

Socioeconomic inequalities in attending the mass screening for breast cancer in the south of the Netherlands–associations with stage at diagnosis and survival

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HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés. Socioeconomic inequalities in attending the mass screening for breast cancer in the south of the Netherlands – associations with stage at diagnosis and survival

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Running title: Socioeconomic status and the participation in mass breast cancer screening

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Abstract

Purpose: The associations of socioeconomic status (SES) and participation in the breast cancer screening program, as well as consequences for stage of disease and prognosis were studied in the Netherlands, where no financial barriers for participating or health care use exist.

Methods: From 1998 to 2005 1,067,952 invitations for biennial mammography were sent to women aged 50-75 in the region covered by the Eindhoven Cancer Registry. Screening attendance rates according to SES were calculated. Tumor stage and survival were studied according to SES group for patients diagnosed with breast cancer between 1998 and 2006, whether screen-detected, interval carcinoma or not attended screening at all.

Results: Attendance rates were rather high: 79%, 85% and 87% in women with low, intermediate and high SES (p<0.001). Compared to the low SES group, odds ratios for attendance were 1.5 (95%CI:1.5-1.6) for the intermediate SES group and 1.8 (95%CI:1.7-1.8) for the high SES group. Moreover, women with low SES had an unfavorable TNM stage compared to those with high SES. This was seen in non-attendees, among women with interval cancers and with screen-detected cancers. Among non-attendees and interval cancers the socioeconomic survival disparities were largely explained by stage distribution (48% and 35%) and to a lesser degree by therapy (16% and 16%). Comorbidity explained most survival inequalities among screen-detected patients (23%).

Conclusions: Despite the absence of financial barriers for participation in the Dutch mass screening program, socioeconomic inequalities in attendance rates remain present, and women with low SES had a significantly worse tumor stage and lower survival rate.

Keywords: breast cancer; mass screening; socioeconomic factors; participation; stage at diagnosis; survival

Introduction

Breast cancer screening programs aim to reduce breast cancer mortality rates through early cancer detection. To optimize the effectiveness of the current screening programs it is especially important to reach women at high risk of advanced stage disease at diagnosis and concomitant lower survival rates.

In many countries, the proportion of women having a screening mammogram has been highest among those with high socioeconomic status (SES), independent of the presence of organized breast screening programs [1-4]. For example, between 2000 and 2005, in the U.S. 65% of women aged 40 years or older with a low income had a screening mammogram within the previous two years compared to 83% of women with a high income [1].

Patients with low SES have a more advanced stage distribution than those with high SES [5-7], which may be due to their lower screening attendance. Furthermore, breast cancer survival rates are highest among patients with high SES [8-11]. Conflicting reports exist as to whether socioeconomic differences in breast cancer survival are due to socioeconomic differences in stage distribution [12-14]. The presence of concomitant diseases may also partly explain a SES gradient in breast cancer survival [15].

Socioeconomic inequalities in adherence to mammography screening have been found in several countries [1-4]. For the Netherlands, a country with equal access to screening and care for all women, these data are lacking. We hypothesized that Dutch women with low SES also show lower screening attendance rates, more advanced stage breast cancers and worse survival. Therefore, we conducted a regional study on SES and screening attendance and we explored the consequences of socioeconomic differences in attendance rate for the stage distribution at diagnosis and survival.

Materials and Methods

The population-based screening program for breast cancer in southern Netherlands (Bevolkings Onderzoek Borstkanker Zuid, BoBZ) was started in 1991 and fully implemented in 1996. The program initially offered biennial screening mammography to women aged 50-69 years; in 1998 the upper age limit was extended to 75. The attendance rate was more than 84% [16]. The BoBZ database was used to select all women invited for screening from 1998 to 2005. These women received an invitation letter approximately 2 weeks before the screening. Reminder letters with a new appointment were sent to women who did not appear.

The Eindhoven Cancer Registry (ECR) records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with currently 2.4 million inhabitants (about 15% of the Dutch population) and only non-university hospitals. Trained registry personnel actively collects data on diagnosis, staging (Tumor-Node-Metastasis [17]), treatment and comorbidity (slightly adapted from Charlson [18]) from the medical records after notification by pathologists and medical registration offices. Previous admissions, letters from and to general practitioners and other specialists, medical history and preoperative screening were used as sources. Pathological and clinical TNM were combined into one variable, primarily referring to the pathological stage unless missing.

The regions of the BoBZ and ECR cover an area of approximately 2.2 million inhabitants. Linkage of the databases of BoBZ and the ECR enabled us to compare stage at diagnosis of patients who attended with those who did not attend screening in the two years preceding diagnosis. Only invasive breast cancers and ductal carcinoma *in situ* (DCIS) were included. Screen-detected breast cancers were defined as registry-ascertained cancers if breast cancer had been diagnosed within 1 year following positive screening mammography (i.e., a woman had been referred for evaluation of a screening abnormality). Interval cancers were registry-ascertained cancers if 1) breast cancer had been diagnosed within 24 months following a negative screen (i.e., a woman had not been referred after screening mammography); or 2) breast cancer had been diagnosed 12-24 months after a positive screen. Patients with breast cancer diagnosed more than 2 years after screening mammography were considered to have not attended the screening program.

Statistics Netherlands developed an indicator of SES, using individual fiscal data based on the economic value of the home and household income. This SES indicator is provided at an aggregated level for each postal code (covering an average of 17 households). SES was categorized as low (deciles 1-3), medium (deciles 4-7), or high (deciles 8-10). A separate class was used for postal codes in areas comprising a long-term care providing institution (such as a nursing home) [19].

Statistics

Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). All tests were two-sided and considered significant if $p \le 0.05$. The distribution of sociodemographic and

clinical characteristics were studied across the SES strata. Significance was tested with non-parametric tests (continuous variables) and χ^2 -tests (categorical variables). Attendance rates according to SES were computed according to year of invitation and age category. Stage comparisons were based on invasive and non-invasive tumors. Survival analyses were based on invasive cancers only. Survival time was defined as the time from diagnosis to death or January 1st, 2009 for the patients who were still alive. Survival analyses were stratified into 1) screen-detected cancers, 2) interval cancers 3) patients who did not attend the screening program.

Univariate SES differences in survival were evaluated with the log rank test. The crude survival was calculated with the life test method and the independent prognostic effect of SES was estimated using Cox regression analyses. The hazard rates for death were adjusted for age (51≤60 versus ≤50, $61 \le 70$, $71 \le 75$ or ≥ 76). Subsequently we added the mediators stage (stages I versus II, III, IV or unknown) and therapy (surgery+radiotherapy versus surgery+radiotherapy+systemic therapy, surgery alone, surgery+systemic therapy or systemic therapy alone/other therapy/unknown), and the confounder comorbidity (no versus yes or unknown), and the combination of these to investigate whether the effect of SES on prognosis could be explained by differences in stage, treatment or comorbidity. Hazard ratios (HR) with 95% confidence intervals were reported. The relative contributions of comorbidity, treatment or stage were calculated with the formula: (((HR model adjusted for age) - (HR model adjusted for age +comorbidity or stage or treatment))/(HR model adjusted for age - 1))*100.

Results

Attendance rates

From 1998 to 2005, the BoBZ sent 1,112,263 invitations for breast examination to women living in the area covered by the ECR. Those with unknown SES (11,166) and those living at a postal code that includes an institution, such as nursing homes or rehabilitation centers, (33,145) were excluded, leaving data of 1,067,952 invitations to be analyzed (Figure 1, Table 1).

Attendance rates showed a positive correlation with increasing SES and were respectively 79%, 85% and 87% for women with low, intermediate or high SES (p<0.001). Among screening attendees, the first screening mammography was made for 12%, 14% and 15% of low, intermediate and high SES. During the study period, attendance increased slightly from 77%, 84% and 86% to 80%, 87% and 88% for low, intermediate and high SES (Figure 2). The socioeconomic inequalities in screening attendance

was significant in all years and in all age categories (p<0.001). Among non-attendees, women with high SES more often informed the screening organization about their refusal (54%) than women with low SES (38%). The most common reason for not attending the screening was "having a self-reported medical condition related to the breast."

After adjustment for age and year of invitation, an odds ratio (OR) for attending breast screening of 1.75 (95% confidence interval: 1.7-1.8) was found if comparing women with high SES to women with low SES, whereas women with intermediate SES had an OR of 1.54 (95% CI: 1.5-1.6, Table 1). The odds of attending the screening increased from the age of 50 until 70 and with each year of invitation.

Stage at diagnosis

From 1998 to 2006 6,086 women eligible for screening were diagnosed with invasive breast cancer or DCIS in the overlapping regions of the BoBZ and IKZ. After exclusion of patients with non-carcinoma (N=22: 3 benign neoplasms NOS; 1 leiomyosarcoma NOS; 2 carcinosarcomas NOS; 2 malignant myoepitheliomas; 12 phyllodes tumours; 2 hemangiosarcomas), data on 6,064 patients could be analyzed (Figure 1).

Among patients with screen-detected cancer, those with high SES had slightly more *in situ* tumors and less stage 1 tumors (17% versus 12% *in situ* and 56% versus 52% stage 1, p<0.01, Figure 3). For patients with interval cancer, stage 4 disease was significantly less common in the high SES group compared to the low SES group (2% versus 8%, p<0.05). Within the SES groups of both screen-detected and interval cancers, no differences were observed in stage distribution between tumors detected by the initial screening mammogram versus those detected by subsequent mammograms (data not shown). Among non-attendees, stage 4 cancers were found in respectively 10% and 5% of women with low SES or high SES (p<0.01). No significant differences in stage distribution were found for low versus intermediate and intermediate versus high SES in non-attenders.

In low stages of disease treatment differences were present. In stage 1, high SES patients more often received radiotherapy in addition to surgery for screen-detected cancers, and less often received surgery alone or the combination of surgery, radiotherapy and systemic therapy for interval cancer. In stage 2, surgery plus radiotherapy was less common in high SES patients with interval, while high SES patients who did not attend the screening program more often received surgery alone.

Survival

Complete follow up had been obtained of all but 18 (0.3%) patients with invasive cancer. Crude five-year survival was 89% among screening attendees (N=4,098), more specifically 83% in interval cancers (N=852), 91% in screen-detected cancers (N=3,246), and 77% among non-attendees (N=1,233, log-rank test p<0.001). A socioeconomic gradient in survival was observed, with worst survival for women with low SES and best survival for women with high SES (Figure 4). Patients with low SES and screen-detected cancer had worse survival (89%) compared to patients with intermediate SES (91%, log rank-test p<0.01) and high SES (91%, p<0.01). Patients with low SES and interval cancer had a worse survival (81%) compared to those with high SES (89%, p<0.01), and those with intermediate SES and interval cancer had worse survival rates than those with high SES as well (81%, p=0.02). Within the groups of screen-detected and interval cancer, no significant differences were observed for survival of initial versus subsequent screening mammography (data not shown). Patients with low SES and who had not attended screening showed significantly worse survival compared to women with intermediate SES (81%, p<0.01).

The socioeconomic inequalities in survival remained after age adjustment, with a hazard ratio (HR) of 1.4 (1.1-1.9) for low SES if compared to high SES in non-attendees, and 1.3 (1.0-1.7) and 1.7 (1.1-2.6) for screen-detected cancers and interval cancers (Table 2). As comorbidity was inversely associated with SES (46%, 39% and 32% in low, intermediate and high SES), we additionally adjusted for comorbidity in the age-adjusted model. Socioeconomic inequalities in breast cancer survival seemed to be related to socioeconomic inequalities in presence of comorbidities in screen-detected cancers (23%), but had less impact in interval cancers or in non-attenders. In these latter two groups, survival disparities seemed to be largely related to stage, which explained respectively 35% and 48% of the survival disparities, while treatment had a minor role (16% and 16%, respectively).

Discussion

The current study shows that women with high SES show higher attendance rates for breast cancer screening in the south of the Netherlands. Socioeconomic inequalities persist resulting in significantly worse stage and lower survival for women with low SES. Compared to other European countries, Dutch screening attendance rates are rather high: 84% compared to 65% in Sweden (1990-2003, clinical trial) [20], 73% in England (3-year screening, 2007-2008)[21] and 63% (1999-2001) in Copenhagen [22]. Comparable attendance rates were reported in another Danish region (around 84% from 1991-2001 [23]) and in a Spanish screening program (82%, 1995-1998) [24]. The socioeconomic inequalities in attendance rates in this study (OR 1.75 for high compared to low SES) are somewhat smaller than the results presented by others, although the magnitude seems to depend on the SES indicator used [2,20,25]. Studies on the association with education however have given mixed results, with some showing higher educational levels had a tendency toward lower non-attendance rates [2,25] and one study shown higher [20] non-attendance rates. A U-shaped association has also been reported [26].

In contrast to many European countries, breast cancer screening in the U.S. is done opportunistically. This may contribute to the larger socioeconomic inequalities in attendance rates in the U.S., where around 60% of women with low and 75-80% with high income (or education) (self)reported to have had a mammogram or clinical breast examination in the past 2 years [1,3,27,28]. In line with the trend we observed, U.S. participation rates increased over time from 77% (1988-1990) to even 92% (1998-2000) in the health-aware nurses in the Nurses Health Study [29].

Not attending screening may be related to inadequate knowledge of cancer, attitudes, health consciousness, cultural differences, language problems and illiteracy [3,30]. These are all more often seen in people with low SES [31,32] and could thus have contributed to the socioeconomic gradient in attendance rate. In the Netherlands, immigrants were found to have lower attendance rates [33], which might be attributed to a lack of proficiency of the Dutch language [30]. Nowadays, the Dutch screening organization has invitations and accompanying information leaflets in the Dutch, English, Turkish and Arabic language. Presence of financial and health system barriers also have been suggested as reasons for not attending the screening [3]. However, the Dutch government offers mammographies free of charge, thus this is unlikely to play a role in the Netherlands. Because non-attendees are not inclined to seek mammography elsewhere [34], it is very important to reach all women for screening.

In previous studies having a low SES has also been associated with more advanced stage at diagnosis [5-7,11,35] but to our knowledge this has not been studied in association with attendance to screening. It is likely that at least part of this association can be attributed to socioeconomic inequalities in attendance rates of screening programs. For example, 36-47% of the breast tumors in Switzerland is

stage 2 or higher in regions with screening programs, compared to 50-64% in regions without a screening program [36]. Studies from Italy and Sweden found comparable results [20,37]. Not surprisingly, patients who attended screening had a more favorable stage distribution than those who did not attend, and patients with high SES had less advanced tumors than low SES. Remarkable socioeconomic stage differences were observed in screen-detected cancer, suggesting other tumor biology [38]. In screen-detected cancers, we observed small differences in morphology (65% had infiltrating duct carcinoma versus 71% in low SES), estrogen receptor status (88% ER+ versus 85%) and progesterone receptor status (10% PR+ versus 12%) but not in tumor size or grade. For cervical cancer higher proliferation rates have been suggested in low SES [39], which could hold for breast cancer as well.

The presence of a socioeconomic gradient in breast cancer survival has been reported in previous studies [8,11,12,40] and our results show that this is, at least partly, related to screening attendance. The crude 5-year survival rates we observed (respectively 89% and 76% for those who did and did not attend screening, i.e. RR 1.2) were fairly comparable to results reported in Sweden, where the age and stage adjusted relative risk of death was 1.4 for non-attenders [20]. Moreover, the crude 5-year survival rates observed in our study (77% for patients with cancers not detected by screening versus 91% for those with screen-detected cancers) are comparable to the rates of 84% and 94% observed in a study performed in Northern Italy [37]. Unfortunately, no SES-specific life tables were available to estimate breast cancer specific survival according to SES. Similar patterns to overall survival were observed when using general life tables, although this may lead to underestimation of the relative survival rates in low SES and overestimation in high SES.

In this study, Cox' regression has been applied to assess causality in socioeconomic inequalities in survival from breast cancer. This method requires several stringent assumptions to be satisfied and does not allow for interactions between exposure (SES) and mediators (stage and treatment) [41]. Furthermore, for hazard ratios the decomposition into effects was stated not to be valid [41]. To the best of our knowledge, there is no accessible better way to analyze mediation than via Cox' regression. Although interpretation of effects from regression models should be guarded, these results suggest an effect of stage on survival differences for interval cancers and in non-attenders, while comorbidities affected survival in screen-detected patients. The socioeconomic differences in stage at diagnosis explained some of the socioeconomic inequalities in breast cancer survival. Stage distribution was only slightly different between the SES categories in screen-detected cancers, while differences were larger in patients who did not attend the screening and especially in interval cancers. In these latter two groups, stage indeed explained (part of) the socioeconomic differences. In three other studies in the UK and France socioeconomic inequalities in breast cancer survival were ascribed to stage [6,11,13]. However, in an older study from the UK, including patients diagnosed between 1980 and 1987, tumor stage or biology did not contribute to the socioeconomic gradient in breast cancer survival [14]. More recently, a study in the Netherlands on breast cancer patients diagnosed from 1995 to 2005 observed that 10-year relative survival rates were 79% in high SES compared to 74% in low SES, and the accompanying relative excess risk of dying from breast cancer was 1.19. This was after adjustment for (among others) grade, stage, nodal status, treatment [12]. Only one of the foreign studies took into account the role of breast cancer screening and compared the survival of cancers detected clinically with those detected in the screening program. Survival inequalities were only present for stage 3 [11].

Interventions to increase screening participation have been reviewed and distinguished into factors related to invitees, health-care providers, health-care context, and media and financial factors [42]. Most important to increase participation in the Netherlands will be the factors related to invitees, e.g. by timing of invitation, personal factors (perceived risk of cancer, perceived self-efficacy), customizing invitation to the individual needs (for example by telephone counseling), and address psychological mediators of cancer screening behavior [42].

A limitation of this study is the fact that we do not know the reasons of non-participation in 54% of the cases. To increase attendance rates, this should be studied. Comorbidity could explain (part of) the non-participation, as it was present at diagnosis in 42% of the women who did not compared to 37% in women who did attend. As stated earlier, we used an indicator of SES based on the postal code of a residential area and not on individual data on income, education, etc. Since this aggregate covers a relatively small geographical area (on average 17 households), it is likely to represent a reliable approximation of individual SES. Furthermore, routinely collected income tax data have been found to provide reliable estimates of household income [43]. Previous studies in the Netherlands have proven that socioeconomic differences based on neighborhood data tend to reflect socioeconomic differences

accurately at the individual level [43-45]. In addition, we defined non-participation in patients as women who did not attend the screening program within the last 2 years before diagnosis. In fact, 64% of these women indeed never attended, but 32% had attended more than 3 but less than 4 years before diagnosis, and 4% had attended the program more than 3 years before diagnosis.

Despite these limitations, the results of this study form an important contribution to the limited information available on socioeconomic inequalities in screening attendance and the consequences in terms of stage at diagnosis and survival in the Netherlands. Moreover, in this large population-based study we included all women being eligible for breast cancer screening and all breast cancer patients.

In conclusion, despite the absence of financial barriers for participation in the Dutch mass screening program, socioeconomic inequalities in attendance rates remain present, resulting in a significantly worse tumor stage and lower survival rate for women with low SES. Therefore, these results underline the importance of increasing participation among women of all SES groups, with special attention to those with low SES.

Conflict of interest statement

None declared.

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Table 1. Characteristics of women invited for mass breast cancer screening and multivariable analyses of

		Chara	cteristics	Multivariable analyses				
	Not atte	nded	Atte	nded	Odds of attending			
	Ν	%	Ν	%	OR	(95%CI)		
Age								
<50	12586	8%	67768	8%	0.96	(0.9-1.0)		
50-54	34097	20%	190490	21%	1.00			
55-59	34533	21%	207443	23%	1.08	(1.1-1.1)		
60-64	27779	17%	169409	19%	1.13	(1.1-1.2)		
65-69	25886	16%	147179	16%	1.08	(1.1-1.0)		
70-75	27247	16%	108970	12%	0.73	(0.7-0.7)		
>75	4269	3%	10296	1%	0.31	(0.3-0.4)		
Year of invitation								
1998	19329	12%	95121	11%	1.00			
1999	20007	12%	100765	11%	1.09	(1.1-1.1)		
2000	21490	13%	113472	13%	1.11	(1.1-1.1)		
2001	20487	12%	103502	11%	1.09	(1.1-1.1)		
2002	22396	13%	123958	14%	1.15	(1.1-1.2)		
2003	19427	12%	114023	13%	1.26	(1.2-1.3)		
2004	23397	14%	132171	15%	1.16	(1.1-1.2)		
2005	19864	12%	118543	13%	1.27	(1.2-1.3)		
Socioeconomic status								
Low	54008	32%	201396	22%	1.00			
Intermediate	65015	39%	381152	42%	1.54	(1.5-1.6)		
High	47374	28%	319007	35%	1.75	(1.7-1.8)		

the odds of attending the mass breast cancer screening in southern Netherlands

All values are adjusted for age, year of invitation and socioeconomic status. OR: odds ratio, 95% CI: 95%

confidence interval. Values in bold are significant.

Women <50 were included as they are first invited in the year of their 50th birthday. Some women aged

>75 were included as they received their last invitation just before their 76th birthday.

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Table 2. Hazard ratios of death from breast cancer according to screening attendance and the contribution of comorbidity and stage to socioeconomic differences

	Model fo	l adjusted Model adjust or age age + como		del adjuste e + comor	ed for Model adjuste bidity age + stav		ed for Ige	Model adjus age + th		sted for erapy	Model adjusted for age + comorbidity + stage + therapy			
	HR§	(95%CI)	HR	(95%CI)	Relative contribu -tion comor- bidity#	HR	(95%CI)	Relative contribu -tion stage \$	HR	(95%CI)	Relative contribu- tion therapy +	HR	(95%CI)	Relative contribution stage, comorbidity and therapy*
Screening attendees		.						- ·			• •			
Screen-detected	1.30	(1.0-1.7)	1.23	(1.0-1.6)	23%	1.32	(1.0-1.7)	-7%	1.26	(1.0-1.6)	13%	1.23	(0.9-1.6)	24%
Interval	1.72	(1.1-2.6)	1.67	(1.1-2.6)	7%	1.47	(1.0-2.3)	35%	1.60	(1.0-2.4)	16%	1.45	(0.9-2.2)	37%
Non-attendees Not screened	1.42	(1.1-1.9)	1.37	(1.0-1.8)	12%	1.22	(0.9-1.6)	48%	1.35	(1.0-1.8)	16%	1.17	(0.9-1.6)	60%

§ HR = Hazard Ratio, low versus high socioeconomic status. Values in bold are significant.

((HR model adjusted for age - (HR model adjusted for age+comorbidity))/(HR adjusted for age - 1))*100%

\$ ((HR model adjusted for age - (HR model adjusted for age+stage))/(HR adjusted for age - 1))*100%

+ ((HR model adjusted for age - (HR model adjusted for age+therapy))/(HR adjusted for age - 1))*100%

* ((HR model adjusted for age - (HR model adjusted for age+comorbidity +stage))/(HR adjusted for age - 1))*100%

Figure 1. Flow-chart of the invitations and attendance of breast cancer screening according to

socioeconomic status.



Int.: intermediate, interv: interval cancer, SD: screen-detected cancer, SES: socioeconomic status.

Figure 2. Attendance of breast cancer screening according to socioeconomic status in southern Netherlands 1998-2005.



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* p<0.05

** p<0.01

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