The Gothenburg Breast Cancer Screening Trial: Preliminary Results on Breast Cancer Mortality for Women Aged 39–49

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We carried out a randomized trial of invitation to screening mammography in the city of Gothenburg, Sweden, to estimate the effect of screening on breast cancer mortality in women under age 50 years. A total of 11,724 women aged 39–49 were randomized to the study group, which was invited to mammographic screening every 18 months; 14,217 women in the same age range were randomized to a control group, which was not invited to screening until the fifth screen of the study group. Breast cancers diagnosed in both groups between randomization and immediately after the first screen of the control group were followed up for death from breast cancer to the end of December 1994. There was a significant 44% reduction in mortality from breast cancer in the study group compared to the control group (relative risk [RR] = 0.56, \( P = 0.042 \), 95% confidence interval [CI]: 0.32–0.98). A conservative estimate based on removal of the cancers detected at the first screen of the control group gave an RR = 0.59 (\( P = 0.069 \), 95% CI: 0.33–1.05). The true answer is likely to lie between the two estimates. These data suggest that mammographic screening can reduce breast cancer mortality in women under age 50, particularly if high-quality mammography is used and a short interscreening interval is adhered to. [Monogr Natl Cancer Inst 1997;22: 53–55]

The effect of mammographic screening for breast cancer in women under age 50 years is an issue of controversy, partly due to the lesser effect on breast cancer mortality observed in this age group than in older women, and partly to the variation in estimated effects between randomized trials (1–7). Meta-analyses have not resolved the issue: even when several trials are combined there is still a relatively small number of breast cancer deaths in this age group, so that confidence intervals remain wide (8–11). There is evidence that interval cancer rates are higher in this age group (12), and that screening sensitivity is lower (11), probably due to a high prevalence of mammographically dense tissue in premenopausal women. These findings suggest that in women under age 50, screening has to be more frequent than in older women, and that measures must be taken to minimize the number of false negative screens—measures such as careful attention to mammographic quality, two-view mammography, and double reading (11).

Subjects and Methods

The subjects in this trial were the entire female population of the city of Gothenburg born between the years 1923 and 1944 inclusive. All women with a history of breast cancer prior to randomization were excluded. There were 51,611 women aged 39–59 at randomization. In this paper, we restrict analysis to the 25,941 women aged 39–49.

We planned to screen every 18 months. With the resources available, this dictated that the group invited to screening must number around 21,000 women. We therefore randomized to the study or control group in a ratio of 1 to 1.2 in the 39–49 age group and 1 to 1.6 in the 50–59 group. Randomization took place within each year of birth cohort successively. Thus, the 1923 cohort was randomized in December 1982 and the study group members invited to their first screen between December 1982 and February 1983. The last cohort to be randomized, women born in 1944, was randomized in April 1984 and the study group members received their first invitation in May, 1984. The randomization was by cluster, based on day of birth in the 1923–1935 cohorts, and by individual for the 1936–1944 cohorts, as the computer software for screening invitation was amended during the period of the trial to enable individual randomization. In the 39–49 age range, the final sample comprised 11,724 in the study group and 14,217 in the control group. The mean ages in the study and control groups were 43.9 years and 43.8 years respectively.

The study group members were invited to screening every 18 months. The control group members received a single screen immediately following the fifth screen in the study group. The cancers diagnosed from the time of randomization up to immediately after the first screen of the control group (which was completed on average around seven years after randomization) were then followed up for breast cancer mortality.

The screening modality was mammography. Two-view mam-
mography was used at the first screen, and single view at later screens, unless the density of the breast at the first screen indicated that single-view mammography would be inadequate. Screening took place in a stationary unit with specially trained radiology nurses. Mammography was performed using a unit with CGR Senograph 500 T with moving grid. We used the Kodak Min R imaging system, with extended film processing (three minutes). Films were single read at the first three screening rounds and double read thereafter, and those recalled were subject first to supplementary mammography, and, if necessary, to physical examination by a surgeon and to fine needle aspiration cytology.

The primary outcome was mortality from breast cancers diagnosed during the period of the trial, as defined above. Mortality data were available up to December 31, 1994. Breast cancer deaths were identified from the Swedish cause of death register, which was shown in the overview of Swedish breast screening trials to be reliable (13). Mortality was compared between the study and control groups using Poisson regression (14).

**Results**

Table 1 shows attendance rates and cancers diagnosed at each screen. Attendance was between 75% and 85% in the study group and was 66% at the first screen of the control group. The cancer detection rate at the first screen of the control group was higher than that for the study group, as the women in the control group were on average six years older at their first screen.

During the screening period of the trial, there were 144 breast cancers diagnosed in the study group and 195 breast cancers in the control group. There were 18 deaths and 138,402 person-years to the end of 1994 in the study group, and 39 deaths and 168,025 person-years in the control group. A significant reduction in mortality was observed in the study group (P = 0.042), with a relative risk (RR) of 0.56. Figure 1 shows cumulative mortality over time in the study and control groups. The mortality of the two groups began to separate between six and eight years after randomization, and the gap continued to widen thereafter.

Table 2 gives the cancer incidence during the screening phase of the trial. There was a 10% lower incidence in the study group. This difference was not significant (but see Discussion below).

**Discussion**

The results above are consistent with previous findings of reduced breast cancer mortality from screening women under age 50 years (11). The present results also suggest that with high-quality mammography and a short screening interval, the benefit can be substantial. This is the first internal analysis of mortality in the Gothenburg trial, and further follow-up is necessary to ensure that the mortality benefit is maintained. Since a number of screens were performed after age 50, further analyses are required to determine the magnitude of the benefit from screening with respect to cancers diagnosed before age 50.

Although the difference in breast cancer incidence between the study and control groups is not significant (relative incidence = 0.90; 95% confidence interval [CI]: 0.72–1.13), it is advisable to consider the possibility of bias. For example, the higher incidence in the control group may be due to the fact that the first screen of the control group ended on average a few months later than the fifth screen of the study group. Indeed, it is at this first screen of the control group that the excess incidence in the control group occurs, as shown in Table 1. Because the closure of the screening phase of the trial occurred at the same point in time for both the study and control groups, there is more opportunity for lead time cancers to be diagnosed and therefore followed up in the control group than in the study group (due to the later screen).

To obtain a more conservative estimate, we excluded all cancers in the control group diagnosed after the start of screening the control group, and therefore the five breast cancer deaths among these. This left 151 breast cancers and 34 breast cancer deaths in the control group. However, without an adjustment to the person-years, this exclusion would have biased the results in the opposite direction, with a considerable deficit of cancers in the control group. We therefore made the following adjustment to the person-years: since we had additional cancers in the study group due to lead time from the final screen, and no such cancers in the control group, we added the corresponding person-years to that of the study group. Using the method of Paci and Duffy (15), we estimated the expected lead time as 2.21 years and the sensitivity as 0.87. The additional number of person-years equaled the number screened at the final screen of the study group times the sensitivity (0.87) times 2.21–0.81 (the lead time minus the time from screening the study group to closing the recruitment period in years). Thus, we added 1.4 × 8,675 × 0.87 = 10,566 to the person-years of the study group. We also subtracted from the person-years in the control group 0.19 (the average time in years taken to screen each year of birth cohort in the control group) times the number in the control group at the time of the invitation, 13,947. This gave a total of 91,907 person-years in the study group during the cancer recruitment period and 96,098 in the control group. The relative incidence was now 1.00. Performing the same adjustment to the person-years of total follow-up and recalculating the breast cancer mortality, we arrived at 18 deaths and 148,968 person-years in the study group, 34 deaths and 165,375 person-years in the control group, and an RR of 0.59 (P = 0.069; 95% CI: 0.33–1.05). This is likely to be conservative, as it involves removing 23% of the cancers in the control group but adjusting the person-years for mortality by only 8% in the study group and 2% in the control group. The true RR may lie between the 0.59 calculated here and the 0.56 given above.

The attendance rates in the study group were between 75% and 85%, in line with other Swedish programs (9). In a survey

### Table 1. Attendance rates and diagnostic work-up by screening round

<table>
<thead>
<tr>
<th>Screening round</th>
<th>Invited</th>
<th>Attended (%)</th>
<th>Cancers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Study)</td>
<td>11,720*</td>
<td>9,921 (85)</td>
<td>17 (0.17)</td>
</tr>
<tr>
<td>2 (Study)</td>
<td>11,679</td>
<td>9,157 (78)</td>
<td>10 (0.11)</td>
</tr>
<tr>
<td>3 (Study)</td>
<td>11,624</td>
<td>9,150 (79)</td>
<td>15 (0.16)</td>
</tr>
<tr>
<td>4 (Study)</td>
<td>11,571</td>
<td>8,914 (77)</td>
<td>21 (0.23)</td>
</tr>
<tr>
<td>5 (Study)</td>
<td>11,519</td>
<td>8,675 (75)</td>
<td>20 (0.23)</td>
</tr>
<tr>
<td>1 (Control)</td>
<td>13,947*</td>
<td>9,167 (66)</td>
<td>40 (0.44)</td>
</tr>
</tbody>
</table>

*Numbers are smaller than total cohort because of losses between randomization and first screen.
of 1,641 controls in this age group, 19% reported having had a mammogram in the last two years. Thus, there may have been some ‘‘voluntary’’ screening in Gothenburg before and during the trial, and the mortality benefit observed in this trial is likely to be a result of enrollment in an organized program with a strict 18-month interscreening interval and high-quality mammography. This is further supported by the fact that 33% of the deaths in the study group were from the nonattenders.

In conclusion, this trial adds to the evidence of a reduction in breast cancer mortality in women under age 50 invited for mammographic screening, and suggests that a substantial mortality benefit can result from a strict 18-month interval between screens.

References