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ORIGINAL PAPER

A remarkable reduction of breast cancer deaths in screened versus unscreened women: a case-referent study

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Abstract
Objective We designed a case-referent study to investigate the effect of mammographic screening at the individual level, looking at the association of breast cancer death with screening history.
Methods The study population included all women aged 50–75 in the province of Limburg, the Netherlands who had been invited to the screening program from 1989 to 2006. From this population, 118 cases originated who died of breast cancer in 2004 or 2005. The screening history of these cases was collected and compared with a sample of the invited population. The breast cancer death rate in the screened relative to the unscreened women was estimated as the odds ratio (OR). This OR was adjusted for self-selection bias, the difference in baseline risk for breast cancer death between screened and unscreened women.
Results Analysis of the data showed a breast cancer mortality reduction of 70% in the screened versus the unscreened women (OR = 0.30, 95% CI 0.14–0.63). The magnitude of self-selection was estimated specifically for Limburg. After correction for self-selection bias, the effect of screening increased to 76% (OR = 0.24, 95% CI 0.10–0.58).
Conclusion Screening resulted in a remarkable reduction in breast cancer mortality. Contrary to findings in other countries, adjustment for self-selection in Limburg had no influence on the impact of screening. Thanks to a well-organized centralized screening program, similar results are expected in other regions of the Netherlands.

Keywords Breast cancer · Service screening · Case-referent study

Introduction

Several randomized controlled trials conducted in the 1970s and 80s have shown a breast cancer mortality reduction of 25–30% in those offered mammographic screening [1]. As a consequence, many countries initiated a national or regional service screening program. In the Netherlands, a population-based program was set up in 1989 with a centralized organization, including centralized technical and medical quality control, and audit [2].

Since the introduction of service screening in the Netherlands, there has been a large decrease in breast cancer mortality. A trend study by Otten et al. [3] provided support for a time relation between the implementation of screening and its effect on breast cancer mortality. This mortality reduction was preceded by a significant decrease in advanced disease from 1995 onwards [4]. Although trend studies suggest that screening affects breast cancer mortality, they cannot show a direct link between screening performance and breast cancer death. Other factors like improvements in therapy could also be (partially) responsible for the decrease

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in mortality [5]. Therefore, individual data on screening history, diagnosis and breast cancer death should be analysed.

In the Dutch screening program, women aged 50–75 are invited for biennial mammography screening. During the performance of our study, one of the regions which organized breast cancer screening was the Comprehensive Cancer Centre Limburg (IKL). The IKL covers a large part of the province of Limburg with a female population of 450 000 representing 6% of the Dutch female population.

In this region, no study has yet estimated the relation of breast cancer death with screening history at an individual level. An efficient method for evaluating this relation is the case-referent study [6]. This design requires consideration of self-selection bias since women who accept the invitation to screening may have a different baseline risk for breast cancer death a priori than women who do not accept the invitation [7].

The aim of this study was to evaluate the association between service screening and breast cancer mortality in the province of Limburg using a case-referent design. We were able to adjust this effect for self-selection based on differences in baseline risks of breast cancer death by screening status in the female population of Limburg.

Methods

Study population

The study population included women aged 50–75 who received at least one invitation to the service screening program in the IKL-region. During our study, the IKL included both a cancer and a screening registry. The cancer registry collects data on all patients with breast cancer in the covered region. The screening registry holds individual data on invitation and participation for all women in the target population of the service screening program in the IKL-region.

We applied a case-referent design to evaluate the effect of current mammographic screening on breast cancer mortality. Cases originated from the study population and were defined as women who died from breast cancer in 2004 or 2005. The cause of death as reported in death certificates was obtained through linkage with Statistics Netherlands. Data collection for cases included date of death, date of diagnosis, date of birth and the complete screening history. For each case, one referent was sampled from the study population. The referent was matched for year of birth and area of residence. She had to be free of breast cancer at the moment she received the invitation to screening (index invitation) and had to be alive at time of death of the case. The complete screening history of each referent was also included in the database. The case and her matched referent formed a case-referent set.

Definition of exposure to screening

The screening history of cases and referents included their dates of invitation and the dates of their screening tests if they participated. Screening participation can only influence breast cancer death if the screening examination is performed in the period when the cancer is potentially detectable on the mammogram—in the detectable preclinical period (DPCP). Therefore, for each case, we set the opportunity to exposure to screening to be the most recent invitation date preceding the diagnosis, the index invitation [8]. In the case-referent set, the referent was also assigned an index invitation from the same screening round from which the index invitation of the case was selected. Both the case and the referent are classified as screened if they participated in the screening examination following their index invitation. For screen-detected cases, this was the screening examination at which the breast cancer was detected.

The exact duration of the DPCP varies for cases, but will probably not exceed four to six years, based on estimates of lead time for breast cancer diagnosis [8, 9]. Including only the index invitation to classify exposure to screening could lead to underestimation of the effect of screening [9]. In an additional analysis, we therefore expanded the opportunity for exposure to screening to the invitation preceding the index invitation.

Statistical analysis

The case-referent comparison relates screening participation at the index invitation to breast cancer death. The breast cancer death rate in the screened versus the unscreened women was assessed and represented as an odds ratio (OR). This was achieved by calculating the Mantel–Haenszel odds ratio and its 95% confidence interval by means of conditional logistic regression, taking into account, the matching for year of birth and area of residence. Matching the referent to the case leads to four possibilities for a case-referent set: the case and referent are both screened; the case is screened but the referent not; the case is not screened but the referent is; both the case and referent are not screened. The OR for a matched case-referent study only includes the discordant case-referent sets. The OR is calculated as the number of sets where the case is screened and the referent is not, divided by the number of sets where the case is not screened and the referent is [10].

Self-selection bias

In the evaluation of breast cancer screening, much attention has been paid to self-selection bias [11]. Participation in screening is based on a voluntary decision. Therefore, the baseline risk for breast cancer death could be different beforehand in the screened women compared to the unscreened women, for example due to differences in ethnicity, history of relatives with breast cancer, or socio-economic circumstances [12–14]. To correct for potential self-selection bias, we calculated a correction factor specifically for the IKL-region using the incidence-based mortality (IBM) method of Paci et al. [15]. To this end, we used data of women eligible for invitation to screening during the implementation period of the screening program (1990–1995). For this period, we calculated the IBM rate for women not yet invited to the screening program and for women invited, but not screened. The numerator of the IBM rates included breast cancer deaths of women diagnosed with breast cancer in the years 1990–1995. In total, 188 uninvited and 34 not screened breast cancer deaths were identified. The person years in the denominator were calculated with data on the number of invited, number of screened and the total female population in the years 1990–1995. The correction factor is the relative risk of breast cancer death for not screened versus not yet invited women [16]. For the IKL-region, the correction factor was 0.84 (95% CI: 0.58–1.21), indicating a lower baseline risk in women who do not attend screening. This factor was used in a formula developed by Duffy et al. to correct the estimated odds ratio for self-selection bias [16, 17].

Results

In total, 118 cases and 118 referents were selected in the IKL-region. The mean age at index invitation for the cases was 61.7 (range 49.4–75.3). Table 1 shows the number of case-referent sets according to their participation in screening following the index invitation. The breast cancer mortality reduction was 70% in screened women compared to unscreened women (OR = 0.30, 95% CI 0.14–0.63). As mentioned in the methods section, this odds ratio has to be corrected for self-selection bias. Table 2 shows the formula of Duffy et al.: $OR_{adjusted} = p\,\psi\,D_r/(1-(1-p)D_r)$, where p is the attendance rate for service screening in Limburg (82%), ψ the uncorrected odds ratio (0.30) and D_r the correction factor for self-selection bias (relative risk of breast cancer death; 0.84). This formula results in a mortality reduction of 76% (OR = 0.24, 95% CI 0.10–0.58) [16].

If we expanded the opportunity for exposure to screening to the invitation preceding the index invitation in the analysis, the achieved mortality reduction changed slightly from 70 to 73% (OR = 0.27, 95% CI: 0.12–0.62).

Table 1 Case-referent sets, their participation in the screening examination following their index invitation and the calculated odds ratios

	Number of case-referent sets
Case and referent both screened	69
Case screened, referent unscreened	9
Case unscreened, referent screened	30
Case and referent both unscreened	10
Total of case-referent sets	118
Odds ratio (95% CI)	0.30 (0.14–0.63)
Odds ratio adjusted for self-selection (95% CI)	0.24 (0.10–0.58)

Table 2 Effect of screening on breast cancer mortality: odds ratio adjusted for self-selection bias

Formula of Duffy	$p\,\psi\,D_r/(1-(1-p)D_r)$
Where	
ψ = unadjusted odds ratio (95% CI)	0.30 (0.14–0.63)
p = attendance rate of screening in Limburg	0.82
D_r = correction factor for self-selection in IKL-region (95% CI)	0.84 (0.58–1.21)
	0.82 × 0.30 × 0.84/(1–0.2 × 0.84)
OR adjusted for self-selection bias (95% CI)	= 0.24 (0.10–0.58)

Discussion

In this study, we report two important findings, namely a remarkable breast cancer mortality reduction of 70% in screened women compared to unscreened women, and continuation of this effect of screening after adjustment for self-selection bias. In other countries, estimates of the impact of service screening on breast cancer mortality showed reductions of 34–65%, however, with no adjustment for self-selection bias [18]. In view of these findings, our results indicate a higher impact of mammographic service screening on breast cancer mortality in the IKL-region.

A number of reasons for this remarkable effect of screening in the Netherlands can be put forward. It could result from the high-quality screening in a centrally organized program [2]. A second reason could be improvements due to progression in quality assurance and advancements in mammographic techniques. In addition, improvements in therapy could also have resulted in a larger combined effect of screening and therapy. Breast cancer screening can only reduce mortality if early diagnosis is followed by appropriate (early) treatment. For example, adjuvant systemic therapy was introduced and used on a large scale before the implementation of the screening program, which probably contributed considerably to the breast cancer mortality reduction [5].

The influence of self-selection in the province of Limburg was minor. After adjustment for self-selection, the mortality reduction in screened women changed from 70 to 76% compared to unscreened women. This is contrary to results obtained in other countries, where the impact of screening reduced after correction for self-selection (breast cancer mortality reductions of 34–65% before and 25–50% after adjustment for self-selection) [18].

In our study, we calculated a correction factor for self-selection specifically for the province of Limburg, indicating a lower baseline mortality risk in women not attending screening.

Recent case–control studies used a correction factor for self-selection based on data from randomized controlled trials in Sweden and Canada [7, 16, 17]. This correction factor was 1.36, indicating a higher baseline mortality risk in the unscreened women. Two other case–control studies also calculated their own correction factor, of 1.11 and 1.17 [19, 20]. These differences show that self-selection can differ in magnitude and direction between countries or regions. This demonstrates the importance of using a regional or national correction factor for self-selection, where possible. Factors which could be associated with lower breast cancer risk factors in unscreened women in Limburg are unclear, but could for example be due to a lower number of relatives with a history of breast cancer, to differences in socio-economic status, to ethnicity, or to screening outside the screening program in unscreened women [13, 14, 21–24]. Further research should explore the background of the lower baseline risk for breast cancer death in unscreened women in the IKL-region.

The primary analysis of the association included participation of the case and referent following the index invitation. The additional analysis including the invitation prior to the index invitation, resulted in a small change in the mortality reduction from 70 to 73%. This indicates that the underestimation of the DPCP is of minor impact in our study.

Because the region of the IKL is small, the number of cases and referents is quite low (118 case-referent sets). Despite this low number, the confidence interval has an acceptable range: from 0.14 to 0.63. This is also true for the calculation of the correction factor for self-selection. At this moment, more regions in the Netherlands are being included in a multi-region study to support our findings in the IKL-region. Thanks to the well-organized centralized and medically audited screening program, we expect similar results in these regions [2].

In conclusion, the service screening in Limburg resulted in a remarkable reduction of breast cancer mortality. This study includes a correction factor calculated specifically for this region using the incidence-based mortality method. Contrary to other countries, adjustment for self-selection had no influence on the impact of screening. Although disadvantages of screening exist, for example overdiagnosis [25, 26], the positive results from our study show a clear breast cancer mortality reduction, the ultimate benefit of breast cancer screening.

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Conflict of interest We declare that we have no conflicts of interest.

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