The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/22454

Please be advised that this information was generated on 2019-08-28 and may be subject to change.
MAMMOGRAPHIC SCREENING AFTER THE AGE OF 65 YEARS: EVIDENCE FOR A REDUCTION IN BREAST CANCER MORTALITY

Jos A.A.M. Van Duijk1,2,8, André L.M. Verbeek1,2, Louk V.A.M. Beex3, Jan H.C.L. Hendriks3,4, Roland Holland2,5, Marcel Marvunac6, Huub Straatman1 and Jan M. Werre7

Departments of 1Epidemiology, 2Endocrinology, 3Radiology, and 5Pathology, and the 7National Expert and Training Center for Breast Cancer Screening in The Netherlands, University Hospital and University of Nijmegen, Nijmegen; 6Department of Pathology, Canisius-Wilhelmina Hospital, Nijmegen; 7Red Cross Blood Bank, Arnhem, The Netherlands.

We evaluated whether regular mammographic screening of women aged 65 years or older affected breast cancer mortality. In Nijmegen, a population-based screening program for breast cancer was started in 1975, with biennial mammography for women aged 35–64 years. Since 1977, elderly women have also been participating. For the present case-control study, women were selected who were over 64 years of age at the most recent invitation. Eighty-two of them had died from breast cancer. For these cases, 410 age-matched population controls were selected. The ratio of breast cancer mortality rates of the women who had participated regularly (i.e., in the 2 most recent screening rounds prior to diagnosis) vs. those who had not participated in the screening was 0.56 (95% CI = 0.28–1.13). The rate ratio was 0.45 in the women aged 65–74 years at the most recent invitation (95% CI = 0.20–1.02), whereas it was 1.05 in the women aged 75 years and older (95% CI = 0.27–4.14). While the breast cancer survival rate of the non-participant patients was fairly equal to that of patients from a control population, the underlying incidence rate of breast cancer was higher in the participants than in the non-participants. Therefore, we conclude that bias was present, but that it had decreased our effect estimate. The real reduction in breast cancer mortality due to regular screening will be even larger. Regular mammographic screening of women over age 65 (at least up to 75 years) can reduce breast cancer mortality by approximately 45%.

© 1996 Wiley-Liss, Inc.

In women, the life-time risk of developing breast cancer has been estimated at 8.4–9.4% (Schouten et al., 1994). For women aged 65–69 years the probability of developing breast cancer before the age of 85 years is 1 in 16 and for those aged 70–74 years 1 in 20 (Campbell et al., 1994). Thus, even in the very elderly, many cases of breast cancer are diagnosed. The proportion of patients who die from this disease is as large as it is in younger women (Beex and Wobbes, 1986). In patients aged 65–84 years, 5-year relative survival rates vary from about 90% for those with localized disease to 66–69% for those with regional disease and to 17–20% for those with distant disease (Yancik et al., 1989).

In the past few decades, several randomized and non-randomized trials have been undertaken to evaluate the effect of mammographic screening on breast cancer mortality. Extensive evaluations on the available evidence have led to the conclusion that a 30–40% reduction in breast cancer mortality can be achieved by periodic screening of women aged 50–65 or 70 years (Peeters et al., 1990; Rutqvist et al., 1990; Hurley and Kaldor, 1992; Fletcher et al., 1993; Nyström et al., 1993; De Koning et al., 1995). In women over the age of 70 years, evidence for a possible reduction in breast cancer mortality due to screening is lacking, because most trials did not include elderly women (Fletcher et al., 1993; Morrison, 1992).

In the late eighties and the early nineties, national screening programmes were initiated in several European countries, such as the United Kingdom, The Netherlands and Sweden (Shapiro, 1992). The lack of data showing that screening was of benefit to elderly women was the principal argument for not inviting women aged 65 years and more to screening programs in the UK (Woodman et al., 1995) and for excluding women aged 70 years and older from programs in The Netherlands (NETB, 1995). Nevertheless, the question still remains as to whether continuing to screen women after they have reached these upper age limits will further reduce breast cancer mortality. With 18 years of follow-up data available in our Nijmegen screening program from the first screening round-up to December 31, 1993, we elected to conduct a case-control study on the effect of long-term participation after the age of 65 years on breast cancer mortality.

STUDY POPULATION AND METHODS

Study setting

In the city of Nijmegen, population-based screening for breast cancer has been ongoing since 1975. Biennially, nearly 30,000 women aged 40 years and older are personally invited to have a one-view mammogram. From round 2 (1977–1978) onwards, about 10,000 women aged 65 years and older have also been invited to participate. At each screening round, individual data on invitation and participation are stored in a computer file. Another file is kept on all Nijmegen breast cancer patients diagnosed within and outside the screening program. The follow-up of the population is registered with the help of the local authorities, who provide weekly lists of deceased women and those who have moved out of Nijmegen. Details of the program have been reported previously (Peer et al., 1994; Otten et al., 1996, in press).

Study design and population

Within the Nijmegen population of invited women, we conducted a case-control study to investigate the effect of regular participation in the screening program from age 65 years onwards on breast cancer mortality. The study population consisted of women who 1) had been invited to participate at the age of 65 years or older and 2) had been free of breast cancer at the first screening invitation at age 65 years or older.

The cases were the patients who had died of breast cancer before January 1, 1994. The cause of death was classified by a panel of physicians who were unaware of the screening history of the patients and was based on the clinical course of the disease and information about serious co-morbidity. Breast cancer was defined as the cause of death if the disease had progressed to distant sites and this progression was ultimately responsible for the death of the patient, or if in the presence of advanced disease other causes of death could be excluded. Patients with advanced breast cancer who died of other, unrelated causes were not included as cases. The study population comprised 82 cases. The screening round in which the case had received the most recent invitation just before the diagnosis of primary breast cancer was defined as the index.

To whom correspondence and reprint requests should be addressed, at the Department of Epidemiology, University of Nijmegen, P.O. Box 9101, NL-6500 HB Nijmegen, The Netherlands. Fax (+31) 24-361-3505.

Received: December 1, 1995 and in revised form February 23, 1996.
round. For screen-detected cases the round in which the cancer had been detected was the index round.

For each case, a group of eligible population controls were selected who 1) were alive and residing in Nijmegen at the time of death of the case, 2) had been invited to participate in the index round of the case, 3) were free of breast cancer at their index invitation, and 4) were of the same age as the case at the index invitation. At random, 5 controls were selected for each case. Thus, the total number of controls was 410.

**Definition of contrasted screening histories**

A history of no screening was defined as no participation in the 5 most recent screening rounds up to and including the index round. Women in this category represented the reference category.

A history of regular screening was defined as participation in the index round and having had a negative screening examination 1 round (approximately 2 years) earlier.

Histories that did not meet the criteria for "no screening" or "regular screening" were classified as otherwise and formed a category in which we took no interest.

Cases and controls were classified according to these categories of screening histories.

**Statistical analysis**

We calculated the odds ratio with its 95% confidence interval (95% CI) as an estimator of the ratio of breast cancer mortality rates (RR) in women with a history of regular screening versus those with a history of no screening (Miettinen, 1976). Owing to the matched design, we used conditional logistic regression analysis with the software package EGRET.

**RESULTS**

Age at the index invitation was identical for cases and their matched controls (range, 65–92 years). At the index invitation, 33% of the study population were 65–69 years old, 24% were 70–74 years, 32% were 75–79 years and 11% were 80 years or older. The number of invitations was virtually the same for the cases and controls. Up to and including the index round, 23% of the cases and 21% of the controls had been invited only once, and 35% and 41% had been invited 2–4 times, respectively, whereas 41% and 39% had been invited 5–8 times, respectively.

Table 1 shows the results of the conditional logistic regression analysis. The ratio of the breast cancer mortality rates (RR) of regularly screened women vs. unscreened women was 0.56 (95% CI = 0.28–1.13). In women aged 65–74 years at the index invitation the RR was 0.45 (95% CI = 0.20–1.02); in women aged 75 and older, the RR was 1.05 (95% CI = 0.27–4.14).

**TABLE I - BREAST CANCER MORTALITY RATIO FOR SCREENING HISTORY ACCORDING TO AGE AT INDEX INVITATION**

<table>
<thead>
<tr>
<th>Age at index invitation (years)</th>
<th>Screening history</th>
<th>Number of cases/controls</th>
<th>Breast cancer mortality rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages (65–92)</td>
<td>No screening</td>
<td>40/166</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Regular screening</td>
<td>15/101</td>
<td>0.56 (0.28–1.13)</td>
</tr>
<tr>
<td></td>
<td>Otherwise</td>
<td>27/143</td>
<td>0.77 (0.44–1.34)</td>
</tr>
<tr>
<td>65–74</td>
<td>Regular screening</td>
<td>20/69</td>
<td>0.45 (0.20–1.02)</td>
</tr>
<tr>
<td></td>
<td>Otherwise</td>
<td>12/87</td>
<td>0.64 (0.30–1.38)</td>
</tr>
<tr>
<td>75 and older</td>
<td>Regular screening</td>
<td>15/79</td>
<td>0.64 (0.30–1.38)</td>
</tr>
<tr>
<td></td>
<td>Otherwise</td>
<td>3/14</td>
<td>1.05 (0.27–4.14)</td>
</tr>
</tbody>
</table>

No participation in index round and 4 preceding rounds.—Participation in index round and negative mammogram in preceding round.—Not meeting the criteria for “unscreened” or “screened”.

**DISCUSSION**

All over the world, the age-specific incidence of breast cancer is rising, especially among elderly women (Harris et al., 1992). At the time of diagnosis, elderly patients are more likely to have distant metastases or unknown stage disease than younger women (Yancik et al., 1989; Bergman et al., 1992). In the Nijmegen group of non-participants aged 70 years and older, 85% had stage II or stage II+ cancer, in contrast to 77% of those aged 50–69 years. Among the regular participants, these percentages were 33% and 30%, respectively (Peer et al., 1994).

After menopause, a large proportion of the fibroglandular breast tissue is replaced by fatty tissue, with greater radiological transparency (Costanza et al., 1992), thereby facilitating the detection of breast cancer by mammography. In addition, the proportion of false-positive screening results will be lower because of the decreased frequency of benign breast disease. The growth rate of breast cancer is relatively low in elderly women. Peer et al. (1993) estimated that the median tumor volume doubling time is 80 days in patients younger than 50 years, 157 days in patients aged 50–70 years and 188 days in older patients. The lower growth rate is in concordance with the higher rate of steroid-positive tumors (Clark et al., 1984). Life expectancy is relatively long, about 14 years at age 70 and about 8.5 years at age 80 years (Wegman, 1993). For the reasons given above, an important reduction in breast cancer mortality can also be expected in elderly women due to mammographic screening.

The few studies on the effect of breast cancer screening in women aged 65 years and older are small and have methodological flaws. For instance, age-specific analyses involve age at entry to the screening program instead of age at screening, and the comparisons are made between the “invited group” and the “control group” or between women “screened once” and those “never screened” (Verbeek et al., 1984, 1985; Morrison et al., 1988; Brown and Hulka, 1988; Tabár et al., 1995; Chen et al., 1993). The most recent results from the Swedish 2-county trial for women aged 70–74 years at their first invitation for screening showed for the invited women a relative risk of 0.79 for death from breast cancer (95% CI = 0.51–1.22), compared with the non-invited women (Tabár et al., 1995). Analysis of the women aged 65–74 years at their first invitation revealed RR = 0.68 (95% CI = 0.51–0.89) (Chen et al., 1995). In the Nijmegen program, a case-control study was conducted on women who had been invited at least twice (Van Dijck et al., 1994). In this study, 33 cases and 165 controls aged 65 years and over at the index invitation were included. For women who had participated in the index screening, compared with those who had not participated, the RR was 0.58 (0.24–1.41). For women aged 65–74 years at the index invitation, the RR was 0.34 (95% CI = 0.12–0.97), whereas in the older women, an excess of mortality was found that could be attributed to self-selection bias (Van Dijck et al., 1994). In the present study, with 5 more years of follow-up and twice as many patients, the RR for women screened regularly compared with those not screened was 0.56 (95% CI = 0.28–1.13); for women aged 65–74, the RR was 0.45 (95% CI = 0.20–1.02); and for women aged 75 or over, the RR was 1.05 (95% CI = 0.27–4.14). The agreement in the results, in spite of the difference in the definition of the relevant screening histories (participation in the index round for the former study and participation in both the index round and one round earlier in the present study), is noteworthy.

Screening can only improve the prognosis of breast cancer if it can detect more breast cancer cases in a curable phase than can be diagnosed without screening. Maximum benefit can only be expected if a woman participates on a regular basis. In our study, the definition of a regular screening history applied
to women who continued to participate up to and including the index round and had had a negative screening mammogram approximately 2 years earlier. This definition guaranteed that in regularly screened patients, breast cancer had been diagnosed as early as possible in the given screening program. Screening mammograms performed 2 or more rounds before the index invitation were not expected to have any influence on the diagnosis of breast cancer and were therefore not taken into consideration. The reference category with a history of no screening was also designed explicitly. After a negative screening result, a woman’s risk of developing breast cancer is low initially, but it approaches that of unscreened women after several years. After about 10 years, preceding screening can be expected to have lost its effect. We therefore defined a history of no screening as being present if a woman had never participated at all, or if she had rejected the index invitation and the 4 preceding ones. With this carefully designed contrast, we estimated that in women aged 65 years and older the reduction in breast cancer mortality for regularly screened women relative to the unscreened women was 44%.

Non-randomized studies are liable to self-selection bias that may (in part) explain the breast cancer mortality rate ratio observed in the screened vs. the unscreened group. Besides age, which was controlled for by matching, we only reviewed the information on previous referral for diagnostic work-up. Only 3 controls and no cases had been referred previously, so this cannot have caused any bias. However, there may have been a difference in the underlying breast cancer mortality between the screened and unscreened groups that had biased our results. To gain an insight into the direction of the bias, we first calculated the survival rate (Kaplan-Meier method) from diagnosis to death from breast cancer for the Nijmegen non-participant patients and compared it with that of Arnhem patients. Arnhem is a neighboring city with a similar population size as in Nijmegen, where population screening for breast cancer was started in 1989. The cause of death of the Arnhem patients was determined in the same way as in Nijmegen. We selected patients aged 65 years or older at diagnosis who were diagnosed in 1977-1989. Figure 1 shows that the curve for the 99 Nijmegen non-participants was fairly similar to that of the 372 Arnhem patients.

Next, we compared the incidence rate of breast cancer in Nijmegen with that in Arnhem. In the period from January 1, 1979 (after the Nijmegen population had undergone its first round of screening) to December 31, 1988, the incidence rate of breast cancer in Nijmegen equalled that in Arnhem (RR = 0.97; 95% CI = 0.83-1.14). We used log-linear modeling with the computer package GLIM and adjusted for age in 5-year categories: 65-69, 70-74, 75-79, 80-84 and 85+. Subsequently, the Nijmegen population was restricted to non-participants. For the Nijmegen non-participants compared with the Arnhem population, the RR was 0.72 (95% CI = 0.56-0.93). In the participants, the incidence of breast cancer must have been much higher than in the non-participants. Therefore, we conclude that the bias had reduced the estimated mortality reduction; the real effect must have been larger.
In a study on the survival of breast cancer patients, Satariano and Ragland (1994) found that women with severe co-morbid conditions did not have a survival advantage because of early diagnosis. Death from other causes than breast cancer was the reason for this observation. We studied the overall survival rate from the date of invitation to round 3 (1979–1980) in women aged 65–66 years at this invitation, who had participated in round 2 (Kaplan-Meier method). Figure 2 shows that the women who participated in round 3 (n = 720) had a far higher survival rate than those who did not (n = 198). Obviously, the participants had fewer co-morbid diseases or they were less severe. This means that the participants were at risk of dying from breast cancer for a longer period. Moreover, we conclude that the women who chose to continue to participate in the screening are those who may benefit from a survival advantage because of early diagnosis.

Classification of the cause of death of deceased breast cancer patients is difficult. Especially in elderly women, some degree of misclassification is unavoidable because of the presence of co-morbid conditions, including other malignancies. In many patients, the origin of newly diagnosed metastases was not confirmed histologically. Autopsy had been performed in 11% of the deceased patients only. This means that a new malignancy, for example of the lung, may have been misdiagnosed as a metastasis originating from the breast cancer (Langer et al., 1993). To avoid different misclassification for screened and unscreened patients, the classification procedure was blinded for screening history. Misclassification that occurs independently of the screening history may have reduced the estimated mortality reduction.

CONCLUSIONS

We conclude that continuing breast cancer screening after the age of 65 years, at least up to 75 years, will lead to a reduction in breast cancer mortality in elderly women. No effect of screening after 75 years was found, but only 8% of these women had participated regularly. However, the extent of harmful side effects of breast cancer screening increases with increasing age. Because the overall death rate is higher, some screen-detected patients may even die before the tumor would have become detectable clinically. The magnitude of both the effects and the side effects of continued mammographic screening after 65 years of age need to be evaluated. As a reduction in breast cancer mortality of 45% can be achieved in women over age 65 years, it seems unfair to exclude these women from national screening programs. A policy of screening elderly women free of charge if they request it, as is the case in the United Kingdom, seems preferable to excluding them totally.

ACKNOWLEDGEMENTS

This study was supported financially by the Dutch Health Insurance Fonds Council “Ziekenfondsraad”. We thank Mr. J.D.M. Otten and Mr. E.P. Brummelkamp for gathering and processing the data, Ms. M.E. Eijgenbergen for producing the figures, Mrs. J. Abma-Hill for her linguistic comments, the Carcinoma Workgroup Arnhem for gathering the Arnhem data, and the Nijmegen and Arnhem general practitioners and the local authorities for their cooperation.

REFERENCES


This study was supported financially by the Dutch Health Insurance Fonds Council “Ziekenfondsraad”. We thank Mr. J.D.M. Otten and Mr. E.P. Brummelkamp for gathering and processing the data, Ms. M.E. Eijgenbergen for producing the figures, Mrs. J. Abma-Hill for her linguistic comments, the Carcinoma Workgroup Arnhem for gathering the Arnhem data, and the Nijmegen and Arnhem general practitioners and the local authorities for their cooperation.


