association with breast cancer

- Case-control analysis
  - 39 prevalent breast cancer cases
  - High vs. Low BPE: ORs = 3.7 to 10.1
  - Associations remained significant after adjustment for amount of fibroglandular tissue seen on MR

King et al, Radiology 2011
MRI BPE association with breast cancer

- Case-control analysis
  - 23 breast cancer cases
    - 6 prevalent
    - 17 incident
  - High vs. Low BPE: OR = 9.0

Dontchos et al, Radiology 2015
MRI background enhancement in BRCA carriers

- UPenn researchers developed quantitative BPE measurement tools for MRI
- 50 BRCA1/2 carriers who underwent risk reducing oopherectomy
  - Pre and post-oopherectomy MRI performed
  - Median 4.8 yrs follow-up
  - 44 with no breast cancer: BPE was reduced after oopherectomy
  - 6 developed breast cancer: BPE was not reduced after oopherectomy

Wu et al, Breast Cancer Res 2016
MRI background enhancement in BRCA carriers

40 yrs old
No cancer at 9 years follow-up
Decrease in MRI-measured FGT
Decrease in BPE

36 yrs old
Cancer diagnosed at 6 years follow-up
No decrease in MRI-measured FGT
No decrease in BPE
MBI and MRI background

- Gadolinium contrast enhancement and sestamibi uptake have similar functional mechanism
  - Perfusion, angiogenesis and vascular permeability
Background on Contrast-enhanced Mammography

• Associated with
  • Menopausal status
  • Prior radiation therapy
  • Hormonal treatment
  • Density
  • MR fibroglanular tissue

• Agreement between MR and CEDM background
  • $\kappa = 0.66$

Sogani et al, Radiology 2016
Background uptake on PET

- Evidence of variability in FDG uptake in breast fibroglandular tissue

- Non-dense on mammography
  - Low FDG uptake

- Dense on mammography
  - High FDG uptake

Mavi et al, J Nuc Med 2010
Summary

- Functional imaging techniques show variability among fibroglandular tissue that appears similar on a mammogram
  - Provide additional risk information beyond mammographic density
  - May depict fibroglandular tissue primed for cancer development

- Functional imaging biomarkers could identify the subset of women with dense breasts who are
  - at greatest risk of breast cancer, and
  - most likely to benefit from tailored screening or risk-reduction strategies
Thank you

Collaborators:

• Kathy Brandt, MD
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• Dan Visscher, PhD