Maxine Jochelson MD
Director of Radiology: Breast and Imaging Center
Memorial Sloan Kettering Cancer Center, N.Y., N.Y.
Associate Professor of Clinical Radiology Weill Cornell Medical School

SCREENING YOUNG WOMEN FOR BREAST CANCER
Outline

- Screening:
  a. Current guidelines vs. USPSTF vs ACS guidelines
  b. Why not screen < 50?
  c. Data for screening average risk women <50
  d. Screening young women at increased risk
- New technologies to improve screening of both groups
- Conclusions
Screening guidelines 2016: average risk

SBI, ACR, ACOG: Current standard
- Annual mammography beginning at 40 until life expectancy < 5 yrs.
- Yearly clinical breast exams

ACS
- Annual mammography from 45-54- but can begin at 40
- Transition to every 2 years after 55 until life expectancy <10 yrs. but can do yearly
- No breast exam by MD, no self exam

USPSTF
- 40-49 discuss w/ MD
- Biennial from 50-74
- No self exam
Why not mammography < 50?

- Missed cancers/dense breasts
- Call backs/ false positives leading to anxiety more frequent in young women
- Not as much mortality reduction
- “Over diagnosis”
Must discuss mortality AND morbidity

Data FOR screening younger women
Average risk women from 40-49

- Screening of Young Women (SCRY): 1986-2005
- Compared women invited vs. not invited to screening
- 16 year F/U
- 26-29% mortality reduction-higher for those actually screened
- Higher reduction in those 45-49

- Hellquist et al Cancer 2010
Average risk women from 40-49

- Longitudinal prospective cohort 1990-2008 compared mammo detected to MD or pt. detected cancers
- N=1977
- Mammo detected more likely to be conservable $p<0.001$
- Mammo detected less likely to receive chemo $p<0.001$
- 5 yr relapse free survival mammo detected 92% vs. 88% $p<0.001$

Malmgren et al Radiol 2012
NY experience: 2007-2010

- 43,351 mammos: 1/3 in their 40’s
- 205 cancers: 20% in their 40’s
- > 50% of cancers in women in their 40’s were invasive

- Arleo et al AJR 2013
Average risk women from 40-49

- Retrospective 2008-2011
- N= 230 patients w/ breast cancer
  - 149 screened/81 non-screened
- Screened vs. non-screened:
  - Earlier stage p= 0.001
  - Negative nodes p=0.005
  - Smaller tumors p<0.001
  - Mastectomy: 48% non-screened vs. 30% p=0.1
  - Chemo: 66% vs. 44% p=0.042

Plecha et al AJR 2014
<table>
<thead>
<tr>
<th>Model</th>
<th>D</th>
<th>E</th>
<th>G</th>
<th>M</th>
<th>S</th>
<th>W</th>
<th># mammograms</th>
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<tbody>
<tr>
<td>USPSTF Biennial 50-74</td>
<td>22%</td>
<td>27%</td>
<td>21%</td>
<td>21%</td>
<td>20%</td>
<td>28%</td>
<td>11,000</td>
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<tr>
<td>STANDARD Annual 40-84</td>
<td>38%</td>
<td>49%</td>
<td>32%</td>
<td>29%</td>
<td>35%</td>
<td>54%</td>
<td>36,500</td>
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For 25,000 more mammograms/1000 women:
6 Model Average Increased Mortality Reduction by **16.3%**

*Cancer Intervention and Surveillance Modeling Network*
CISNET modeling

- Adding annual mammo of women 40-49 to biennial screening 50-74 increases lives saved by 27%
- Increases life years gained by 47%
- Saves 42% more lives & life years than biennial mammo
- Need to screen 588 women to save 1 life w/ annual digital mammo in this age group

- Hendrick et al AJR 2014
Average risk women under 50 should be screened annually
- BRCA 1 or 2 mutation
- Untested first-degree relative of BRCA carrier
- Lifetime risk >20%
  - Defined by BRCAPRO
  - Other models dependent on family history
- Chest XRT – 10 to 30 years of age
Breast MRI

- Breast MRI: most sensitive imaging test for breast cancer detection
- Sensitivity due to imaging of enhancing neovascularity
- Limitations include cost (> $4,000.00), claustrophobia, inability to perform in women w/ metallic implants, Gadolinium allergy & lack of specificity
- Not universally available
How do we identify cancers on MRI?

- Tumors create new vessels (angiogenesis)
  - VEGF
  - Vessels leak
  - A-V shunting

Courtesy of Dr. Elizabeth Morris
Cancer yield of different imaging methods, used alone or in combination.

Kuhl C et al. JCO 2010
<table>
<thead>
<tr>
<th></th>
<th>MRI (n=445)</th>
<th>No MRI (n=830)</th>
<th>p</th>
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<tbody>
<tr>
<td>Cancer</td>
<td>41 (9.2%)</td>
<td>76 (9.2%)</td>
<td></td>
</tr>
<tr>
<td>DCIS/stage 1</td>
<td>13.8%</td>
<td>7.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>Stage II-IV</td>
<td>1.9%</td>
<td>6.6%</td>
<td>0.02</td>
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</table>

Warner E et al JCO 2011
BRCA 1 58% <40; 9.7%<30
More interval cancers in younger patients
43% cancers detected only on MRI
  - 46% of ca in BRCA 1
  - 31% of ca in BRCA 2
  - 41% of ca in high risk
  - 47% in moderate risk
9 mm median, 62% ≤ 1 cm
93% overall survival vs. 74.5% in 26 historical cohorts

Rijnsburger et al 2010 JCO
MORTALITY REDUCTIONS:

- Mammo alone vs. Mammo + MRI
  BRCA1  41.9% vs. 50.1%
  BRCA2  46.8% vs. 61.6%

- MRI alone
  BRCA1  49.0%
  BRCA2  61.0%

<40: 1 invasive cancer detected by mammo only: BRCA1 pt. vs. 7 in BRCA2 carriers

Heijnsdijk et al Cancer Epi, Biomarkers & Prevention 2012
N= 516 w/ breast cancer
159 < 40
Breast MRI detected 97% of all cancers
Mammo detected 79% BRCA 1 & 87% BRCA 2\(p=0.03\)
Only 1 BRCA1 patient under 40 had cancer detected on mammo & not MRI

Krammer...Jochelson to be presented ECR 2016
Frequency of screening for mutation carriers

- Not completely resolved
- Early data seem to suggest MRI/mammo should be done separately at 6 month intervals rather than both at the same time yearly
BRCA 2

5 month interval
Intermediate risk/ dense breasts

- Personal history
- Family history
- ADH
- LCIS
- Dense breasts

Mammo &??????

- DATA FREE ZONE regarding BEST tests to do
Dense breast problem

- Two-fold issue
  1. 4-6 fold increased risk of breast cancer in women with extremely dense breasts compared with fatty breasts
  2. Lower sensitivity of mammography in women with dense breasts leading to missed & interval cancers
**Background** National legislation is under consideration that would require women with mammographically dense breasts to be informed of their breast density & encouraged to discuss supplemental breast cancer screening with their health care providers. The number of US women potentially affected by this legislation is unknown.

**Methods** We determined the mammographic breast density distribution by age & body mass index (BMI) using data from 1,518,599 mammograms conducted from 2007 through 2010 at mammography facilities in the Breast Cancer Surveillance Consortium (BCSC). We applied these breast density distributions to age- & BMI-specific counts of the US female population derived from the 2010 US Census & the National Health & Nutrition Examination Survey (NHANES) to estimate the number of US women with dense breasts.

**Results** Overall, 43.3% (95% confidence interval [CI] = 43.1% to 43.4%) of women 40 to 74 years of age had heterogeneously or extremely dense breasts, & this proportion was inversely associated with age & BMI. Based on the age & BMI distribution of US women, we estimated that 27.6 million women (95% CI = 27.5 to 27.7 million) aged 40 to 74 years in the United States have heterogeneously or extremely dense breasts. Women aged 40 to 49 years (N = 12.3 million) accounted for 44.3% of this group.

**Conclusion** The prevalence of dense breasts among US women of common breast cancer screening ages exceeds 25 million. Policymakers & healthcare providers should consider this large prevalence when debating breast density notification legislation & designing strategies to ensure that women who are notified have opportunities to evaluate breast cancer risk & discuss & pursue supplemental screening options if deemed appropriate.

Sprague et al JNCI 2014
Screening ultrasound

Current default:

- Based on anatomy
- No radiation exposure
- Readily available
- “Inexpensive”
4,897 WOMEN
DENSE BREASTS
31 CANCERS

3/1000 (0.3%) CANCER DETECTION RATE

Kolb et al. 2002
ACRIN 6666 screening US

- N=2637 women
- Dense breasts + 1 other risk factor
- ~3.7 cancers per 1000
- Invasive cancers– not DCIS
- All but 1 node negative
- 8% biopsy recommendation
- 9% short term follow up
- 7.4% positive biopsy rate

Berg W et al. JAMA 2008
N= 72,998 Japanese women 40-49 randomized to US or no US after mammo

- Average risk/ dense breasts
- Sensitivity: 91.1% vs 77% p=0.0004
- Specificity: 87.7% vs 91.4% p=0.0001
- # of cancers 184 vs 117
- Cancers in US group more frequently Stage 0/1 p=0.0194
- Will follow for survival advantage

Ohuchi et al Lancet Nov 2015
Is ultrasound really inexpensive?

- Initial data from Connecticut experience
- N= 72,030 mammograms & 8,647 ultrasounds
- 28 mammographically occult cancers: 3.25/1000
- PPV: 6.7%
- BIRADS 3: 9%
- US charge $250-reimbursed $72
- Professional fee $85 reimbursed $30
- Core $2,400

- $110,241.00 billed; $60,000 paid/ breast cancer detected

- Weigert et al  The Breast Journal 2012
Is ultrasound really inexpensive?

- N = 935 with mixed risks & breast densities
- 3.2 cancers/1000 women screened
- Some were diagnostic patients
- PPV 6.5%
- 187 BI-RADS 3: 47 BI-RADS 4

- $60,267/cancer diagnosed (likely more since some patients were diagnostic)

- Hooley et al Radiol 2012
16/612 (2.6%) breast cancer detected
12 (75%) invasive
14.7 additional cancers per 1000 women screened
9/16 (56%) seen only on MRI
  8/9 (89%) invasive (median 9 mm)
  all node negative
2 (13%) not seen on MR, both DCIS

AVON FUNDED    Berg et al JAMA 2012
Tomosynthesis (DBT)

- Technology based on anatomy
- Peels away overlying tissues
- Lesion conspicuity improves
- Improved margin feature analysis
- Detection of additional lesions
- May show normal tissue when mass suspected

Improves sensitivity & specificity in both dense & fatty breasts
Mammo vs. mammo + tomo: screening

- N=12631
- Prospective trial
- Better detection rates: mammo alone 6.1/1000 vs. mammo + tomo 8.0/1000
- 25(40%) additional INVASIVE cancers detected w/ combo
- No change in DCIS detection
- 15% decrease false positives for combination

Skaane et al Radiol 2012
## Recall rates

<table>
<thead>
<tr>
<th></th>
<th>Reader Study</th>
<th>DM</th>
<th>DM+Tomo</th>
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<tbody>
<tr>
<td><strong>Non-Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>55.1%</td>
<td>16.7%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>48.8%</td>
<td>30.1%</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>87.2%</td>
<td>80.4%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>84.8%</td>
<td>85.7%</td>
</tr>
</tbody>
</table>

Rafferty et al. Radiology 2013; 266: 104-113
Prospective comparison study of 7292 women screened between August 2011- June 2012

CA detection rate:
- MG: 5.3/1000
- MG+DBT: 8.1/1000
Connecticut Study

- N=13,158 at 4 sites: 7,058 MG/6100 MG+DBT
- Recall rate:
  - MG: 12.0%
  - MG+DBT: 8.4%
- Decreased recall rates for DBT among all breast densities and age groups
- Detection of cancer:
  - MG: 5.2/1000
  - MG+DBT 5.7/1000

Haas et al. Radiology 2013; 269: 694-700
Retrospective multicenter trial

- FFDM: 281,187 vs DBT/FFDM: 173,663
- Both academic & private practices
- Recall rate: 10.7-9.1%: significant
- Detection rate: 4.2/1000-5.4/1000: significant
- PPV for recall: 4.3% -6.4%

- Friedenwald et al JAMA 2014
Tomosynthesis
Tomosynthesis

- Detects ~additional 1 to 2 cancers/1000
- Fewer call backs
- PPV improved
- Twice the radiation exposure/ still w/i guidelines
- Takes longer to read
- More expensive
- May replace full field digital mammography for routine screening
Abridged breast MRI

- Abridged MRI screening protocol could:
  - Decrease magnet & technologist time
  - Decrease reading time
  - Decrease cost, possibly making MRI more accessible
Abridged MRI

- Prospectively read 606 screening MRIs in 443 women
- Protocol 3 minutes vs. 17 for full exam
- Full abbreviated protocol 28 seconds to read
  - Sensitivity 100%, Specificity 94.3%
- MIP: 2.8 seconds to read
  - Sensitivity 90.9%

- Kuhl et al J Clin Oncol 2014
Abridged Breast MRI

- N= 100 patients w/ known cancers
- 3 sequences evaluated (15 min to perform) (mean 59 seconds to read)
- >95% of cancers visualized on a single MRI sequence
- Sensitivity increased to 100% w/ history & prior exams

Mango et al Eur J Radiol 2014
Abridged MRI: screen detected cancer

59 y/o female w/ contralateral breast carcinoma. New 1 cm irregularly enhancing mass in LLOQ: IDC
Mango et al
BUT

- MRI not universally available
- Certain patients cannot have MRI due to metallic implants, claustrophobia or allergy to gadolinium
- Very expensive
- Too many false positives
Based on MRI’s ability to detect blood flow for better cancer detection

Contrast Enhanced Mammography
**Intravenous contrast**

- Omnipaque 350; 1.5 ml/kg (CT contrast)
- Injected via power injector: 3ml/sec.
- First imaging ~ 3 minutes post-injection
- 4 views with high and low energy images obtained w/i 5 minutes of completed injection
- Images processed by subtracting out background tissue
What are the risks?

- Iodinated contrast administration
  a. Follow criteria for CT contrast administration
  b. Patients have reactions to Gadolinium too

- Radiation dose ~20% > routine screening mammogram or the equivalent of one extra image
>100,000 performed world wide
44 U.S CESM installations: some w/ > 1 unit
BAIC/MSKCC volume:
2013: 110
2014: 207
2015: 652
Early CESM data

- N=120
- UNILATERAL CESM + mammo c/w mammo or mammo + US:
  - Pts recalled from screening or problem solving
  - Sensitivity: CESM 93% vs mammo 78%
  - 26% benign lesions enhanced
  - CESM + mammo > mammo alone (p=0.045) & mammo + US (trend)
  - CESM + mammo significantly more accurate than mammo + US due to better specificity

Dromain et al Eur Radiol 2011
(Confirmed in multireader study: Breast Cancer Research 2012)
BILATERAL CESM IN KNOWN CANCER

- MAMMOGRAPHY: 42/52 (81%)
- CESM: 50/52 (96%)
- MRI: 50/52 (96%)

Jochelson et al Radiol 2013
Multireader study of mammo vs. contrast mammo
N=70 pts w/ at least 1 suspicious lesion
Sensitivity improved from 35% to 59%

Diekmann et al Eur J Radiol 2011
CESM in dense breasts

- 89 Patients w/ dense breasts
- 100 lesions
- Low energy images were read blinded to post contrast images
- With CESM, sensitivity improved from 71.5% to 92.7%
- Specificity improved from 51.8% to 67.9%

Cheung et al Eur Radiol 2014
## CESM in Normal Risk Screening Patients: 113 pts w/ Abnormal Screening Mammograms

<table>
<thead>
<tr>
<th></th>
<th>MAMMO</th>
<th>CESM</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96.9%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>42.0%</td>
<td>87.7%</td>
</tr>
<tr>
<td>PPV</td>
<td>39.7%</td>
<td>76.2%</td>
</tr>
<tr>
<td>NPV</td>
<td>97.1%</td>
<td>100%</td>
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Mean difference between CESM & pathology 1.4mm

Lobbes et al Eur Radio 2014
Yearly mammography in average risk women from 40-49 significantly reduces mortality
Yearly mammography in average risk women from 40-49 significantly reduces morbidity
Average & intermediate risk women age 40-49 SHOULD undergo annual screening
Intermediate risk/women w/ dense breasts may benefit from additional imaging
High risk women 40-49 benefit from screening w/ mammography & MRI every 6 months
Given the weight of the evidence that mammography screening is associated w/ a significant reduction in the risk of dying from breast cancer after age 40 years, a more productive discussion would be focused on how to improve the performance of mammography screening”*

*Oeffinger et al JAMA 2015
Conclusions

- Ultrasound, tomosynthesis, MRI & contrast mammo will all detect more cancers than mammo alone
- MRI detects ~97% of cancers
- Tomosynthesis reduces call backs
- CESM improves sensitivity & specificity
- Prospective trials comparing the efficacy of these techniques are underway. Physiology will likely trump anatomy
- Proof of clinical advantage will take longer
Don’t stop screening women 40-49: Do it better!!!