Breast Imaging: Now & the Future

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Professor of Radiology
Disclosures

- Pending research agreement with Hologic and Dilon technologies
- Reader study for Naviscan
Objectives

- To understand the current state of breast imaging, including indications for imaging women at high risk for breast cancer
- To understand how screening of average risk women may be improved in the future
- To understand possible future roles of adjunct screening for women at moderate and high risk for developing breast cancer
American Cancer Society Guidelines: Average Risk Women

- Age 20-39
  - Clinical Breast Exam every 3 years

- Age 40 and older
  - Annual mammogram
  - Annual CBE
Breast Cancer mortality declining 2.2%/year since 1990

Figure 6. Trends in Female Breast Cancer Death Rates* by Race and Ethnicity, US, 1975-2004

*Rates are age-adjusted to the 2000 US standard population.

Information is included for all states except Connecticut, Louisiana, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklahoma, Virginia, and Vermont.


American Cancer Society, Surveillance Research, 2007
Breast Density

Sensitivity: 87% → 63%
Specificity: 97% → 89%

Carney PA. Ann Int Med 2003
Improve Anatomic Imaging

UC Davis
Digital Breast Tomosynthesis

- 99 recalls from digital screening
- 52% of lesions would not have been recalled based on tomo
- Recall reduction 40%

Poplack SP. AJR 2007
TomoSynthesis

- 190 women (39 cancers) scheduled for biopsy due to mass seen on mammo, US, or PE
  - 4 additional lesions detected on tomo (2.1%); all IDC 6-14mm
  - 2 fatty/scattered, 2 heterogeneous/dense

Helvie M. RSNA 2008
Breast CT

- Small studies to-date
- 79 women
- CT significantly better for visualizing masses
- Mammo better for calcifications

Lindfors KK. Radiology 2008
American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography

Debbie Saslow, PhD; Carla Boetes, MD, PhD; Wylie Burke, MD, PhD; Steven Harms, MD; Martin O. Leach, PhD; Constance D. Lehman, MD, PhD; Elizabeth Morris, MD; Etta Pisano, MD; Mitchell Schnall, MD, PhD; Stephen Sener, MD; Robert A. Smith, PhD; Ellen Warner, MD; Martin Yaffe, PhD; Kimberly S. Andrews; Christy A. Russell, MD (for the American Cancer Society Breast Cancer Advisory Group)

ABSTRACT  New evidence on breast Magnetic Resonance Imaging (MRI) screening has become available since the American Cancer Society (ACS) last issued guidelines for the early detection of breast cancer in 2003. A guideline panel has reviewed this evidence and developed new recommendations for women at different defined levels of risk. Screening MRI is recommended for women with an approximately 20–25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease. There are several risk subgroups for which the available data are insufficient to recommend for or against screening, including women with a personal history of breast cancer, carcinoma in situ, atypical hyperplasia, and extremely dense breasts on mammography. Diagnostic uses of MRI were not considered to be within the scope of this review. (CA Cancer J Clin 2007;57:75–89.) © American Cancer Society, Inc., 2007.
ACS: Annual Screening MRI

- Women with >20% lifetime risk by BRCAPro or other model dependent on family hx
- BRCA mutation
- 1st degree relative of BRCA carrier, but untested
- Li-Fraumeni, Cowden, and Bannayan-Riley-Ruvalcaba syndromes and 1st degree relatives
- Radiation to chest between age 10 and 30 years

Beginning at age 25
Genetic Risk in the Population

- Genetic Susceptibility: 1%
- Not Likely BRCA or Other Known Mutation Carrier: 99%
## Genetic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Autosomal Dominant</th>
<th>Lifetime Risk</th>
<th>Other Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>X</td>
<td>55-85%</td>
<td>Ovary, liver, testis (male)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>X</td>
<td>25-60%</td>
<td>Male breast, pancreas</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>X</td>
<td>60-90%</td>
<td>Leukemia, sarcoma, adrenal</td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td>X</td>
<td>30-50%</td>
<td>Thyroid (and B9), meningioma</td>
</tr>
</tbody>
</table>
BRCA Patient

1995

2002
Familial Breast Cancer

• Tumor Doubling Time
  – BRCA carriers 45 days (CI 26-73)
  – Non-carriers 84 days (CI 58-131)

• Survival is hereditary
  – 1277 mother-daughter breast cancer pairs showed daughter’s length of survival correlated with mother’s length of survival

Tilanus-Linthorst MM. Eur J Cancer 2005
Hemminki K Br Cancer Res & Treat 2007
### MR screening studies

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Institution</th>
<th>N</th>
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<tbody>
<tr>
<td>1. Kuhl ‘00</td>
<td>U Bonn</td>
<td>192</td>
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<tr>
<td>2. Tilanus-Linthorst ‘00</td>
<td>Rotterdam</td>
<td>109</td>
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<tr>
<td>3. Warner ‘01@</td>
<td>U Toronto</td>
<td>196</td>
</tr>
<tr>
<td>4. Stoujesdijk ‘01</td>
<td>Nijmegen</td>
<td>179</td>
</tr>
<tr>
<td>5. Lo/Schnall ‘01</td>
<td>U Penn</td>
<td>157</td>
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<tr>
<td>6. Heerdt ‘01</td>
<td>MSKCC</td>
<td>124</td>
</tr>
<tr>
<td>7. Morris ‘03</td>
<td>MSKCC</td>
<td>367</td>
</tr>
<tr>
<td>8. Robson ‘01</td>
<td>MSKCC</td>
<td>54</td>
</tr>
<tr>
<td>9. Kriege ‘04</td>
<td>Rotterdam</td>
<td>1909</td>
</tr>
<tr>
<td>10. Warner ‘04</td>
<td>U Toronto</td>
<td>236</td>
</tr>
<tr>
<td>11. MARIBS ‘05</td>
<td>UK</td>
<td>649</td>
</tr>
<tr>
<td>12. Lehman ’05</td>
<td>Multi- North Am</td>
<td>390</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4562</td>
</tr>
</tbody>
</table>
High Risk MRI Screening Results

• 20 – 60 Cancers/1000 women screened
  – versus 3-7/1000 with mammography
• Mean tumor size 0.7-2.0 cm
• 65-100% node negative
Largest Trial

- 1909 women lifetime risk ≥15%
  - 358 mutation carriers
- 2.9 years f/u
- 51 cancers
- Sensitivity for Inv CA:
  - CBE 17.9%
  - Mammo 33.3%
  - MRI 79.5%

Kriege M. NEJM
2004; 351:427-37
Kriege et al

- Compared to control groups (Cancer registry or prospective group), those undergoing MRI had:
  - Larger proportion of invasive cancers <10mm (43% compared to 14% and 12%)
  - Lower axillary metastasis (21% vs. 52% and 56%)
  - More DCIS cases (12% vs. 8% and 0%) (not significant)
DCIS

- Presents as linear ductal non-mass-like enhancement (NMLE)
- Mass-like enhancement less common
- Often with benign enhancement pattern
34 yo High Risk Screening

Multifocal IDC
MRI Performance

• Sensitivity
  – 90-95% for invasive cancers
  – 50-70% for DCIS

• Detection of DCIS varies by grade:
  – 92% sensitivity for high grade
  – 70% intermediate/low grade DCIS
    (Neubauer, Br J Rad 2003)

• Specificity 30-70%
MR in BRCA 1 and 2 Carriers

- 23% of cancers were fibroadenoma-like (80% were in BRCA 1)
  - No internal septations
  - Not persistent enhancement
- BRCA 1- no calcifications
- BRCA 2- similar to sporadic breast cancer

Schrading S and Kuhl CK. Radiology 2008
<table>
<thead>
<tr>
<th>Texture</th>
<th>MRI</th>
<th>Mammo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty</td>
<td>3/3 (100%)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Scattered</td>
<td>14/15 (93%)</td>
<td>5/15 (33%)</td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>22/25 (88%)</td>
<td>4/25 (16%)</td>
</tr>
<tr>
<td>Dense</td>
<td>2/3 (66%)</td>
<td>1/3 (33%)</td>
</tr>
</tbody>
</table>

Bigenwald RZ. Cancer Epid Biomark Prev; 2008
New IDC in fatty breast
# Outcome Screening for BRCA1 Carriers

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clinical</th>
<th>Mammo</th>
<th>MR</th>
<th>Mammo + MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer size, median</td>
<td>2.6 cm</td>
<td>1.9 cm</td>
<td>1.3 cm</td>
<td>1.1 cm</td>
</tr>
<tr>
<td>Ave Life Expectancy</td>
<td>71.2 yrs</td>
<td>+0.8 yrs</td>
<td>+1.1 yrs</td>
<td>+1.4 yrs</td>
</tr>
<tr>
<td>Decrease Rel Mortality</td>
<td>16.8%</td>
<td>17.2%</td>
<td>22.0%</td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td>53.8%</td>
<td>80.2%</td>
<td>84.0%</td>
<td></td>
</tr>
</tbody>
</table>

Lee JM. Radiology 2008
Cost Effectiveness

- BRCA 1
- QALY
- 30-39 mammography 5,200 pds
  - MR 13,486
- 40-49 mammography 2,913
  - MR 7,781

Norman RPA. Eur J Health Econ 2007
Radiation Exposure at Young Age

- Hodgkin's Disease treated with mantle radiation (RR 5.2)
- Risk of breast cancer increases beginning about 7-8 years after treatment, peaking at about 15 years post treatment
- Younger age at treatment = higher risk
- Many unaware of increased risk
- Begin intensive screening 6-7 years after treatment

Clemons M. Cancer Treat Rev 2000
Goss PE. J Clin Onc 1998
Prior Radiation Therapy

- 29 yo woman treated for Hodgkins dz 10 years ago
- Palpable lump left breast
- Biopsy showed invasive ductal carcinoma, grade III
Risk Reduction: High Risk Women

- Early detection- Modified/intensive screening
- Pharmacologic- Tamoxifen, Raloxifene, aromatase inhibitors?
- Surgical- Prophylactic mastectomy, oophrectomy
Risk Evaluation: Identifying Women at Elevated Risk

- Young at onset
- Bilateral breast cancer
- Other cancers in family
- Multiple or male relatives
This family history is worrisome for hereditary breast and ovarian cancer on the paternal side.
Breast Cancer Risk Factors

**Personal**
- Parity
- Age at menarche
- Age at menopause
- Hormone therapy
- Obesity

**Breast Disease**
- ALH
- ADH
- DCIS
- Breast density

**Genetic**
- BRCA
- BRCA carrier
- L-Fraumeni syndrome
- Cowden syndrome

**Models**
- Tyrer-Cuzick Model
- Gail Model
- Claus or BRCA Pro Model
- Syndrome
Breast Cancer Risk in the Population

- Genetic Susceptibility
- High Risk Due to Combination of factors
- Average Risk

MRI
Boyd Classification

Boyd, 1995

Relative Risk

- None: 1
- <10%: 1.2
- 10–25%: 2.2
- 25–50%: 2.4
- 50–75%: 3.4
- >75%: 5.3
Models that Incorporate Breast Density Improve Accuracy

- Breast Cancer Screening Consortium (BCSC) (Barlow WE. JNCI, 2006).
- BCDDP (Chen J. JNCI 2006)
Insufficient Evidence for Screening MRI

• 15-20% lifetime risk (moderate risk)
• LCIS, ADH, or ALH on prior biopsy
• Heterogeneous or dense breast tissue
• Personal history of breast cancer, including DCIS
Personalized Breast Cancer Screening

- Genetic Susceptibility
- High Risk Due to Combination of factors
- Moderate Risk
- Average Risk

MRI
BSGI PEM
CT

MRIs > 20%
15-20%
<15%
The Age of Personalized Medicine

Personalized Medicine
A new era of healthcare through:

Improved diagnoses.
More efficient drug development.
Better medical outcomes.
Earlier interventions.
Tomosynthesis

Whole breast US

MRI

CT

Scintigraphy

PET
New Modalities

- Anatomic
  - Tomosynthesis
  - CT
  - US

- Functional
  - MRI
    - Spectroscopy
    - Diffusion weighted imaging
  - Gamma imaging
  - PET
ACRIN 6666/Avon trial

- 2809 high-risk women had mammo + screening US, 1 year follow-up
- 40 women (41 breasts) with CA
- Additional 4.2 CA/1000
- 8.9% PPV for US lesions

Berg WA. JAMA 2008
Automated Whole Breast US

- 61 women with 14 cancers detected on screening handheld US
  - Sensitivity of Automated Breast US 57-78%
- 101 breasts/87 women had both HH and ABUS
  - 71/78 (91%) lesions on HH also on ABUS
  - 9/11 additional BI-RADS 4-5 lesions on ABUS not reproducible on HHUS

Chang J. RSNA 2008
Hovanessian L. RSNA 2008
## Cancer Detection by Modality

<table>
<thead>
<tr>
<th></th>
<th>Mammo</th>
<th>US</th>
<th>MRI</th>
</tr>
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<tbody>
<tr>
<td>Lehman, 2007</td>
<td>0.6%</td>
<td>1.2%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Kuhl, 2000</td>
<td>1.6%</td>
<td>1.6%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Warner, 2004</td>
<td>3.4%</td>
<td>3.0%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Italian Multi-Center, 2002</td>
<td>1.0%</td>
<td>1.0%</td>
<td>7.6%</td>
</tr>
</tbody>
</table>
**MR vs. Mammo/US**

- 195 high risk women, 171 completed all studies
- 6 cancers, 3.5%

<table>
<thead>
<tr>
<th></th>
<th>Cancers detected</th>
<th>Diagnostic Yield</th>
<th>Biopsy</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>6</td>
<td>3.5%</td>
<td>8.2%</td>
<td>43%</td>
</tr>
<tr>
<td>Mammo</td>
<td>2</td>
<td>1.2%</td>
<td>2.3%</td>
<td>50%</td>
</tr>
<tr>
<td>US</td>
<td>1</td>
<td>0.6%</td>
<td>2.3%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Lehman CD. Radiology; 2007
Breast Specific Gamma Imaging (BSGI)

- Dedicated detector
- Inject 20-30 mCi $^{99m}$Tc sestamibi
- Wait 10 minutes
- Image each breast (about 10 min per view)
Breast Specific Gamma Imaging (BSGI)

- 94 high risk women with negative mammo and CBE
- 16 abnormal BSGI (17%)
  - 2 with invasive cancer at biopsy (PPV 12%)

Brem RF. Radiology 2005
BSGI Performance

• 146 patients with 167 lesions undergoing biopsy (83 cancers)
  – BSGI 80/83 cancers (sensitivity 96%). Smallest IDC and DCIS each 1mm
  – 50/84 true negative benign lesions (specificity 60%)
  – PPV 69%, NPV 94%

Brem RF. Radiology 2008
BSGI Detection of ILC

• Invasive lobular carcinoma
  – 26 women

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammo</td>
<td>79%</td>
</tr>
<tr>
<td>US</td>
<td>68%</td>
</tr>
<tr>
<td>Gamma</td>
<td>93%</td>
</tr>
<tr>
<td>MRI</td>
<td>83%</td>
</tr>
</tbody>
</table>

Brem R. AJR 2009
BSGI compared to MRI

• 48 patients with 63 indeterminate lesions on mammography underwent both BSGI and MRI
  – 21 cancers, 5 high-risk
  – Sensitivity of BSGI 96%, MRI 88%
  – Specificity of BSGI 46%, MRI 27%

Lanzkowsky L RSNA 2008
BSGI: Detection of DCIS

- 20 women with 22 DCIS lesions
  - Mammo, MRI, BSGI
  - 2-21 mm
  - 2 lesions only on BSGI in contralateral breast

<table>
<thead>
<tr>
<th></th>
<th>Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammo</td>
<td>18/22</td>
</tr>
<tr>
<td></td>
<td>(82%)</td>
</tr>
<tr>
<td>MRI</td>
<td>7/8</td>
</tr>
<tr>
<td></td>
<td>(88%)</td>
</tr>
<tr>
<td>BSGI</td>
<td>20/22</td>
</tr>
<tr>
<td></td>
<td>(91%)</td>
</tr>
</tbody>
</table>

Brem R. Acad Rad 2007
Limitations of BSGI

- Hot lab
- No Biopsy capability
- Small series by a limited number of investigators
Hybrid Imaging (BSGI-Digital)

- Fused BSGI and digital mammogram
Positron Emission Mammography (PEM)

- Fasting 4-6 hours
- Inject $^{18}$F-FDG IV
  - 1 Rad whole body dose
  - Shielding
- Wait one hour
  (not active)
Positron Emission Mammography (PEM)

- Small Studies to Date
- 23 BI-RADS 5 lesions
  - Sensitivity 86%
  - Specificity 33%
  - PPV 90%

Rosen EL. Radiology 2005
PEM

- 113 women (133 breasts) with biopsy proven cancer
- PEM detected 107/119 cancers
  - Sensitivity 90%

Schilling K. RSNA 2008
## Lifetime Risk

<table>
<thead>
<tr>
<th></th>
<th>&gt;20%</th>
<th>15-20%</th>
<th>&lt;15%</th>
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<tbody>
<tr>
<td>Mammo</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MRI</td>
<td>X</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>HH US</td>
<td>X</td>
<td>?</td>
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## Lifetime Risk: Future Strategies?

<table>
<thead>
<tr>
<th></th>
<th>&gt;20%</th>
<th>15-20%</th>
<th>&lt;15%</th>
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<tbody>
<tr>
<td>Tomo/CT</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MRI</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABUS</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>BSGI</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>PEM</td>
<td>?</td>
<td>?</td>
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</tr>
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</table>
Conclusions

- Breast MRI highly sensitive for detection of invasive cancer in a high risk population
- Moderate specificity and lower pre-test probability make MRI less useful for screening moderate risk women
- Other modalities, such as whole breast US, BSGI and PEM may play a role in adjunct screening in moderate risk women
# Cancer Risk by Site for BRCA Carriers

**Table 5.** Population relative risks and 95% confidence intervals of cancer by mutation status and cancer site

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>21 (12 to 36)</td>
<td>7.0 (3.1 to 16)</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>11 (7.5 to 15)</td>
<td>4.6 (2.7 to 7.8)</td>
</tr>
<tr>
<td>Males</td>
<td>_↑</td>
<td>102 (9.9 to 1050)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>_↑</td>
<td>1.3 (.35 to 5.1)</td>
</tr>
<tr>
<td>Stomach</td>
<td>4.8 (1.5 to 15)</td>
<td>3.4 (1.87 to 13)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.3 (3.0 to 5.6)</td>
<td>46 (1.02 to 11)</td>
</tr>
<tr>
<td>Kidney, bladder</td>
<td>4.4 (1.5 to 13)</td>
<td>_↑</td>
</tr>
<tr>
<td>Leukemias, lymphomas, etc</td>
<td>3.7 (1.5 to 9.5)</td>
<td>_↑</td>
</tr>
<tr>
<td>Liver, gallbladder, bile duct</td>
<td>8.1 (2.0 to 33)</td>
<td>4.6 (1.73 to 28)</td>
</tr>
<tr>
<td>Prostate</td>
<td>.65 (.051 to 8.3)</td>
<td>2.7 (1.1 to 7.1)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3.1 (1.45 to 21)</td>
<td>6.6 (1.9 to 23)</td>
</tr>
<tr>
<td>Uterus</td>
<td>1.7 (.17 to 17)</td>
<td>1.6 (.15 to 16)</td>
</tr>
<tr>
<td>Testis</td>
<td>17 (1.3 to 230)</td>
<td>_↑</td>
</tr>
<tr>
<td>All cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>6.7 (5.0 to 8.8)</td>
<td>3.0 (2.0 to 4.5)</td>
</tr>
<tr>
<td>Males</td>
<td>1.6 (.87 to 2.9)</td>
<td>1.6 (.85 to 2.9)</td>
</tr>
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</table>

From Risch et al. JNCI 2006.