Update in breast cancer screening for postmenopausal patients

WHICH SCREENING FOR WHICH PATIENT?

Dr Joëlle Desreux on behalf of the BMS study group

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19.02.11
Some definitions

- **Mammography screening = mammotest**: mass screening of all women aged from 50 to 69 years old, without any stratification of risks, by mammography every 2 years. On invitation, two readers, numerized mammographers, quality controls.

- **Early diagnosis = opportunistic screening**: individualized screening adapted to risk factors, on prescription, multimodality, no quality control.
Benefits of screening

- **Ultimate goal**: decrease of overall mortality and breast cancer mortality
- **Good markers of efficacy**:
  - Minimal incidence of clinical interval cancers
  - Decrease of advanced cancers incidence
  - Decrease of cancer incidence in older women
- **Not suitable markers of efficacy**:
  - 5-years survival
  - Percentage of early detected cancers
- **Decrease of therapies aggressiveness (gain in QoL)**
Overall mortality

- Cochrane metaanalysis jan 2011 (Gotzsche):

  all-cause mortality after 13 years of mammography screening in randomized trials:

  \[ RR = 0.99 \ (0.95 - 1.03) \]

www.cochrane.dk
• Observational study comparing breast cancer mortality in screening counties (Copenhagen and Funen) with non-screening counties (about 80% Danish population).
• Very long follow-up, before and after screening establishment.
Denmark

**Fig 1** | Unadjusted breast cancer mortality rates for screened and non-screened areas in Denmark

UK

**Fig 2** | Age adjusted breast cancer mortality rates in the United Kingdom for screened and non-screened age groups. Data from Cancer Research UK²⁶
Effect of Screening Mammography on Breast-Cancer Mortality in Norway

Mette Kalager, M.D., Marvin Zelen, Ph.D., Frøydis Langmark, M.D., and Hans-Olov Adami, M.D., Ph.D.
Pluridisciplinary breast units established in the whole country before the implementation of screening in some counties.

77% participation, follow-up 2.2 y (max 8.9 y)
Design

A : Reduction of mortality not related to screening (Improving care)

B : Reduction of mortality related to improving care + screening

B – A = reduction of mortality related to screening
Results

The graph shows the comparison of breast-cancer mortality rates between historical and current periods for nonscreening and screening groups. The y-axis represents the number of deaths per 100,000 person-years, ranging from 0 to 30. The graph indicates a 18% reduction in mortality for the current screening group compared to the historical screening group, and a 10% reduction for the current nonscreening group compared to the historical nonscreening group. The time effect is also noted for both groups.
Results

> 70 years in screening counties vs in non screening counties: - 8% mortality related to breast units establishment. So the relative reduction of mortality due to mammography screening alone could be as low that 2%.
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Screening doesn’t catch the fast growing tumors.

<table>
<thead>
<tr>
<th>Interval cancers, false negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st round</td>
</tr>
</tbody>
</table>

- Low growth
- Fast growth
- Abnormal cell
- Symptoms

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Diagram:

- First round: Low growth → Fast growth
- Second round: Low growth → Fast growth

Note: The diagram illustrates the progression of abnormal cells and symptoms over two rounds, highlighting the concept of interval cancers, false negatives.
To increase the screening frequency for decreasing interval cancers?

<table>
<thead>
<tr>
<th>False positive rate for an individual test</th>
<th>Every year</th>
<th>Every two years</th>
<th>Every three years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>10%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>2%</td>
<td>18%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>3%</td>
<td>26%</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>5%</td>
<td>40%</td>
<td>23%</td>
<td>14%</td>
</tr>
<tr>
<td>10%</td>
<td>65%</td>
<td>41%</td>
<td>27%</td>
</tr>
</tbody>
</table>

_table 3_ Cumulative risk of one or more false positive tests in a 10-year program of screening

_Chance of having at least one false positive over ten years when screened:_

Welch H.G., Schould I be tested for cancer?, University of California Press, 2004
Decrease of cancer incidence in older women?

Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends

Karsten Juul Jørgensen, researcher Peter C Gøtzsche, director

UK
Benefits of screening

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5-years survival is not a marker of screening efficacy

Before screening:
- Clinical diagnosis at 67 y old
- Death at 70 y old
- 5-years survival = 0%

Now:
- Screening diagnosis at 60 y old
- Death at 70 y old
- 5-years survival = 100%

Screening gives an advance in diagnosis and increases artificially 5-years survival without any indication about the effect on global mortality.

LEAD-TIME BIAS
5-years survival is not a marker of screening efficacy.

Before screening:
- 1000 women with a progressive cancer
  - 5 years later: 600 are dead, 400 are alive
  - 5-years survival = 400 / 1000 = 40%

Now:
- 1000 women with a progressive cancer
- 1000 women with a non-progressive cancer
  - 5 years later: 600 are dead, 400 are alive, 1000 are alive
  - 5-years survival = 1400 / 2000 = 70%

Screening increases pseudodiseases diagnostics and increases artificially 5-years survival without any indication about the effect on global mortality. LENGHT-TIME BIAS
Percentage of early detected cancers is not a marker of screening efficacy: the theory.
Observed rates of advanced breast cancer

Figure 2. Age-Adjusted Incidence Rates of Breast and Prostate Cancer Over Time and by Prescreen and Postscreen Snapshot

Incidence

Localised cancer as a percentage of total cancer incidence

Incident invasive cancer

Total Localised Regional Metastatic
Mammography screening in Flanders

Figure 11. pStage distribution by age for breast cancer (2001 – 2006).
A gain in quality of life?

- Observed increase of mastectomy rates, induced in part by an increase of diagnosed DCIS and of preoperative RMI use
- Overdiagnosis and overtreatment of pseudodiseases: 30%
- Less chemotherapy?
  - Tumoral size and positive nodes are not the only criteria for chemotherapy indications.
  - Advanced tumors incidence is not well decreased by screening
Harms of screening mammography

- Overdiagnosis and overtreatment
- Psychological stress of false positives
- False reassurance of false negatives
Only the patients with tumors C benefit from screening. Patients with tumors B will have an overdiagnosis and overtreatment (pseudodiseases). Patients with tumors D will have a clinical interval cancer.
If the death occurs earlier, the risk of detecting a pseudodisease is increased. Screening an older population exposes to more overdiagnosis and overtreatment.
Overdiagnosis and overtreatment

Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends

Karsten Juul Jørgensen, researcher, Peter C Gøtzsche, director

<table>
<thead>
<tr>
<th>Geographical area</th>
<th>Rate ratio (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and Wales</td>
<td>1.57 (1.53 to 1.61)</td>
</tr>
<tr>
<td>Manitoba, Canada</td>
<td>1.44 (1.25 to 1.65)</td>
</tr>
<tr>
<td>New South Wales, Australia</td>
<td>1.53 (1.44 to 1.63)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.46 (1.40 to 1.52)</td>
</tr>
<tr>
<td>Norway</td>
<td>1.52 (1.36 to 1.70)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.52 (1.46 to 1.58)</td>
</tr>
</tbody>
</table>

Heterogeneity: I² = 59.0%
At 50 years, the proportion of life-saving screenings is 5 %, which means that mammography has to detect 21 cancers to save 1 life.
Conclusions

- As the treatment performances and the « breast awareness » of the women will improve, the efficacy of the mammography screening will decrease, despite the progress of mammography quality.
- Nowadays, it seems reasonable to participate to mammography screening but it seems also reasonable NOT to participate.
A shift in strategy: options for the future

- Development and validation of prognostic markers
- Reduce treatment for minimal-risk diseases and offer treatments adapted to tumor biology
- Informed decisions about prevention, screening (www.cochrane.dk), biopsies, treatments
- Identify higher-risk patients, target preventive interventions and tailored screening
- (Maybe no screening anymore for lower risk patients?)
Tailored screening: identify high risk women

Cancer Causes Control (2011) 22:23–31
DOI 10.1007/s10552-010-9663-x

ORIGINAL PAPER

Complementary approaches to assessing risk factors for interval breast cancer

Jan T. Lowery · Tim Byers · John E. Hokanson · John Kittelson · John Lewin · Betsy Risendal · Meenakshi Singh · Judy Mouchawar
Tailored screening: identify high risk patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Risk of interval breast cancer (per 10,000 negative screens) (95%CI)</th>
<th>Risk ratio adjusted (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>29.5</td>
<td></td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDR any age</td>
<td>59.8 (50.2 – 69.3)</td>
<td>2.23 (1.85 – 2.70)</td>
</tr>
<tr>
<td>No family history</td>
<td>24.8 (22.4 – 27.2)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Current hormone use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27.0 (22.7 – 31.4)</td>
<td>1.54 (1.20 – 1.97)</td>
</tr>
<tr>
<td>No</td>
<td>15.9 (12.9 – 18.9)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Breast density</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremely dense</td>
<td>46.3 (34.0 – 58.6)</td>
<td>3.84 (2.76 – 5.35)</td>
</tr>
<tr>
<td>Heterogeneously dense</td>
<td>38.0 (32.5 – 43.5)</td>
<td>2.95 (2.33 – 3.75)</td>
</tr>
<tr>
<td>Entirely fat/ scattered</td>
<td>15.0 (12.2 – 17.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>fibrodensities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Tailored screening: identify high risk patients

http://www.ems-trials.org/riskevaluator/

Google → IBIS risk evaluator
### Tailored screening: multimodality

#### Evidence of the effect of adjunct ultrasound screening in women with mammography-negative dense breasts: Interval breast cancers at 1 year follow-up

Vittorio Corsetti, Nehmat Houssami, Marco Ghirardi, Aurora Ferrari, Michela Speziani, Sergio Bellarosa, Giuseppe Remida, Cristina Gasparotti, Enzo Galligioni, Stefano Ciatto

<table>
<thead>
<tr>
<th>Breast density</th>
<th>Per 1000 screens</th>
<th>&lt; 50 y</th>
<th>&gt; 50 y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIRADS 1 – 2</strong> (M only)</td>
<td>Cancers detected</td>
<td>2.7</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>Interval cancers</td>
<td>0.45</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Screening sensitivity</td>
<td>85.7 %</td>
<td>83.1 %</td>
</tr>
<tr>
<td><strong>BIRADS 3 – 4</strong> (M and US)</td>
<td>Cancers detected by M</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Additional cancers detected by adjunct US</td>
<td>3.5</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>Interval cancers</td>
<td>1.5</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Screening sensitivity (M + US)</td>
<td>80.6 %</td>
<td>93.1 %</td>
</tr>
</tbody>
</table>
BRCA, lifetime risk (Claus or Gail) $\geq 25\%$, LCIS, ADH, ALH, recent personal history of cancer in the contralateral breast, chest wall irradiation before puberty
RMI: for which women?

High breast density was not an inclusion criteria. The RMI specificity is very low in dense breasts, especially in young women.
Principles for tailored screening

- **Begin** from the age at which the breast cancer risk is equal to that for an average women aged 50 years (≈ 3 % in the next 10 years or remaining lifetime risk ≈12 %)
- **Adapt** modality and frequency to the individual level of risk
- **Reassess** regularly risk level and screening modality
- **Inform** carefully the patient about the balance risks/benefits and accept an eventual toughtfull refusal
- **Stop** when the risk of co-mortality exceeds the risk of breast cancer mortality
Breast cancer screening: proposition of decision algorithm

- **Low to moderate risk**
  - First evaluation by mammography (≈ 40 y)
  - Non-dense breasts
- **High risk (RR ≥ 2)**
  - Yearly digital mammography + US + clinical breast examination
  - If positive
- **Breasts awareness and discuss mammography screening from 50 to 74 years old (and/or clinical breast examination?)**
  - (USPSTF 2009)
- **Very dense breasts (BIRADS 4)**
- **RMI: only in very high risks**