Research Article

Mammography Screening and Risk of Breast Cancer Death: A Population-Based Case–Control Study

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Abstract

Background: Because the efficacy of mammography screening had been shown in randomized controlled trials, the focus has turned on its effectiveness within the daily practice. Using individual data of women invited to screening, we conducted a case–control study to assess the effectiveness of the Dutch population–based program of mammography screening.

Methods: Cases were women who died from breast cancer between 1995 and 2003 and were closely matched to five controls on year of birth, year of first invitation, and number of invitations before case's diagnosis. ORs and 95% confidence intervals (CI) for the association between attending either of three screening examinations prior to diagnosis and the risk of breast cancer death were calculated using conditional logistic regression and corrected for self-selection bias.

Results: We included 755 cases and 3,739 matched controls. Among the cases, 29.8% was screen-detected, 34.3% interval-detected, and 35.9% never-screened. About 29.5% of the never-screened cases had stage IV tumor compared with 5.3% of the screen-detected and 15.1% of the interval-detected cases. The OR (95% CIs), all ages (49–75 years), was 0.51 (0.40–0.66) and for the age groups 50–69, 50–75, and 70–75 years were 0.61 (0.47–0.79), 0.52 (CI 0.41–0.67), and 0.16 (0.09–0.29), respectively.

Conclusion: The study provides evidence for a beneficial effect of early detection by mammography screening in reducing the risk of breast cancer death among women invited to and who attended the screening.

Impact: This is the first case–control study that accurately accounts for equal screening opportunity for both cases and matched controls by number of invitations before case's diagnosis. *Cancer Epidemiol Biomarkers Prev; 21(1); 66–73. ©2011 AACR.*

Introduction

Because the efficacy of mammography screening had been shown in randomized controlled trials (1, 2), the focus has turned on its effectiveness within the daily practice. Using aggregated data obtained from cancer and causes of death registries, the observed reduction of breast cancer mortality is as high as that observed in the randomized trials (3), depending on the follow-up time. Nevertheless, the effect of being invited to and actually attending mammography screening within a service pro-gram requires individual data on screening history, breast cancer diagnosis, and cause of death. As a consequence, case–control study design is increasingly used, showing reductions in the risk of breast cancer death varying between 32% and 48% in the evaluation of organized mammography screening programs (4–9).

In the Netherlands, the nationwide screening program was gradually implemented from 1989 to 1997 for women aged 50–69 years. As of 1998, the upper age limit was extended to 75 years (10), currently the only program screening up to this age. The recall rate (i.e., the rate at which screened women are recalled for further diagnostic work-up) in this program is consistently between 1% and 2% (11), lower than other organized population-based programs (12–14). Correcting for the gradual implementation, we showed that the downward trend in breast cancer mortality rates in the Netherlands was directly related to the initiation of the screening program (15). However, in this trend analysis, we were unable to isolate breast cancer deaths arising from diagnosis before the introduction of screening or before the first invitation to screening within the context of the national organized program.

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In this article, we report the results of the case–control study conducted in the Southwest region of the Netherlands to assess the effectiveness of mammography screening in reducing the risk of breast cancer mortality among women who had received at least one invitation to mammography screening.

Methods

Setting and source population

The background, implementation, and organization of the Dutch mammography screening program had been described in detail before (10). The program is carried out by regional screening organizations that personally invite all female residents in the targeted age range by mail for an appointment at a fixed date and time in a (mobile) screening unit. For this study, we used data of all women who were invited in the period 1990 to 2003 in the Southwest region of the Netherlands, who did not object to registration or exchange of their records, and were either still alive or died of any cause between 1995 and 2003. The Southwest is one of the largest screening regions, where the screening program was gradually implemented between 1990 and 1996. Between 1990 and 2003, 1.3 million invitations to screening were sent with an attendance rate of 76% (nationally 9.9 million and 79%; ref. 16). Of the women screened, 13.2 per 1,000 were referred for further diagnostic work-up (recall rate, 1.32%), yielding a detection rate of 5.1 per 1,000 (recall rate, 1.13% and detection rate, 4.8 per 1,000 nationally). The study was approved by the National Supervisory Committee of Population Cancer Screening Registry.

We had access to the data of 375,068 women. Records of 4,872 women were excluded because of unknown date of birth ($n = 200$), missing screening status ($n = 91$), breast cancer diagnosed before the first screening invitation ($n = 4,577$), and died before first screening invitation ($n = 4$). After linkage with cause of death registry and cancer registry, another 108 records of deceased women whose cause of death was unknown were also excluded (0.6% of all deceased women). Among the women without breast cancer in the source population, 319 were further excluded as they were found to have died from breast cancer ($n = 281$ underlying cause or $n = 38$ contributory cause), whereas no date of diagnosis was registered at the cancer registry. About 78.1% of these women never responded to an invitation for screening, which suggests that either the breast cancer was diagnosed before the start of the cancer registry in the Netherlands (1989) or was diagnosed in a region that is not covered by the Comprehensive Cancer Center Rotterdam and thus were not registered in this database. The final source population from which the cases and controls were selected consisted of 369,769 women (Fig. 1).

Of each eligible women, we had the date of birth, date of screening invitations, date of screening examinations, screening status coded by attendance or nonparticipation, and the date of death, if applicable. Data on breast cancer diagnosis, tumor stage according to the tumor node metastasis (TNM) classification of malignant tumors, and primary treatment were obtained from the Comprehensive Cancer Center Rotterdam. Causes of death were obtained through linkage with Statistics Netherlands. Death certificates of the cases were not reviewed; however, we do not assume a systematic misclassification of the cause of death but cannot exclude that this might have happened in some cases. In the Netherlands, all causes of death are classified and coded by coders of Statistics Netherlands based on clinical information they get from the treating physician, which usually contains no information on the method of detection or diagnosis of a disease. Furthermore, treating physicians are not involved in the breast cancer screening program, so that a specific interest in favor or against mammography screening does not play a role. Harteloh and colleagues reported the coding of breast cancer as the underlying cause of death by Statistics Netherlands to be reliable in 95% of the investigated cases (17).

Definition of index invitation, index period, and screening exposure

The index date is the date of the most recent invitation to mammography screening that preceded the breast cancer diagnosis of the case subject. This invitation to screening is subsequently referred to as the index invitation (8). For cases with screen-detected cancer, this was the invitation to the screening examination at which the breast cancer was detected. For cases with interval cancer and cases that did not attend screening, this was the invitation that preceded their symptomatic diagnosis. An index period was defined as the time period (exposure window) from the index invitation backward to a maximum of two invitations prior to this index invitation. This implies that the total number of invitations in this index period varied between 1 and 3 per case–control set.

Screening is defined as attending the mammography examination after receipt of an invitation to screening sent by the screening organization. Each invitation has a code whether the invitee had attended screening (attendance with the date of the screening) or not (nonparticipation). The screening status (attendance or nonparticipation) of the index and all preceding invitations was traced back for each member of the case–control set. Invitations of the controls after the index invitation were excluded from analyses. Mammograms taken out of the context of the screening program, for example, for diagnostic work-up, are not registered in the databases of the screening organization.

Selection of cases and controls

Cases were women diagnosed with breast cancer and who died of the disease between 1995 and 2003. Each case was matched to 5 controls on the basis of year of birth. Controls were women who were still alive at the date of death of the case and were breast cancer free at the date of breast cancer diagnosis of the case. To ensure that both case and matched controls had the same opportunity to
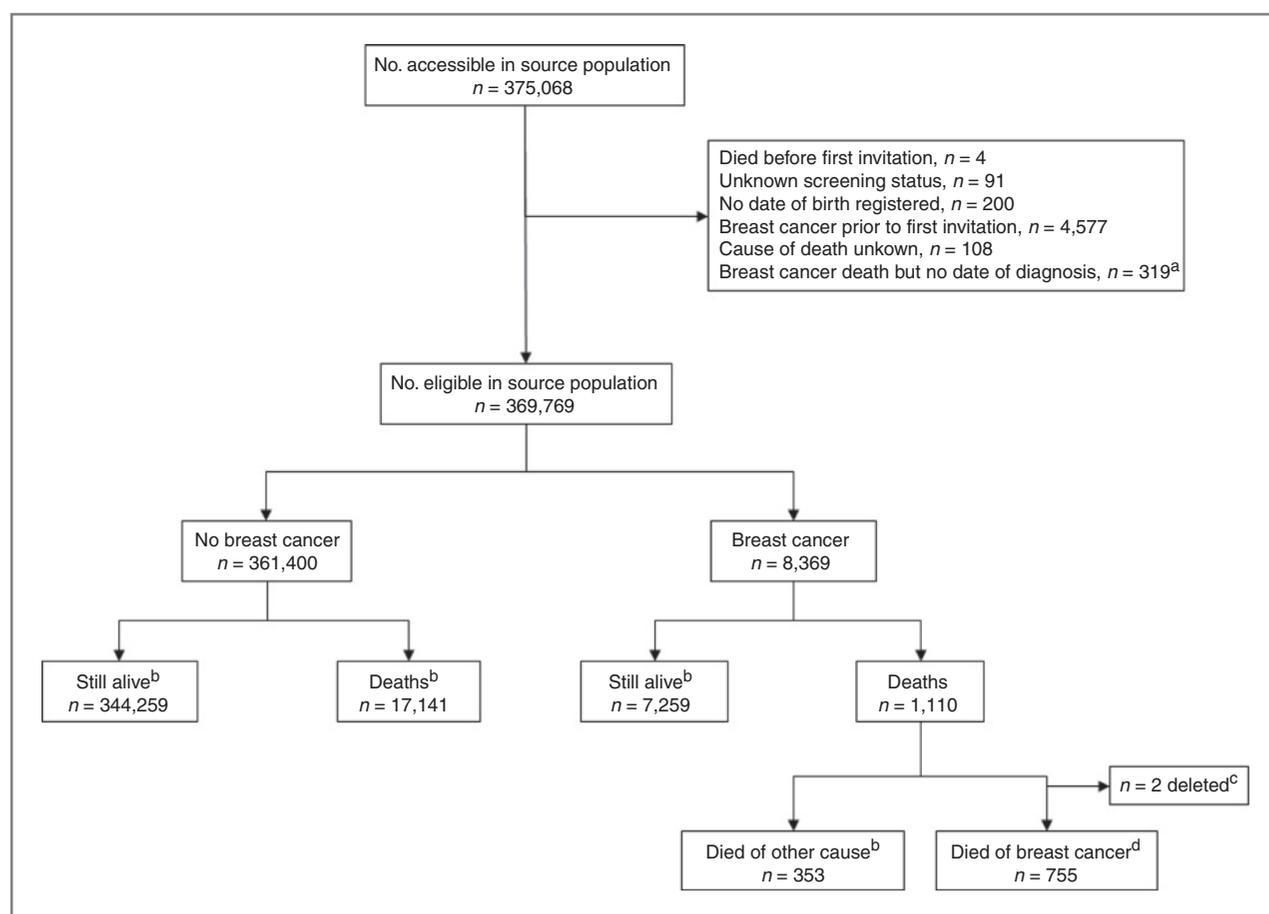
Figure 1. Overview of the number of women eligible for selection of case and control subjects. [a]Died of breast cancer as underlying or contributory cause, but date of diagnosis is unknown. [b]Eligible for selection as control subjects. [c]$n = 2$ excluded as the interval between the date of last invitation to screening and the date of breast cancer diagnosis was longer than the mean interval in the national program of 2.5 years. [d]Eligible for selection as case subjects.

undergo a screening examination following the receipt of an invitation (18), cases and their matched controls should have received their first invitation in the same calendar year, at same age, and same number of invitations including the index invitation. In an organized program where women receive their invitation to screening at fixed interval and with fixed screening appointments, the controls matched to a screen-detected case may not have had the opportunity to be screened yet before the screen-detected case subject was diagnosed (18, 19).

Statistical analysis

The association between attending screening and the risk of death from breast cancer was estimated by ORs with 95% confidence intervals (CI) using the conditional logistic regression, retaining the matching variables described above (STATA version 9.2, StataCorp). We calculated the ORs of attending screening as a result of the index invitation and of attending screening in the index period for all ages (49–75) and the age groups 50–75 years (current target population), 50–69 years (age group initially invited for screening), 70–75 years (age

group with which the initial upper age limit was expanded), and 55–74 years (age group used in the annual evaluation of trends in the breast cancer mortality).

As women attending screening might differ from those not participating with regard to the risk of developing and dying of breast cancer, the ORs were corrected for a possible self-selection bias, using the method of Duffy and colleagues (20),

$$\text{corrected OR} = \frac{p\,\psi\,D_r}{1 - (1 - p)D_r}.$$

where p is the attendance rate, ψ the estimated OR, and D_r is the correction factor for self-selection, which is calculated as the relative risk of death from breast cancer among nonparticipants compared with uninvited women. The mortality rate among uninvited women was estimated using data on age-specific breast cancer deaths in 1986 to 1989 of Statistics Netherlands, before start of the screening program and the mortality rate among nonparticipants were estimated from data of women invited but never screened in current study. The attendance rate, 75.1%, was derived from the attendance

Table 1. T-stage distribution and initial therapy among women with breast cancer in the source population

	Still alive ($N = 7{,}259$), %	Died of breast cancer ($N = 757$), %	Died of other cause ($N = 353$), %
pT-stage			
Tis	11.2	1.6	7.4
T1	55.9	28.6	47.9
$T2^+$	28.4	47.5	31.7
TX/Unknown	4.5	22.3	13.0
Therapy			
Surgery	95.0	73.2	85.6
Non-surgery	2.8	23.2	7.9
Unknown	2.2	3.6	6.5
Never screened	12.9	35.9	24.6

Abbreviation: pT-stage, pathologic T-stage.

among the 369,769 women in the study population. The D_r was estimated at 1.11 (95% CI, 0.99–1.25).

Results

There were 8,369 women with breast cancer diagnosed in the source population of whom 1,110 have died. Of these, 757 died of breast cancer and were potential cases. As shown in Table 1, these women had the highest proportion of $T2^+$ cancer (47.5%) than those women with breast cancer who were still alive (28.4%) and those who died of other causes (31.7%). Nonsurgical therapy was also often applied in this group who died of breast cancer (23.2% vs. 2.8% and 7.9%).

Of the 757 potential cases, 2 women were excluded, as the interval between the date of last invitation to screening and the date of breast cancer diagnosis was longer than the mean interval of 24.5 months in the national screening program (6.5 and 4.2 years, respectively), which hampered the selection of controls. We included 755 cases and 3,739 controls. The mean age at first invitation to screening and at index invitation was same in the 2 groups, 58.3 years (49–75) and 60.3 years (49–75), respectively. Mean age at diagnosis in the case group was 61.5 years (49–78). Among the cases, 29.8% were diagnosed as a result of a screening examination, either initial or subsequent (screen-detected cancer) and 34.3% between screening rounds (interval cancer). The remaining 35.9% was women who never responded to any invitation to screening. Among the controls, 18.1% had never responded to an invitation. For 46.1% of the cases ($n = 348$), the index invitation was the first and only invitation before their breast cancer diagnosis.

Table 2 shows the distribution of the tumor stage and initial treatment of the cases by method of detection. Of the cases, 17.6% were detected at a localized stage, which was particularly high among those with a screen-detected tumor (34.2% vs. 10.8% and 10.3%

among those with an interval cancer and nonparticipants). A similar proportion, 17.4%, was detected with distant tumors, which was more common among women who were never screened (29.5%) than women with screen-detected (5.3%) or interval cancers (15.1%; Table 2). The treatment patterns showed high proportion of surgery 73.4%, which was the treatment of preference in the women who attended screening (92.4% screen-detected and 77.6% interval cancer) than in nonparticipants (53.5%), among whom chemotherapy and hormonal therapy were more frequently applied (38.0% vs. 4.5% and 18.5%, respectively).

Table 3 presents the ORs for the risk of breast cancer death for the matched case–control sets. About 63.2% (477 of 755) of the cases were screened within the index period and 58.4% (441 of 755) upon their invitation to screening prior to the breast cancer diagnosis. For the controls, these figures were 77.4% (2,893 of 3,739) and 72.9% (2,727 of 3,739), respectively. The ORs corresponding with screening within the index period and screening following the index invitation yielded an estimate of 0.45 (95% CI, 0.37–0.54) and 0.48 (95% CI, 0.41–0.58), respectively. Corrected for self-selection bias, the ORs still indicated a significant association between mammography screening and risk of breast cancer death, that is, OR of 0.51 (95% CI, 0.40–0.66) for attending screening in the index period and OR of 0.56 (95% CI, 0.44–0.71) for responding to the index invitation.

As inclusion of breast cancer diagnosis and deaths arising in the early years of screening could have an influence on the estimated impact of screening, we restricted the analysis to only the cases and their matched controls who were invited for the first time after 1994 ($n = 405$ case–control sets). The ORs corrected for self-selection were 0.36 (95% CI, 0.27–0.49) and 0.35 (95% CI, 0.26–0.46), respectively.

Table 4 shows the results for the different age groups by age at index invitation. The corrected OR estimates of the current target age group, 50–75 years, showed a benefit of screening of 43% upon index invitation and of 48% when

Table 2. Distribution of the breast cancer stage at diagnosis and primary treatment of the case subjects

	All cases (n = 755)	Screen-detected cases (n = 225, 29.8%)	Interval cases (n = 259, 34.3%)	Nonparticipant cases[a] (n = 271, 35.9%)
	n (%)	%	%	%
Stage[b]				
0–I	133 (17.6)	34.2	10.8	10.3
IIA	189 (25.0)	32.4	29.0	15.1
IIB	178 (23.6)	20.4	29.7	20.3
IIIA	36 (4.8)	2.2	6.2	5.5
IIIB	61 (8.1)	1.8	5.8	15.5
IV	131 (17.4)	5.3	15.1	29.5
Unknown	27 (3.6)	3.6	3.5	3.7
Therapy				
Breast-conserving surgery	221 (29.3)	45.3	27.0	18.1
Mastectomy	333 (44.1)	47.1	50.6	35.4
Primary radiotherapy	2 (0.3)	0	0.4	0.4
Chemotherapy	103 (13.6)	3.6	13.9	21.8
Hormonal therapy	58 (7.7)	0.9	4.6	16.2
Other/unknown[c]	38 (5.0)	3.1	3.5	8.1

[a]Cancer detection in women who never attended screening.
[b]Stage based on pathologic TNM classification; in case of missing, clinical TNM staging was used instead.
[c]Other includes metastasectomy and palliation.

the screening status within the index period was considered. Narrowing the age group to 55–74 years showed larger effects of screening in reducing the risk of dying from breast cancer. High benefit of screening was observed among women aged 70–75 years, likely attributed to a long-term effect of screening participation in the age group 50–69 years. The ORs by age at first invitation were comparable with those for age at index invitation (data not shown).

Discussion

We have found that mammography screening is associated with a decreased risk of dying from breast cancer.

Table 3. ORs of the association between breast cancer death and attending screening

	Cases, n	Controls, n	OR (95% CI)	OR (95% CI) corrected for self-selection[a]
Index invitation				
1990–2003				
Not screened	314	1,012		
Screened	441	2,727	0.48 (0.41–0.58)	0.56 (0.44–0.71)
1995–2003				
Not screened	201	503		
Screened	204	1,516	0.30 (0.24–0.38)	0.35 (0.26–0.46)
Index period				
1990–2003				
Not screened	278	846		
Screened	477	2,893	0.45 (0.37–0.54)	0.51 (0.40–0.66)
1995–2003				
Not screened	182	461		
Screened	223	1,558	0.31 (0.25–0.40)	0.36 (0.27–0.49)

NOTE: CI calculated using conditional logistic regression.
[a]Self-selection bias factor: 1.11.

Table 4. ORs of the association between breast cancer death and attending screening by category of age at index invitation

Age group	Number of cases/controls	Index invitation		Index period	
		OR (95% CI)	OR (95% CI) corrected for self-selection[a]	OR (95% CI)	OR (95% CI) corrected for self-selection[a]
50–69	653/3,239	0.58 (0.48–0.70)	0.67 (0.52–0.86)	0.53 (0.43–0.64)	0.61 (0.47–0.79)
50–75	728/3,606	0.49 (0.41–0.58)	0.57 (0.44–0.72)	0.45 (0.37–0.54)	0.52 (0.41–0.67)
55–74	547/2,702	0.46 (0.38–0.57)	0.53 (0.41–0.69)	0.41 (0.33–0.51)	0.47 (0.36–0.62)
70–75	77/375	0.13 (0.07–0.23)	0.15 (0.08–0.27)	0.14 (0.08–0.25)	0.16 (0.09–0.29)

NOTE: CI calculated using conditional logistic regression.
[a]Self-selection bias factor: 1.11.

We observed a 49% reduction in the breast cancer mortality for attending either of 3 screening examinations prior to diagnosis, providing evidence that the long-standing mammography screening in the Netherlands is effective in reducing the risk of breast cancer death upon attending the mammography examination after receipt of the invitation to screening. This confirms our earlier finding of a relationship between the initiation of screening and the annual decrease in the trend of breast cancer mortality (15).

Our present finding is consistent with the outcomes of recent case–control studies of organized population-based mammography screening programs in Europe (5, 6) and Australia (7), with different performance indicators than seen in the Dutch program (12–14). While the Dutch program knows participation rates around 80% with recall rates consistently between 1% and 2% (11), comparable participation rates accompanied by higher recall rates, ranging from 2.1 to 18.4 for initial and 1.8 to 17.5 for subsequent screenings were seen in these programs (12–14). In the period that our study was conducted, recall rates of 5.1% (21), 4.0% (22), and 5.8% (23) were reported for screening examinations in England, Australia, and Italy, respectively, compared with 1.3% in the Netherlands (1.5% in the Southwest region), where recall has been increasing from 0.84% in 1996. Nevertheless, the risk reduction in breast cancer mortality by 49% we found in our study is of the same magnitude as estimated in these programs. Puliti and colleagues (6) showed that service screening reduced the probability of breast cancer death with 45% among women invited for screening in 17 areas in central and northern Italy. Evaluation of the National Health Service (NHS) breast cancer screening program in the East Anglian region (United Kingdom) showed a 48% reduction in the risk of breast cancer death (5) comparable with the estimate of 41% reduction for BreastScreen South Australia (7).

Modeling techniques have shown that both screening and advancement in treatment contributed to the fall observed in breast cancer mortality rate (24, 25). We were not able to disentangle the contribution of treatment. We observed that women with breast cancer who died of the disease less often underwent surgery compared with those still alive, which is likely according to their advanced stage at diagnosis as emphasized by the high proportion of surgery among the screen-detected cases. It has been shown that method of detection and not the difference in therapy is an important prognostic factor for breast cancer, even after adjusting for known tumor characteristics (26).

The case–control design has raised a lot of skepticism on its ability to evaluate the impact of screening activities. Case–control study design on cancer screening requires sophisticated selection procedures to identify all eligible cases within a source population, to select cases and matched controls according to eligibility criteria that ensure equal access to screening during the exposure period, and to distinguish between screening and diagnostic work-up (19). The major strength of our study is that it was designed to correct for the aforementioned drawbacks. We included a large number of case and control subjects that were derived from the same and well-defined cohort of women invited by the screening organization in the Southwest Netherlands. The adopted selection criteria enabled equal opportunity of exposure to screening for both cases and controls, as matching was not only based on year of birth and index invitation but also on the year of first invitation, same age, and number of invitations up to and including the index invitation. The screening histories for all women ever invited for a mammographic screening examination were systematically retrieved from the same database. Thus, any difference in screening history between cases and their matched controls would be attributed to different rates of acceptance of the screening and not due to differential misclassification of the screening exposure status, which can affect the estimates of a case–control study as shown before when the screening exposure was measured by medical chart review (27).

Large effects were observed among women aged 70–75 years. As aforementioned, the target age group

of 50–69 years was broadened to 50–75 years in 1998, so that the current finding for the age group 70–75 years probably might be attributable to a long-term beneficial effect of screening participation in the former target age group. About 45% of the controls were screened more than once in the index period (18% of the cases). Several other case–control studies found that the effect of screening on the risk of breast cancer mortality increases with the number of screens (4, 28, 29). Further analysis showed that the majority of the reduction observed is particularly due to nonattendance of screening examination among those who received their first invitation between age 70 and 75 years: 19% (27 of 141) of the controls never attended screening compared with 82% of the cases (23 of 28). In contrast, the women who were 70–75 at the index invitation but received their first invitation at the age group 50–69 (the former target age group), 11% of the controls (25 of 234) were never screened compared with 37% of the cases (18 of 49).

The most potential limitation of current study is self-selection bias. We had limited information on breast cancer mortality among uninvited women in the Southwest region to estimate the correction factor, as access to data of uninvited women is restricted by Dutch privacy rules. We were, therefore, not able to quantify the breast cancer mortality rate among uninvited women in the Southwest region for which we used national data for the period 1986 to 1989 instead. Our estimated correction factor of 1.11 (95% CI, 0.99–1.25) for the Southwest region was comparable with the estimate reported by Puliti and colleagues (6), 1.11 (95% CI, 0.87–1.40) but higher than that recently applied for the South Dutch region, 0.84 (95% CI, 0.58–1.21; ref. 30) and suggests higher risk of breast cancer among nonparticipants in the Southwest region. The issue of analysis by stratification on risk has been addressed earlier by Elmore and colleagues (27). Such analysis would probably overcome the aspect of differences in breast cancer risk, however, is limited as information on risk factors are not recorded in the screening database and as recently shown by Van Schoor and colleagues (31), adjusting for the confounding effect of risk factors, beside age, does not have a great effect on these estimates of the impact of screening on breast cancer mortality.

Death certificates of the cases could not be reviewed because privacy regulations only allow for the use of anonymous data of nonparticipants. However, the lack of death certificate review only has an effect on the overall interpretation of the study outcome, if deceased nonscreened patients with breast cancer have a different chance to be classified as dead because of breast cancer than deceased women with screen-detected breast cancer (32). For the organized mammography screening programs in Italy, Goldoni and colleagues (33) showed that the misclassification of cause of death for breast cancer cases was not affected by modality of breast cancer diagnosis (screen-detected or not). The misclassification rates between deceased women with screen-detected (4.7%) and women with symptomatically detected (4.3%) breast cancers were comparable.

Another possible limitation is opportunistic mammography screening which is not registered in databases of the screening organizations. In our current study, we only included women who had ever received an invitation to the screening program. It is quite possible that some had opportunistic screenings before their first invitation, but this would account for both cases and controls. On the other hand, it may be argued that women with breast complaints would attend screening instead of directly seeking medical advice from their physician that would lead to inclusion of such cases. Previous study on false reassurance in the Dutch screening program showed this to be marginal, as only 3.8% of the women with a screen-detected cancer had previous symptoms (34).

In conclusion, we report on the findings of the largest Dutch case–control study on mammography screening and risk of breast cancer, which included closely matched case–control sets arising from same well-defined source population, with equal opportunity to screening for cases and their matched controls and accurate measurement of exposure to screening. The findings provide robust evidence on the beneficial effect of screening in reducing the risk of breast cancer mortality among women invited and participated in national mammography screening program in the Southwest region of the Netherlands.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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