Research Article

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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 tumors.

Methods: We utilized data from the Swedish Two-County Trial, which randomized 77,080 women ages 40 to 74 to invitation to screening and 55,985 for usual care. We tabulated cancers by histologic grade and then compared mortality from cancers specific to histologic 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 tumors diagnosed within the screening phase of the trial. Finally, we cross-tabulated grade with tumor size and node status, to assess downstaging within tumor grades.

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

Conclusions: The combination of prevention of tumors progressing to grade 3 and detection at smaller sizes and lesser rates of lymph node metastases within grade 3 tumors 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. *Cancer Epidemiol Biomarkers Prev; 27(2); 154–7. ©2017 AACR.*

Introduction

The randomized 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 programs 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 tumor. 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 histologic grade at diagnosis. Although emphasis on prognostic factors has shifted toward molecular features of tumors (10), histologic grade still is a strong breast cancer prognostic factor, and it reflects the aggressive potential of the tumor (11). If the assertion that screening does not primarily improve outcome in more aggressive tumors 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 article, we investigate this issue using data from the Swedish Two-County Trial of mammographic screening (1).

Materials 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, ages 40 to 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 ages 40 to 49 at allocation were offered screening on average every 24 months. Women ages 50

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Table 1. Breast cancer cases by grade and trial arm

	No. (%) of cases	
Grade	**PSP[a]**	**ASP[a]**
1	171 (18.9)	314 (25.8)
2	356 (39.3)	436 (35.8)
3	378 (41.8)	467 (38.4)
NK/in situ	137	209
Total	1,042	1,426
Total subjects	55,985	77,080

[a]ASP, active study population, invited to screening; PSP, passive study population, not invited.

to 74 were offered screening every 33 months. After 6 to 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. In the mortality analyses that follow, we use incidence-based mortality from the screening phase of the trial, that is, deaths only from tumors diagnosed in the ASP and PSP between randomization 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 histologic grade to assess whether there was evidence of prevention of grade 3 cancers by early detection. We then compared mortality from cancers specific to histologic 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 tumor size and node status, to assess the extent to which tumors of differing grade were detected early in their development.

Results

Table 1 shows the cancers diagnosed in the two arms of the trial by histologic grade. The distribution of grade is significantly more favorable in the ASP ($P < 0.001$). The absolute incidence rate of grade 3 cancers was 378/55,985 = 6.8 per 1,000 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 was 47, from grade 1 cancers was two, and from grade missing/*in situ* tumors was six. Thus, both the relative and absolute effects of screening on breast cancer mortality were by far the largest in grade 3 cancers.

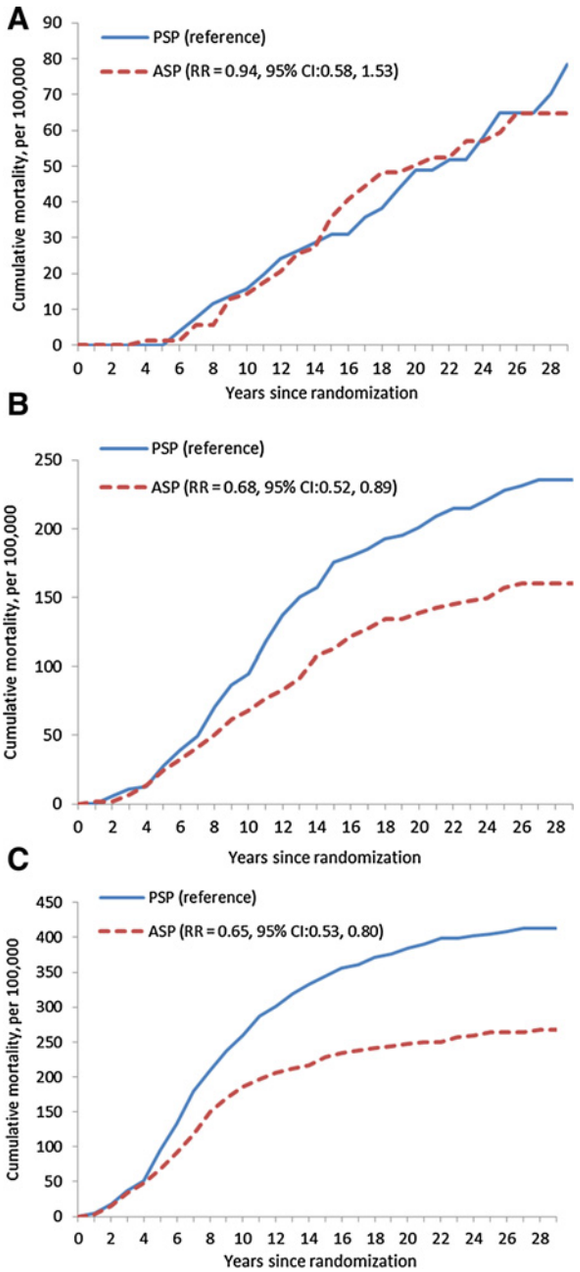

Figure 1.
A, Cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histologic grade 1. **B,** Cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histologic grade 2. **C,** Cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histologic grade 3.

Table 3 shows the size distribution by grade for the ASP and PSP separately. For cancers of each histologic grade, the proportion of tumors of size 15 mm or larger was substantially reduced in the ASP. This was statistically significant in all three histologic malignancy grades, including the grade 3 tumors ($P < 0.001$). The corresponding results for node status by grade are shown in Table 4. There is a similar reduction in the proportion of node-positive

Table 2. Breast cancer deaths by grade and trial arm

	Breast cancer deaths		
Grade	**PSP[a]**	**ASP[a]**	**RR (95% CI)**
Not known/DCIS	32	38	0.87 (0.55–1.40)
1	29	37	0.94 (0.58–1.53)
2	107	99	0.68 (0.52–0.89)
3	199	177	0.65 (0.53–0.80)

[a]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

	PSP* no. (%) of cases		ASP* no. (%) of cases	
Grade	**<15 mm**	**≥15 mm**	**<15 mm**	**≥15 mm**
1	92 (53.3)	79 (46.2)	205 (65.3)	109 (34.7)
2	114 (32.0)	242 (68.0)	212 (48.6)	224 (51.4)
3	49 (13.0)	329 (87.0)	123 (26.3)	344 (73.7)

*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

	PSP* no. (%) of cases		ASP* no. (%) of cases	
Grade	**Node negative**	**Node positive**	**Node negative**	**Node positive**
1	124 (80.0)	31 (20.0)	274 (91.0)	27 (9.0)
2	221 (65.8)	115 (34.2)	282 (69.3)	125 (30.7)
3	157 (44.7)	194 (55.3)	251 (56.8)	191 (43.2)

[a]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.

cases in the ASP in all three grades, including within the grade 3 tumors ($P = 0.001$). The difference in distributions between ASP and PSP will reflect differences in incidence by these characteristics associated with invitation to screening, as the overall cumulative incidence is almost exactly equal between the ASP and PSP.

Discussion

Our results suggest that screening prevents tumors from progressing to grade 3 and also detects grade 3 tumors 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 with the PSP, corresponding to 95 deaths prevented, almost double the number of deaths prevented for grades 1 and 2 tumors combined. This indicates that the notion that mammographic screening only affects outcome in nonaggressive, 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 tumors. The RRs of mortality from grade 1, 2, and 3 cancers were 0.94, 0.68, and 0.65, respectively. The corresponding RRs of incidence of grade 1, 2, and 3 tumors were 1.33, 0.89, and 0.90. Dividing RRs 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 tumors is driven by the increased incidence of these tumors, 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 tumors will progress from lower to higher histologic grade, and that early detection can arrest this progression (13, 18, 19). There is also evidence that such progression is rare. Schymik and colleagues found that very few tumors in a series of 865 cancers had mixed grade 1 and grade 3 appearance (20). Weigelt and colleagues observed that gene expression profiles were similar between primary tumor and distant metastatic sites (21). Our two observations that absolute incidence of grade 3 cancers was lower and the distributions of tumor size and lymph node status were more favorable 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) minimizes 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 will take place at different ages, may have different attendance rates, and would exclude different tumors. 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 interscreening interval in ages 50 to 74 and an average 24-month interval in ages 40 to 49 (1). The 33-month interval for the older group is longer than that used in most modern screening programs, and a greater advance in earlier diagnosis might be expected from these programs. We have previously presented data with respect to histologic grade that suggested that had the interval in the 40 to 49 age group been shorter, say 12 to 18 months, the effect on mortality from grade 3 cancers would have been larger (23). Other data published since then support this conclusion (24).

It has already been observed that screen-detected tumors have more favorable grade than symptomatic (25). This may have stimulated the concern noted above that screening might not substantially alter outcome in more aggressive tumors (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 program in the United Kingdom, 1988–1996 (26). In the UK Breast Screening Age Trial, a small (nonsignificant) 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 and colleagues found a high proportion of node-negative cases among screen-detected grade 3 cancers, also consistent with our findings (29). Furthermore, 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 histologic grade 3 cancers in a randomized trial of breast cancer screening with mammography, indicating that screening does improve outcome in more aggressive, rapidly progressing cancers and may interrupt the progression of the subset of grade 1 and 2 cancers that would progress to grade 3 and worse prognosis if not detected by screening.

Disclosure of Potential Conflicts of Interest

S.W. Duffy reports receiving a commercial research grant from Philips. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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