The impact of population-based screening with mammography on breast cancer mortality: issues in mortality trends evaluation

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Trend studies of mammographic screening

- Studies of trends in breast cancer mortality rates in a population as a whole in relation to the introduction and/or extent of mammographic screening

- Usually based on aggregated data obtained from routine sources
Hierarchy of epidemiological evidence

- randomised controlled trials
- cohort studies
- case control studies
- ecologic studies
## Comparison of RCTs and trend studies

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Trend studies</th>
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<tbody>
<tr>
<td>only include deaths from breast cancer in women diagnosed after invitation to screening ('refined' mortality)</td>
<td>effect of screening diluted due to use of unrefined mortality</td>
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<tr>
<td>measure exposure of all women from date of randomisation (effectively first invitation)</td>
<td>implementation of screening usually phased over several years</td>
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<td>have an appropriate contemporaneous comparison group (the control arm)</td>
<td>difficult to identify appropriate comparison group</td>
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Possible comparison groups for ecological studies

- age groups outside age range invited for screening
- same region/country before introduction of screening
  ‘local historical’
- geographic areas with no organised screening
  (concurrent and / or historical)
Sources of bias in ecologic studies

- differential changes in treatment effectiveness between time periods/regions
- ‘contamination’ – opportunistic screening before introduction of programme and / or outside invited age range
- differences in underlying risk of BC between regions, time periods and age-groups
Other influences on breast cancer mortality trends

- ‘halo effect’ of screening programme
- changes in cause of death coding
EUROSCREEN mortality group

- Denmark
  - Elsebeth Lynge
  - Sisse Njor
- Italy
  - Eugenio Paci
  - Nereo Segnan
- Sweden
  - Håkan Jonsson
  - Lennarth Nyström
- The Netherlands
  - Mireille Broeders
  - Ellen Paap
- UK
  - Stephen Duffy
  - Natalie Massat
  - Sue Moss
Review of published papers

Objective: to estimate the effectiveness of service-screening programmes with mammography in West-Europe

- Studies included – study design:
  - trend studies (n=17)
  - incidence-based mortality studies (n=20)
  - case-control studies (n=8)
Trend studies (Moss et al, JMS 2012)

- \textit{Only descriptions} of the trend in BCM
  - in relation to the timing of the introduction of organised screening (n=5)
- Included a more detailed \textit{analysis}
  - with the aim of \textit{quantifying} the impact of screening on BCM (n=12)
  - Poisson regression with or without age-cohort modelling
  - Joinpoint regression to identify ‘break points’ at which changes in mortality trends occurred
Table 2  Summary of trend studies that gave a quantified estimate of the effect of screening

<table>
<thead>
<tr>
<th>Reference and study area</th>
<th>Service screening programme</th>
<th>Start</th>
<th>100% coverage</th>
<th>Age group invited</th>
<th>Time period studied</th>
<th>Age range studied</th>
<th>Method</th>
<th>Comparison /reference group</th>
<th>Reduction in breast cancer mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barchelli and Paci⁸</td>
<td>Florence, Italy</td>
<td>1970 (73%)</td>
<td>1970–1997</td>
<td>25+</td>
<td>Poisson</td>
<td>Florence v. rest of Tuscany</td>
<td>Similar reduction in both areas</td>
<td></td>
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<tr>
<td>Otto et al.⁹⁰</td>
<td>Netherlands</td>
<td>1989</td>
<td>50–69</td>
<td>1980–2001</td>
<td>55–74</td>
<td>Poisson</td>
<td>Before/after: Clustered by start date</td>
<td>1989–2001: 1.7% [95% CI 0.0–2.4] reduction per yr after start of screening</td>
<td></td>
</tr>
<tr>
<td>Otten et al.¹¹</td>
<td>Netherlands</td>
<td>1989</td>
<td>50–69</td>
<td>1975–2006</td>
<td>35–85</td>
<td>Joingment</td>
<td>Before/after in age group 55–74</td>
<td>1994–2006: 2.3% per yr [95% CI 1.6–3.0] v. 2.8% per yr [95% CI 2.2–3.4] reduction</td>
<td></td>
</tr>
<tr>
<td>Pons-Vigues et al.¹³</td>
<td>Barcelona, Spain</td>
<td>1995</td>
<td>50–69</td>
<td>1984–2004</td>
<td>50–74</td>
<td>Poisson</td>
<td>Before/after: Grouped by start date</td>
<td>1995–2004: 5% [95% CI 1–8] reduction per yr v. 1% [95% CI 1–2%] before start</td>
<td></td>
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<tr>
<td>Haakka et al.¹⁵</td>
<td>Sweden (9 counties)</td>
<td>1980–1990</td>
<td>40–69</td>
<td>1974–2003</td>
<td>40–69, 70–79</td>
<td>Poisson regression</td>
<td>Screening effect allowing for lead time and secular trend. Grouped by start date</td>
<td>16% reduction [40–69 yr] [95% CI 9–22] 11% reduction [70–79 yr] [95% CI 2–20] after start of screening</td>
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</tbody>
</table>
Problems with selected studies

- inadequate follow up (< 10 years from year complete coverage of screening was achieved)
- inclusion of early years after introduction of screening
- not restricted to appropriate age range
- fail to consider rates/trends prior to start of screening

Duffy et al JMS 2010
Duffy et al JMS 2010

- compared with other age groups there was a highly significant 28% reduction in breast cancer mortality in the age group invited to screening in 1995-2004 vs 1974-1988
- includes age group 50-54
- ignores possible different trends between age groups

“we have deliberately derived simple age-specific estimates from the English incidence and mortality rates. More complex age–period–cohort analyses might yield different estimates”
Autier et al concluded:

‘The contrast between the time differences in implementation of mammography screening and the similarity in reductions in mortality between the country pairs suggests that screening did not play a direct part in the reductions in BCM’
Autier et al BMJ 2011

- differences between neighbouring countries
- declines in mortality occurring prior to introduction of screening
- conclusions based on mean rate for all ages (% change 1989 vs 2006)
  - e.g. NI vs Rep of Ireland -29.6% vs -26.7%
  - age group 50-69 -36.7% vs -27.7%
- ignores opportunistic screening in Norway before start of programme
Summary of Euroscreen review of trend studies

For studies with adequate follow-up:
• 1-9% reduction in BCM per year in post-screening period
• 28-36% reduction in BCM in post vs. pre-screening period

No pooled estimates:
• due to differences in methodology, comparisons and outcome measures

Moss et al JMS 2010
“Descriptive studies have both strengths and weaknesses. Often, the data are already available and thus inexpensive and efficient to use. Furthermore, few ethical difficulties exist. However, descriptive studies have important limitations. Temporal associations between putative causes and effects might be unclear. A dangerous pitfall is that the investigators might draw causal inferences when none is possible”
Conclusions

- trend studies are an ‘obvious’ approach to evaluation of population screening
- numerous sources of bias
- interpret with caution
- need for more rigorous individual based studies