Stratification of screening?

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Benefits of Breast Screening

Relative risk reduction from screening is around 20%

Based on meta-analysis 11 RCTs 0.80 (95% CI 0.73–0.89)

Recent observational studies suggest larger benefit

Marmot M et al Lancet 2012
“Over diagnosis” = cancers detected at screening which would not have otherwise become clinically apparent in the woman’s lifetime

**Around 20% screen detected cancers are over diagnosis**
Benefits and Harms of Breast Screening

SEER database 9 sites 10% of USA population

Reduction 30/100,000 >2cm
Increase 162/100,000 <2cm
Overdiagnosis 132/100,000

Figure 2. Breast-Cancer Tumor-Size Distribution and Size-Specific Incidence among Women 40 Years of Age or Older in the United States, 1975–2012.

Table 1. Change in Size-Specific Incidence of Breast Cancer among Women 40 Years of Age or Older after the Introduction of Screening Mammography.

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Size-Specific Incidence per 100,000 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large tumors</td>
<td></td>
</tr>
<tr>
<td>≥5.0 cm</td>
<td>29</td>
</tr>
<tr>
<td>3.0 to 4.9 cm</td>
<td>56</td>
</tr>
<tr>
<td>2.0 to 2.9 cm</td>
<td>60</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>145 (144 to 147)</td>
</tr>
<tr>
<td>Small tumors</td>
<td></td>
</tr>
<tr>
<td>1.0 to 1.9 cm</td>
<td>59</td>
</tr>
<tr>
<td>&lt;1.0 cm</td>
<td>13</td>
</tr>
<tr>
<td>In situ</td>
<td>10</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>82 (81 to 83)</td>
</tr>
</tbody>
</table>
Is it time to redesign our screening strategy?

**USA**
- 32,500,000 Screening Mammograms
- 3,500,000 Recalled for assessment
- 1,600,000 Biopsies
- 297,290 Cancer

**UK**
- 2,105,454 Screening Mammograms
- 87,737 Recalled for assessment
- 40,500 Biopsies
- 18,105 Cancer

MSQA National Statistics 2015
NHS Breast Screening Programme (2014-2015)
UK Screening recommendations

- Three yearly mammography offered to women 50-70 years.
- Cancer detection rate (CDR) of 8.2/1000
- Interval cancer (IC) rate of 2.9/1000
- Only 53% of the invasive cancers detected were small cancers <15mm

......Two thirds of invasive cancers in 50-70 year old >15 mm in size......
Can we stratify our screening?

- We offer genetic testing to those with strong family history
- We offer annual MRI plus mammography to those at high risk
- We offer annual mammography to those with moderate risk
Evidence for MRI screening High Risk

<table>
<thead>
<tr>
<th>Author/Country</th>
<th>Cancers (DCIS)/Women</th>
<th>Mean Age</th>
<th>Mammography</th>
<th>Ultrasound</th>
<th>MRI</th>
<th>CBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warner et al 2004 Canada</td>
<td>22(6)/236</td>
<td>47</td>
<td>36% 100%</td>
<td>33% 96%</td>
<td>77% 95%</td>
<td>9% 99%</td>
</tr>
<tr>
<td>Kriege et al 2004 Netherlands</td>
<td>50(6)/1909</td>
<td>40</td>
<td>40% 95%</td>
<td>- -</td>
<td>71% 90%</td>
<td>17.8% 98%</td>
</tr>
<tr>
<td>Leach et al 2005 UK</td>
<td>35 (6)/649</td>
<td>40</td>
<td>40% 93%</td>
<td>- -</td>
<td>77% 81%</td>
<td>- -</td>
</tr>
<tr>
<td>Kuhl et al 2005 Germany</td>
<td>43(9)/529</td>
<td>42</td>
<td>33% 97%</td>
<td>40% 91%</td>
<td>91% 97%</td>
<td>5% 100%</td>
</tr>
<tr>
<td>Hagen et al 2007 Norway</td>
<td>25(3)/491</td>
<td>41</td>
<td>50% -</td>
<td>- -</td>
<td>86% -</td>
<td>- -</td>
</tr>
<tr>
<td>Sardanelli et al 2007 Italy</td>
<td>14(4)/278</td>
<td>46</td>
<td>59% -</td>
<td>65% -</td>
<td>94% -</td>
<td>50% -</td>
</tr>
</tbody>
</table>
Can we stratify our screening?

- We better understand breast cancer risk from dense breast tissue
- We have new imaging technologies
- We have inexpensive genetic tests
- We can undertake risk profiling to determine cancer risk

Now is the time to rethink our screening strategies
Density and mammographic sensitivity

Increasing breast density results in decreasing sensitivity
Breast Density – Masking & Risk

111,898 DM examinations (2003-2011) from one screening unit of the Dutch biennial screening program (50-75 years)

Volumetric breast density assessed

667 screen-detected and 234 interval cancers

Interval cancers were identified through linkage with the Netherlands Cancer Registry.

<table>
<thead>
<tr>
<th></th>
<th>VDG A</th>
<th>VDG B</th>
<th>VDG C</th>
<th>VDG D</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Examinations</td>
<td>21.6</td>
<td>41.5</td>
<td>28.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Cancer Detection Rate/1000</td>
<td>3.7</td>
<td>6.4</td>
<td>6.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Interval Cancer Rate/1000</td>
<td>0.7</td>
<td>1.9</td>
<td>2.9</td>
<td>4.4</td>
</tr>
<tr>
<td>Sensitivity % (p&lt;0.001)</td>
<td>85.7</td>
<td>77.6</td>
<td>69.5</td>
<td>61.0</td>
</tr>
</tbody>
</table>

Digital Breast Tomosynthesis

Decreases overlapping shadows – Reduced FP

Increases conspicuity of small lesions – Reduced FN

Prospective trials showed 30% increase cancer detection and 15% reduced recall rates (Oslo, STORM)

Malmo single view DBT trial
43% increase cancer detection but 43% increase in recall rate

Proportionately more grade 1 cancers although smaller and more node negative
Prospective Observational US studies

Retrospective time series before and after DBT

13 sites
454,850 examinations (281,187 2D alone, 173,663 with 2D + DBT)

Cancer detection increased 29%
4.2/1000 to 5.4/1000 p<0.001

Recall rate – decreased 9.3%
10.7% to 9.1%

What type of cancers are these additional cases - are they overdiagnosis?
Automated Breast Ultrasound

**Technique**
- Whole breast US using gantry
- Trained sonographers
- 20 minutes exam time
- 10 minutes reading time

**Advantages**
- Excellent in dense breasts
- Additional cancers 4/1000
- No radiation
- Acceptable for women
- CAD tools being developed

**Disadvantages**
- Lower sensitivity compared to MRI
- Large amount of images to read
- Few trained radiographers
- Radiologists not keen
Screening with Ultrasound

- Berg et al ACRIN 6666 - 4.2/1000 more cancers found women at increased risk and with dense breasts using hand held ultrasound and mammography combined than mammography alone.

- Italian study, 38% of all screened women who had BIRADS C/D breast density were offered ultrasound after a negative mammogram and an additional 4/1000 cancers were found.

- Japan Strategic Anti-cancer Randomized Trial (J-STaRT) of 72,998 women between 40-49 years old screened annually with mammography alone or additional ultrasound
  - sensitivity mam 77.0%, 95% CI 70.3-83.7
  - mam + US 91%, 87.2-95.0 p=0.0004
Screening with Automated Ultrasound

- Kelly et al demonstrated ABUS increased cancer detection rate from 3.8 per 1000 with mammography alone to 7.2 per 1000 using both modalities.

- The multicentre SomoInsight study of 15,000 women with dense breasts and some with a personal history of breast cancer found an additional 1.9/1000 cancers with ABUS. These tumours were mainly small invasive node negative cancers.

- In a single centre Swedish study, 1668 women with dense breasts had a significant increase in cancer detection rate to 6.6/1000 with the addition of ABUS from 4.2/1000 with FFDM alone.
Recall Rates with Ultrasound

- Recall rates are higher when US is used as a supplemental tool to mammography compared with mammography alone.

- In the ACRIN 6666 trial, recall rates with US alone were 21% in the prevalent round dropping to 11% in round 2 and 3 compared to mammography recall rates of 12% and 9%.

- J-STaRT study the recall rate increased from 9% to 12% with ultrasound.

- The SomoInsight study recall rate was 15% for FFDM and 29% for combined FFDM and ABUS.

- The Swedish study recall rate increased from 1.4% to 2.3% with the addition of ABUS.
Conclusion:

Density ratings may be recategorized on serial screening mammography.

Supplemental screening of women with dense breasts finds additional breast cancer but increases false-positive results.

Use of DBT may reduce recall rates.

Effects of supplemental screening on breast cancer outcomes remain unclear.
**Contrast Enhanced Spectral Mammography**

**Technique**
- Low and high kV mammogram
- IV contrast 300mg Iodine (same as CT)
- Take standard views of each breast
- 15 min examination time
- Read Mammo then contrast exam

**Advantages**
- Diagnostic accuracy nearly as good as MRI
- Rapid examination
- Low kV exam similar to FFDM

**Disadvantages**
- Contrast reactions – 1:40,000 severe
- Misses Low grade DCIS
### Comparison of CESM and MRI in Dense breasts (BIRADS 3 & 4)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>MRI</th>
<th>CESM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity (%)</td>
<td>PPV (%)</td>
</tr>
<tr>
<td>Jochelson (2013)</td>
<td>52</td>
<td>96</td>
<td>85</td>
</tr>
<tr>
<td>Lee-Felker (2017)</td>
<td>120 lesions in 52 women</td>
<td>99</td>
<td>60</td>
</tr>
<tr>
<td>Fallenberg 2016</td>
<td>155</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Jochelson (2017)</td>
<td>304 (3)</td>
<td>100</td>
<td>14</td>
</tr>
</tbody>
</table>

- Lower energy component of the CESM study is equivalent to FFDM
- Dose is around 1.2 times FFDM (within UK and European quality assurance guidelines.)
ABBreviated MRI

**Technique**
Shortened MRI examination
IV contrast
Read MIP and first contrast exam

**Advantages**
Diagnostic accuracy almost as high as standard MRI
Higher sensitivity than CESM, DBT, FFDM+US
10 minute examination
More acceptable for women
Cheaper

**Disadvantages**
Will miss a few cancers
Lower specificity compared to other tests
ABBreviated MRI

- 443 women at mild to moderate risk underwent two annual screening rounds (606 MRI examinations).
- 11 cancers (4 DCIS).
- Acquisition time 3 minutes, reading time 28s for normals 3 minutes if cancer present; equivalent diagnostic accuracy – sensitivity 96%, specificity 94%.

Kuhl et al JCO 2014
Meta-analysis ABBreviated MRI

Pubmed All years-2016
269 Citation(s)

Scopus All years-2016
3 Citation(s)

Web of Science All years-2016
9 Citation(s)

Cochrane Library All years-2016
0 Citation(s)

RSNA conference proceedings
2012-2016
2 Citation(s)

271 Non-Duplicate Citations Screened

Observational, prospective and retrospective studies exploring abbreviated MRI in breast cancer screening

10 Articles Retrieved

Inclusion/Exclusion Criteria Applied

2 Articles Excluded After Full Text Screen

1 Article Excluded During Data Extraction

7 Articles Included

261 Articles Excluded After Title/Abstract Screen

Selamoglu A unpublished
Meta-analysis ABBreviated MRI

Summary ROC curve

AB-MRI AUC 0.88, standard MRI AUC 0.92,
~20% of population are low risk (<1/3)
~4% of breast cancer

~4% of women are high risk
~18% of breast cancer

BRCA1/2 account for:
~0.4% of women at high risk
~3.5% of breast cancer

Combined risk distribution for known risk factors

Courtesy Prof Doug Easton, Cambridge
Costs of Whole Genome Sequencing

Falling fast

In the first few years after the end of the Human Genome Project, the cost of genome sequencing roughly followed Moore’s law, which predicts exponential declines in computing costs. After 2007, sequencing costs dropped precipitously.

In UK whole genome £300
~ £50 for SNPs
Personalised Screening – Risk Adaptive Approach

Increasing risk

Low
- No screening
- Or 5 yearly FFDM

Medium
- FFDM compared to DBT
  2-3 yearly

High Density
- Annual DBT+US or CESM or AB-MRI

- Annual AB-MRI or MRI
And a huge thanks to...

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