EFFECT OF MAMMOGRAPHY SCREENING ON MORTALITY BY HISTOLOGICAL GRADE

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Abstract

Background: It has been asserted that mammography screening preferentially benefits those with less aggressive cancers, with lesser or no impact on more rapidly progressing and therefore more life-threatening tumours.

Methods: We utilized data from the Swedish Two-County Trial, which randomized 77,080 women aged 40-74 to invitation to screening and 55,985 for usual care. We tabulated cancers by histological grade and then compared mortality from cancers specific to histological grade between the invited and control group using Poisson regression, with specific interest in the effect on mortality from grade 3 cancers. We used incidence-based mortality from tumours diagnosed within the screening phase of the trial. Finally, we cross-tabulated grade with tumour size and node status, to assess downstaging within tumour grades.

Results: There was a major reduction in mortality from grade 3 tumours (RR = 0.65, 95% CI 0.53-0.80, p<0.001), and more deaths prevented from grade 3 tumours (N=95) than grade 1 and 2 tumours combined (N=48) in the invited group. The proportions of tumours ≥15 mm or larger and node positive tumours were substantially reduced in the grade 3 tumours in the invited group.

Conclusions: The combination of prevention of tumours progressing to grade 3 and detection at smaller sizes and lesser rates of lymph node metastases within grade 3 tumours results in a substantial number of deaths from grade 3 cancers being prevented by invitation to mammographic screening.

Impact: Mammography screening prevents deaths from aggressive cancers.
Introduction

The randomised trials of mammographic screening show a substantial and significant reduction in breast cancer mortality with invitation to mammographic screening (1,2). Since then, observational studies within service screening programmes have shown similar or larger reductions in breast cancer mortality (3). These are reviewed in the recent handbook on the subject from the International Agency for Research on Cancer (4).

It is generally understood that the effect of screening on breast cancer mortality will vary by the aggressive potential of the tumour. More recently, it has been asserted that screening preferentially benefits less aggressive, less life-threatening cancers, with lesser or no impact on more aggressive, rapidly progressing, and therefore more life-threatening cancers (5-9).

This question can be addressed by considering the effect of screening on mortality from breast cancers by histological grade at diagnosis. While emphasis on prognostic factors has shifted towards molecular features of tumours (10), histological grade still is a strong breast cancer prognostic factor and it reflects the aggressive potential of the tumour (11). If the assertion that screening does not primarily improve outcome in more aggressive tumours is true, this would be reflected in a lesser effect on mortality from grade 3 cancers compared with grade 1 and 2 cancers among women invited to screening within a screening trial. If, on the other hand, screening does improve outcome in the more aggressive cancers, this will be reflected in a substantial effect of invitation to screening on mortality from grade 3 cancer, whether by improving stage at diagnosis of such cancers or detecting these cancers before dedifferentiation, therefore preventing progression to grade 3, or both (12,13).

In this paper, we investigate this issue using data from the Swedish Two-County Trial of mammographic screening (1).

Material and Methods

The design and procedures of the Swedish Two-County Trial have been described elsewhere (1,12). Briefly, between 1977 and 1981, 77,080 women in Dalarna and Östergötland counties, Sweden, aged 40–74 were allocated to invitation to periodic mammographic screening (active study population, ASP) and 55,985 to no invitation (passive study population, PSP). Women in the ASP aged 40–49 at allocation were offered screening on average every 24 months. Women aged 50–74 were offered screening every 33 months. After 6–7 years, the PSP was invited to screening and the screening phase of the trial closed, but follow-up continued for deaths from breast cancers diagnosed during the screening phase.
the mortality analyses below, we use incidence-based mortality from the screening phase of the trial, that is, deaths only from tumours diagnosed in the ASP and PSP between randomisation and the completion of the single round of screening of the PSP. The screening in the trial took place between 1977 and 1988. We have follow-up data on deaths from breast cancer to 2005 in Dalarna county and 2006 in Östergötland, with total person-years of follow-up of 1,632,492 in the ASP and 1,200,887 in the PSP.

We first tabulated cancers detected in the two trial arms by histological grade to assess whether there was evidence of prevention of grade 3 cancers by early detection. We then compared mortality from cancers specific to histological grade between the ASP and PSP using Poisson regression (14), to give relative rates (RR) and confidence intervals (CI), with specific interest in the effect of invitation to screening on mortality from grade 3 cancers. Finally, we cross-tabulated grade with tumour size and node status, to assess the extent to which tumours of differing grade were detected early in their development.

Results

Table 1 shows the cancers diagnosed in the two arms of the trial by histological grade. The distribution of grade is significantly more favourable in the ASP (p<0.001). The absolute incidence rate of grade 3 cancers was 378/55,985 = 6.8 per 1000 population in the PSP and 467/77,080 = 6.1 per 1000 in the ASP. Although this difference did not reach statistical significance (p=0.1), the absolute incidence rate of grade 2 and 3 cancers combined was significantly lower in the ASP (RR=0.89, 95% CI 0.81-0.99, p=0.02).

Figure 1 shows cumulative mortality from invasive breast cancers of grade 1, 2 and 3 respectively by trial arm. Clearly there is a major reduction in mortality from grade 3 breast cancers in the ASP (RR = 0.65, 95% CI 0.53-0.80, p<0.001). Table 2 shows deaths from cancers by grade and trial arm, in situ disease and missing grade combined. The absolute numbers of deaths prevented in the ASP from grade 3 breast cancers is estimated as

$$\frac{177}{0.65} - 177 = 95$$

The corresponding numbers of deaths prevented from grade 2 cancers combined was 47, from grade 1 cancers 2, and from grade missing/in situ tumours 6. Thus, both the relative and absolute effects of screening on breast cancer mortality were by far the largest in grade 3 cancers.
Table 3 shows the size distribution by grade for the ASP and PSP separately. For cancers of each histological grade, the proportion of tumours of size 15 mm or larger was substantially reduced in the ASP. This was statistically significant in all three histological malignancy grades, including the grade 3 tumours (p<0.001). The corresponding results for node status by grade are shown in Table 4. There is a similar reduction in the proportion of node positive cases in the ASP in all three grades, including within the grade 3 tumours (p=0.001). The difference in distributions between ASP and PSP will reflect differences in incidence by these characteristics, since the overall cumulative incidence is almost exactly equal between the ASP and PSP.

Discussion

Our results suggest that screening prevents tumours from progressing to grade 3, and also detects grade 3 tumours at smaller sizes with lower rates of lymph node metastases. These combined effects of screening prevented a substantial number of deaths from grade 3 cancers in the ASP (invited arm) in this mammographic screening trial. There was a 35% reduction in breast cancer mortality from grade 3 cancers in the ASP compared to the PSP, corresponding to 95 deaths prevented, almost double the number of deaths prevented for grades 1 and 2 tumours combined. This indicates that the notion that mammographic screening only affects outcome in non-aggressive, slowly progressing cancers (7,15) is unfounded. More recently, measures of aggression based on gene expression have shown a strong relation to prognosis (16). These measures are also correlated with grade (17). It would be interesting to see results on gene expression and outcome in relation to screening.

The results showed no significant reduction in mortality in the ASP from grade 1 cancers. This may be because the lower incidence of grade 2 and 3 cancers in the ASP was balanced by larger numbers of grade 1 tumours. The RR's of mortality from grade 1, 2 and 3 cancers were respectively 0.94, 0.68 and 0.65. The corresponding RR's of incidence of grade 1, 2 and 3 tumours were 1.33, 0.89 and 0.90. Dividing RR's for mortality by those for incidence, we obtain 0.71, 0.76 and 0.72, very similar figures. This suggests that the lack of a mortality reduction in grade 1 tumours is driven by the increased incidence of these tumours, with a corresponding reduction in incidence of grade 2 and 3 cancers, and that the effect of screening on case fatality is similar for all grades.

We and others have published evidence in the past that some tumours will progress from lower to higher histological grade, and that early detection can arrest this progression (13,18,19). There is also evidence that such progression is rare. Schymik et al found that very few tumours in a series of 865
cancers had mixed grade 1 and grade 3 appearance (20). Weigelt et al observed that gene expression profiles were similar between primary tumour and distant metastatic sites (21). Our two observations that absolute incidence of grade 3 cancers was lower and the distributions of tumour size and lymph node status were more favourable in the ASP than in the PSP suggest that the reduction in mortality from grade 3 cancers was driven by a combination of earlier detection that prevents progression to grade 3 cancers and by diagnosis at an earlier stage within the grade 3 cancers. Whatever the mechanism, mortality from grade 3 cancers was reduced substantially in the ASP.

As in other mammography trials, the screening period was shorter than the period of follow-up for mortality, which can lead to conservative estimates. However, the inclusion of a closure screen of the control group (the PSP in our terminology) minimises this bias (22). When comparing incidence by grade between ASP and PSP, one could attempt to obtain two parallel incident groups by removing the prevalence screen in the ASP at the beginning of the screening phase of the trial and that in the PSP at its end, but these take place at different ages, had different attendance rates, and would exclude different tumours. Again, the inclusion of the closure screen of the PSP will mean that incidence is approximately equivalent between the two trial arms.

Our trial had an average 33-month inter-screening interval in ages 50-74 and an average 24-month interval in ages 40-49 (1). The 33-month interval is for the older group is longer than that used in most modern screening programmes, and a greater advance in diagnosis might be expected from these programmes. We have previously presented data with respect to histological grade that suggested that had the interval in the 40-49 age group been shorter, say 12-18 months, the effect on mortality from grade 3 cancers would have been larger (23). Other data published since then supports this conclusion (24).

It has already been observed that screen-detected tumours have more favourable grade than symptomatic (25). This may have stimulated the concern noted above that screening might not substantially alter outcome in more aggressive tumours (7,15). As noted above, the results here indicate that such concerns are unwarranted, and other studies support this conclusion. The West Midlands Screening Histories Project reported a substantial and statistically significant reduction in the odds of grade 3 cancers during the period of initiation of the breast cancer screening programme in the UK, 1988-96 (26). In the UK Breast Screening Age Trial, a small (non-significant) reduction in incidence of grade 3 cancers was observed in the intervention arm (27). In Providence, Rhode Island, during a period of increasing mammographic screening activity, both the proportional and absolute rates of grade 3
cancers decreased (28). Evans et al found a high proportion of node negative cases among screen-detected grade 3 cancers, also consistent with our findings (29). Further, a recent study in Italy has shown a significant reduction in the incidence of grade 3 cancers associated with invitation and exposure to screening (30).

In conclusion, we found a substantial and significant reduction in mortality from histological grade 3 cancers in a randomised trial of breast cancer screening with mammography, indicating that screening does improve outcome in more aggressive, rapidly progressing cancers.

References


Table 1. Breast cancer cases by grade and trial arm

<table>
<thead>
<tr>
<th>Grade</th>
<th>No. (%) of cases</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSP*</td>
<td>ASP*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>171 (18.9)</td>
<td>314 (25.8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>356 (39.3)</td>
<td>436 (35.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>378 (41.8)</td>
<td>467 (38.4)</td>
<td></td>
</tr>
<tr>
<td>NK/in situ</td>
<td>137</td>
<td>209</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1042</td>
<td>1426</td>
<td></td>
</tr>
<tr>
<td>Total subjects</td>
<td>55985</td>
<td>77080</td>
<td></td>
</tr>
</tbody>
</table>

*ASP= Active study population, invited to screening; PSP= Passive study population, not invited
Table 2. Breast cancer deaths by grade and trial arm

<table>
<thead>
<tr>
<th>Grade</th>
<th>Breast cancer deaths</th>
<th></th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSP*</td>
<td>ASP*</td>
<td></td>
</tr>
<tr>
<td>Not known/DCIS</td>
<td>32</td>
<td>38</td>
<td>0.87 (0.55, 1.40)</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>37</td>
<td>0.94 (0.58, 1.53)</td>
</tr>
<tr>
<td>2</td>
<td>107</td>
<td>99</td>
<td>0.68 (0.52, 0.89)</td>
</tr>
<tr>
<td>3</td>
<td>199</td>
<td>177</td>
<td>0.65 (0.53, 0.80)</td>
</tr>
</tbody>
</table>

*ASP= Active study population, invited to screening; PSP= Passive study population, not invited
Table 3. Size distribution of invasive cancers by grade for each trial arm

<table>
<thead>
<tr>
<th>Grade</th>
<th>PSP No. (%) of cases</th>
<th>ASP No. (%) of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 15 mm</td>
<td>&gt;= 15 mm</td>
</tr>
<tr>
<td>1</td>
<td>92 (53.3)</td>
<td>79 (46.2)</td>
</tr>
<tr>
<td>2</td>
<td>114 (32.0)</td>
<td>242 (68.0)</td>
</tr>
<tr>
<td>3</td>
<td>49 (13.0)</td>
<td>329 (87.0)</td>
</tr>
</tbody>
</table>

*ASP = active study population, invited to screening; PSP = passive study population, not invited.
Table 4. Node status of invasive cancers by grade for each trial arm

<table>
<thead>
<tr>
<th>Grade</th>
<th>PSP No. (%) of cases</th>
<th>ASP No. (%) of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Node negative</td>
<td>Node positive</td>
</tr>
<tr>
<td>1</td>
<td>124 (80.0)</td>
<td>31 (20.0)</td>
</tr>
<tr>
<td>2</td>
<td>221 (65.8)</td>
<td>115 (34.2)</td>
</tr>
<tr>
<td>3</td>
<td>157 (44.7)</td>
<td>194 (55.3)</td>
</tr>
</tbody>
</table>

*ASP= active study population, invited to screening; PSP = passive study population, not invited; 67 ASP and 63 PSP cases did not have node status ascertained*
**Legends to Figures**

Figure 1. (a) Cumulative breast cancer mortality, grade 1 cancers.

Figure 1 (a) shows cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histological grade 1.

Figure 1 (b) Cumulative breast cancer mortality, grade 2 cancers.

Figure 1 (b) shows cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histological grade 2.

Figure 1 (c) Cumulative breast cancer mortality, grade 3 cancers.

Figure 1 (c) shows cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histological grade 3.
Figure 1 (a)

![Graph showing cumulative mortality per 100,000 over years since randomization for PSP (reference) and ASP (RR=0.94, 95% CI: 0.58, 1.53).]
Figure 1 (b)
Figure 1 (c)

![Graph showing cumulative mortality per 100,000 individuals over years since randomization. The graph compares PSP (reference) and ASP (RR=0.65, 95% CI: 0.53, 0.80).]
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