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Breast cancer screening effect across breast density strata: A case–control study

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Breast cancer screening is known to reduce breast cancer mortality. A high breast density may affect this reduction. We assessed the effect of screening on breast cancer mortality in women with dense and fatty breasts separately. Analyses were performed within the Nijmegen (Dutch) screening programme (1975–2008), which invites women (aged 50–74 years) biennially. Performance measures were determined. Furthermore, a case–control study was performed for women having dense and women having fatty breasts. Breast density was assessed visually with a dichotomized Wolfe scale. Breast density data were available for cases. The prevalence of dense breasts among controls was estimated with age-specific rates from the general population. Sensitivity analyses were performed on these estimates. Screening performance was better in the fatty than in the dense group (sensitivity 75.7% vs 57.8%). The mortality reduction appeared to be smaller for women with dense breasts, with an odds ratio (OR) of 0.87 (95% CI 0.52–1.45) in the dense and 0.59 (95% CI 0.44–0.79) in the fatty group. We can conclude that high density results in lower screening performance and appears to be associated with a smaller mortality reduction. Breast density is thus a likely candidate for risk-stratified screening. More research is needed on the association between density and screening harms.

Breast cancer is the cancer that causes most death in women worldwide, even though mortality has been decreasing over time.[1,2] Screening programmes, aimed to detect breast cancer at an early stage, have contributed to this mortality reduction. According to the independent UK panel, which used published trial data, invitation to screening will reduce breast cancer mortality by 20%.[3] Developments in the field of screening techniques, however, have not stopped after completion of these screening trials.[3] For example, screen-film mammography has been replaced by full-field digital mammography, which produces higher quality images. In addition, the survival improvements due to the introduction and increasing uptake of new adjuvant therapies since 1970 may have changed the synergistic dynamic between treatment and screening.[4,5] As a result, trial data cannot be used to draw conclusions on the current screening programme or to explore opportunities for improvement, such as the inclusion of breast cancer risk factors in determining screening regimens. Observational study designs are thus needed in the evaluation of continuing programmes.

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Several case–control studies have estimated the effect of participating in breast cancer screening on breast cancer mortality.[6–14] None of these studies have, however, addressed potential differences in screening effect (effect modification) by risk factors other than age. The assessment of effect modification is important for the identification of relevant risk groups in the context of risk-stratified or personalised screening. Alternative screening regimens could potentially be applied in these groups for an optimal benefit–harm ratio. The effect of screening may, for example, vary across breast density strata. Dense tissue can mask tumours on a mammogram, and a high breast density is associated with greater tumour size and possibly lymph node involvement at the time of diagnosis.[15] Furthermore, mammographic density is an independent breast cancer risk factor.[16] If the screening effect is indeed heterogeneous and the differences are clinically relevant, adapting screening based on breast density level may improve the benefit–harm ratio of screening for individual participants. Possibilities include the use of additional imaging techniques, for example, ultrasound or MRI. With these techniques, breast density would give little-to-no hindrance in tumour detection.

The problem with breast density, and many other risk factors, is that often very limited information is available from the general screening population, particularly at the individual level. This is an important limitation, most profoundly in studies based on existing data. Obtaining complete risk factor information can be difficult, especially in women who choose not to participate in breast cancer screening. Adequate methodology

What's new?

High breast density is known to increase breast cancer risk and decrease sensitivity of mammographic screening. As a result, women with dense breasts may not benefit from screening to the same extent as women with lower breast density. Here, using data from the Nijmegen (Dutch) screening programme, differences in screening effect on breast cancer mortality were assessed among women with either dense or fatty breasts. Compared to fatty breasts, high breast density was associated with reduced screening performance and reduced effects on mortality. The findings suggest that modifications in effect are relevant for risk-stratified and personalized screening.

therefore has to be developed to study subgroup effects while dealing with missing risk factor information.

Here, we address screening performance and the effect of screening on breast cancer mortality in different breast density strata, while dealing with incomplete risk factor information in the control group. Data from the long-running Nijmegen (Dutch) screening programme were used in this study. The screening effect in women with dense breasts and in women with fatty breasts was assessed with case–control analyses.

Methods

Setting

Breast cancer screening was introduced in Nijmegen (the Netherlands) in 1975. In this programme, all women aged 50–75 years biennially receive an invitation to participate. They can be screened at fixed or mobile screening units. Mammograms are evaluated by certified screening radiologists in an independent double-reading setting. When suspect findings are observed, the woman will be recalled for additional imaging and, if necessary, a biopsy. In 2007, the screening programme switched from screen-film to digital mammography. Digital mammography was introduced in the hospitals several years before. In this study, only screen-film mammograms were included. Data on vital status of invited women were obtained via linkage with the Municipal Personal Records Data Base (GBA). All women consented to the use of their anonymous data for scientific research.

Mammographic density assessments

Since 2014, both a mediolateral oblique (MLO) and a craniocaudal (CC) view are obtained in the Dutch screening programme. MLO was the standard view before 2014, whereas a CC was only obligatory at first screening and performed on indication at subsequent screening examinations. Mammographic density assessments were based on all available views. Density patterns were classified visually according to a four-category scale, based on the quantification of the Wolfe breast density pattern (N1, P1, P2, DY): <5%, 5–25%, 25–75%, >75%.[17] Similar to the BI-RADS breast density scale, the highest category (DY or >75%) is associated with a decreased screening sensitivity and an approximately four times increased breast cancer risk compared with the lowest category (N1 or <5%). A strong correlation between the two measures has previously been observed,[18] although the degree of correlation appears to vary between studies. Density estimates were available for clinical mammograms, when additional imaging had been performed, and for screening mammograms (determined by a trained research assistant) for women who had ever been recalled. Breast density was dichotomized into a 'fatty' (≤25%) and a 'dense' (>25%) group to ensure that groups would have sufficient numbers for the statistical analyses.

Breast density and screening test performance

Several screening performance measures were determined for the descriptive analyses (Table 1). This includes the programme sensitivity ($\frac{\text{Screen}-\text{detected}}{\text{Screen}-\text{detected}+\text{Interval}} \times 100\%$) and positive predictive value of recall ($\frac{\text{Screen}-\text{detected}}{\text{Recall}} \times 100\%$). Data were used from the time period before the introduction of digital mammography, up until 2006. The age is based on age at invitation to the screening round. Interval tumours were defined as breast cancer diagnoses within 24 months after a negative screening exam. Log-binomial regression was used to estimate risk ratios (RR).

Breast density and the effect of screening on breast cancer mortality: Case–control analyses

Case and control subjects. Case subjects were women who died of breast cancer in Nijmegen between 1975 and 2008. Each case subject was matched to five control subjects via incidence density sampling.[19] Control subjects had to be alive at the time of death of the matched case. In addition, controls had to be free of breast cancer up until the diagnosis date of the matched case to ensure an equal screening opportunity. This is referred to as the pseudo-diagnosis date of the control subjects. The index round is the screening round at which breast cancer is diagnosed for screen-detected cases, or the round preceding the (pseudo-)diagnosis date (within 2 years) for interval or non-participating cases and controls. Hereinafter 'non-participants' refers to the women who did not participate in screening. All women included in our study – both case subjects and control subjects – had been invited to the index round. Case and control subjects were not matched on age.

For the cases, the breast density pattern was based on the screening mammogram of the index round ($n = 196$). If this was not available (for example, for non-participants), the

Table 1. Screening performance in different time periods for women with dense and fatty mammographic breast patterns

		Breast density pattern, *N* (%)[a]		
	Total	Fatty	Dense	Density unknown
Period 1975–1982				
Recalled	432	269 (62.7)	160 (37.3)	3
Screen-detected cancer	183	131 (71.6)	52 (28.4)	0
False-positive	249	138 (56.1)	108 (43.9)	3
Interval cancer	83	45 (54.9)	37 (45.1)	1
Programme sensitivity	68.80%	74.40%	58.40%	
PPV recall	42.40%	48.70%	32.50%	
Period 1983–1990				
Recalled	268	189 (70.8)	78 (29.2)	1
Screen-detected cancer	177	123 (69.5)	54 (30.5)	0
False-positive	91	66 (73.3)	24 (26.7)	1
Interval cancer	88	40 (45.5)	48 (54.5)	0
Programme sensitivity	66.80%	75.50%	52.90%	
PPV recall	66.00%	65.10%	69.20%	
Period 1991–1998				
Recalled	345	263 (76.2)	82 (23.8)	0
Screen-detected cancer	188	149 (79.3)	39 (20.7)	0
False-positive	157	114 (72.6)	43 (27.4)	0
Interval cancer	75	46 (61.3)	29 (38.7)	0
Programme sensitivity	71.50%	76.40%	57.40%	
PPV recall	54.50%	56.70%	47.60%	
Period 1999–2006				
Recalled	739	513 (69.6)	224 (30.4)	2
Screen-detected cancer	293	212 (72.6)	80 (27.4)	1
False-positive	446	301 (67.6)	144 (32.4)	1
Interval cancer	126	66 (55.9)	52 (44.1)	8
Programme sensitivity	69.90%	76.30%	60.60%	
PPV recall	39.60%	41.30%	35.70%	

Abbreviation: PPV = positive predictive value.
[a]Unless indicated otherwise. The percentages in brackets are row percentages.

estimate was based on the clinical mammogram ($n = 111$) or the screening mammogram from the round preceding the index round ($n = 3$), respectively. Case subjects who still had a missing breast pattern ($n = 23$), only non-participants, were randomly allocated to the dense group ($n = 5$) or the fatty group ($n = 18$) based on the density distribution in the other non-participating case subjects (22.2% high density, 95% confidence interval [CI] 13.6; 30.8). There were no noticeable differences between the non-participating case subjects with and without a registered breast density pattern. The age distribution of the non-participant cases without an estimate of the density pattern (median 62 years, IQR 56–69) was similar to the age distribution of the non-participant cases with a density estimate (median 60 years, IQR 56–69). The case subjects with missing density patterns were diagnosed between 1981 and 2008.

Breast density estimates in the control group were only available for a very selective group, namely, women who had been recalled for additional imaging and/or who had ever been diagnosed with breast cancer. High breast density is, however, associated with recall and breast cancer risk, and the prevalence of dense breasts is therefore expected to be significantly higher in this selective group than in the entire control group. Mammogram data was not available for the other control subjects in this study. We therefore estimated the overall prevalence of dense breasts in the control subjects, to make a contingency table for women with dense and fatty breasts. Based on a sample ($n = 1430$) from the first two

screening rounds in Nijmegen in the same age group, the prevalence of a high breast density was 20% in the population participating in screening. A log-binomial model was fitted with the proportion of dense breasts (dense/fatty breasts) as the outcome and age as the predictor.[20] This resulted in the following formula:

$$\text{Log(Proportion of dense breasts)} = 1.5351 - 0.0517 \times \text{Age}$$

α and its (95% CI): -0.0517 and (-0.0568; -0.0466)

β and its (95% CI): 1.5351 and (1.3013; 1.7688)

The model was used to estimate the prevalence of dense breasts in the participating and the non-participating control subjects. This resulted in the following prevalence estimates: 23% among participants and 19% among non-participants.

In addition, we performed sensitivity analyses with different prevalence estimates (10%–65%) of 'dense breasts' in the participating and non-participating controls. This reflects varying degrees of potential self-selection related to breast density in this population. Controls were randomly allocated to the 'dense' or the 'fatty' group based on the various prevalence estimates.

Statistical analyses. Unconditional logistic regression was used to estimate odds ratios (OR) with corresponding 95% CI for the association between screening exposure and breast cancer mortality. An unconditional analysis gives unbiased results if the ratio of women screened to not screened is stable over time, as seen in the Nijmegen screening programme.[10,21,22] Screening exposure was defined as attending the index screening round and/or the screening examination preceding the index round (pre-index round). This reflects the screening participation within the 4 years before (pseudo-)diagnosis. All analyses were stratified by breast density pattern.

Results

Breast density and screening performance

Table 1 shows the various performance parameters for different time periods since the start of the screening programme in 1975. The proportion of women with dense breasts among the interval cases ranged from 38.7% to 54.5%, and these proportions were always greater than for the screen-detected cases (ranged from 20.7% to 30.5%). For the false-positive recalls, the proportion of women with dense breasts varied from 26.7% to 43.9%, with the highest proportion observed in the first time period. In most screening programmes, recall patterns tend to be different during the first screening round compared with later rounds.

The programme sensitivity remained relatively stable over time in both the dense (overall estimate 57.8%) and the fatty group (overall estimate 75.7%), and the sensitivity was higher in women with fatty breasts in all time periods. There was no consistent trend in PPV recall, which probably reflects the changes in recall over time.[23] The highest PPV in both groups was observed between 1983 and 1990, with the dense group then even having a slightly higher PPV than the fatty group (69.2% vs 65.1%). In all other time periods, the PPV in women with dense breasts (overall 41.4%) was notably lower than the PPV in women with fatty breasts (overall 49.8%). The risk of false-positive recall is thus increased in women with dense breasts (RR 1.17, 95% CI 1.07–1.28). The risk of being diagnosed with an interval cancer rather than a screen-detected cancer is higher in women with dense breasts (RR 1.75, 95% CI 1.48–2.07) as well.

The sensitivity and the PPV were also higher in the women with fatty breasts in all age groups, apart from the 65- to 69-year olds (Supporting Information, Table S1). The PPV in that age group was higher for women with a high breast density, with 54.3% compared to 48.1%. Both the overall sensitivity and the overall PPV increased with age. A similar trend in sensitivity in women with fatty breasts was observed, but not in women with dense breasts.

Table 2. Effect of screening on breast cancer mortality overall and for women having dense or fatty mammographic patterns, using estimates based on the age distribution[a]

	Screened, *N*	Non-screened, *N*	OR (95% CI)
Overall			
Case subjects	220	113	0.67 (0.52–0.86)
Control subjects	1240	425	
Dense			
Case subjects	75	25	0.87 (0.52–1.45)
Control subjects	285	81	
Fatty			
Case subjects	145	88	0.59 (0.44–0.80)
Control subjects	955	344	

[a]The estimated prevalence was 23% in the screened group and 19% in the non-screened group.

Breast density and screening effect: Case–control analyses

Screening effect on breast cancer mortality. Table 2 shows the ORs associated with the effect of breast cancer screening on breast cancer mortality. The analyses were based on 333 breast cancer deaths that occurred between 1978 and 2008. Of these case subjects, 220 (66.1%) had attended screening during the index round and/or the pre-index round. This includes 123 (36.9%) screen-detected tumours. Screening attendance in the last two rounds preceding pseudo-diagnosis was 74.5% ($n = 1240$) among the 1665 control subjects. Overall, screening attendance during the index round and/or pre-index round reduced breast cancer mortality with 33% (OR 0.67, 95% CI 0.52–0.86). Adjustments for age at the index screening round had little effect on the observed mortality reduction (OR 0.69, 95% CI 0.53–0.89).

Study population by breast density. As shown in Table 3, most women ($n = 39$, 41.1%) with dense breasts were aged 50–54 years at index screening. Most women with fatty

Table 3. Age at death, year of diagnosis, and year of screening invitation, and tumour characteristics of all breast cancer deaths according to breast density pattern at diagnosis

	N (%)[a]			
	Total (*N* = 333)	Dense (*N* = 95)	Fatty (*N* = 215)	Density unknown (*N* = 23)
Age at death (years)				
50–54	16 (4.8)	7 (7.4)	6 (2.8)	3 (13.0)
55–59	50 (15.0)	19 (20.0)	27 (12.6)	4 (17.4)
60–64	58 (17.4)	19 (20.0)	34 (15.8)	5 (21.7)
65–69	64 (13.0)	13 (13.7)	48 (22.3)	3 (19.2)
70–74	68 (20.4)	21 (22.1)	43 (20.0)	4 (17.4)
75–79	47 (14.1)	11 (11.6)	32 (14.9)	4 (17.4)
80–84	19 (5.7)	4 (4.2)	15 (7.0)	0 (0.0)
85+	11 (3.3)	1 (1.1)	10 (4.7)	0 (0.0)
Age at invitation (years)				
50–54	81 (24.3)	39 (41.1)	38 (17.7)	4 (17.4)
55–59	73 (21.9)	19 (20.0)	48 (22.3)	6 (26.1)
60–64	70 (21.0)	13 (13.7)	52 (24.2)	5 (21.7)
65–69	58 (17.4)	13 (13.7)	42 (19.5)	3 (13.0)
70+	51 (15.3)	11 (11.6)	35 (16.3)	5 (21.7)
Year of death				
1975–1979[b]	7 (2.1)	0 (0.0)	7 (3.3)	0 (0.0)
1980–1984	55 (16.5)	17 (17.9)	34 (15.8)	4 (17.4)
1985–1989	50 (15.0)	13 (13.7)	36 (16.7)	1 (4.3)
1990–1994	61 (18.3)	19 (20.0)	39 (18.1)	3 (13.0)
1995–1999	60 (18.0)	19 (20.0)	37 (17.2)	4 (17.4)
2000–2004	56 (16.8)	18 (18.9)	35 (16.3)	3 (13.0)
2005–2008	44 (13.2)	9 (9.5)	27 (12.6)	8 (34.8)
Year of diagnosis				
1975–1979	71 (21.3)	23 (24.2)	46 (21.4)	2 (8.7)
1980–1984	69 (20.7)	19 (20.0)	48 (22.3)	2 (8.7)
1985–1989	56 (16.8)	17 (17.9)	37 (17.2)	2 (8.7)
1990–1994	62 (18.6)	18 (18.9)	41 (19.1)	3 (13.0)
1995–1999	35 (10.5)	9 (9.5)	22 (10.2)	4 (17.4)
2000–2004	33 (9.9)	9 (9.5)	18 (8.4)	6 (26.1)
2005–2008	7 (2.1)	0 (0.0)	3 (1.4)	4 (17.4)
Tumour size (in mm)				
<20	79 (23.7)	19 (20.0)	59 (27.4)	1 (4.3)
20–40	164 (49.2)	56 (58.9)	104 (48.4)	4 (17.4)
>40	58 (17.4)	16 (16.8)	36 (16.7)	6 (26.1)
Diffuse	10 (3.0)	1 (1.1)	7 (3.3)	2 (8.7)
Unknown	22 (6.6)	3 (3.2)	9 (4.2)	10 (43.5)

[a]The percentages in brackets are column percentages.
[b]First death occurred in 1978.

breasts, on the other hand, were in the age category 60–64 years ($n = 52$, 24.2%). The first breast cancer death among the women who had been invited to the programme occurred in 1978. Breast cancer deaths were evenly distributed over time. It appeared that a somewhat larger proportion of women had a tumour size <20 mm in the group with fatty

Table 4. ORs for the effect of screening on breast cancer mortality in the dense (D) and the fatty (F) group, based on different breast density prevalence estimates in the participating and non-participating controls

Prevalence density non-participating controls		Prevalence density participating controls											
		10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%
10%	D	1.02	0.68	0.51	0.41	0.34	0.29	0.26	0.23	0.20	0.19	0.17	0.16
	F	0.57	0.60	0.64	0.68	0.73	0.78	0.85	0.93	0.85	1.13	1.27	1.45
15%	D	1.54	1.02	0.77	0.61	0.51	0.44	0.38	0.34	0.31	0.28	0.26	0.24
	F	0.53	0.57	0.60	0.64	0.69	0.74	0.80	0.87	0.80	1.07	1.20	1.37
20%	D	2.05	1.36	1.02	0.82	0.68	0.58	0.51	0.45	0.41	0.37	0.34	0.31
	F	0.50	0.53	0.57	0.60	0.65	0.70	0.75	0.82	0.75	1.01	1.13	1.29
25%	D	2.56	1.71	1.28	1.02	0.85	0.73	0.64	0.57	0.51	0.47	0.43	0.39
	F	0.47	0.50	0.53	0.57	0.61	0.65	0.71	0.77	0.71	0.94	1.06	1.21
30%	D	3.07	2.05	1.54	1.23	1.02	0.88	0.77	0.68	0.61	0.56	0.51	0.47
	F	0.44	0.47	0.49	0.53	0.57	0.61	0.66	0.72	0.66	0.88	0.99	1.13
35%	D	3.58	2.39	1.79	1.43	1.19	1.02	0.90	0.80	0.72	0.65	0.60	0.55
	F	0.41	0.43	0.46	0.49	0.53	0.57	0.61	0.67	0.61	0.82	0.92	1.05
40%	D	4.09	2.73	2.05	1.64	1.36	1.17	1.02	0.91	0.82	0.74	0.68	0.63
	F	0.38	0.40	0.42	0.45	0.48	0.52	0.57	0.62	0.57	0.75	0.85	0.97
45%	D	4.61	3.00	2.30	1.84	1.54	1.32	1.15	1.02	0.92	0.84	0.77	0.71
	F	0.35	0.37	0.39	0.41	0.44	0.48	0.52	0.57	0.52	0.69	0.78	0.89
50%	D	5.12	3.41	2.56	2.05	1.71	1.46	1.28	1.14	1.02	0.93	0.85	0.79
	F	0.31	0.33	0.35	0.38	0.40	0.43	0.47	0.51	0.57	0.63	0.71	0.81
55%	D	5.63	3.75	2.82	2.25	1.88	1.61	1.41	1.25	1.13	1.02	0.94	0.87
	F	0.28	0.30	0.32	0.34	0.36	0.39	0.42	0.46	0.42	0.57	0.64	0.73
60%	D	6.14	4.09	3.07	2.46	2.05	1.75	1.54	1.36	1.23	1.12	1.02	0.94
	F	0.25	0.27	0.28	0.30	0.32	0.35	0.38	0.41	0.38	0.50	0.57	0.65
65%	D	6.65	4.44	3.33	2.66	2.22	1.90	1.66	1.48	1.33	1.21	1.11	1.02
	F	0.22	0.23	0.25	0.26	0.28	0.30	0.33	0.36	0.33	0.44	0.49	0.57

P = participating control; NP = non-participating control; D = dense; F = fatty.
The presence of a 'high breast density' was estimated in the control subjects. The control subjects were divided into screening participants and non-participants. The percentages indicate the different prevalence estimates. The numbers in the table represent the ORs in the different density strata (dense/fatty).

breasts than in the group with dense breasts (27.4% vs 20.0%), with average-sized tumours (20–40 mm) being more common in women with dense breasts (48.4% vs 58.9%).

Screening effect by breast density. A breast density pattern was available for all case subjects who had attended screening recently ($n = 220$). In this group, 75 (34.1%) women had a dense breast pattern. With the prevalence estimates based on the age distribution in participants and non-participants, a greater effect of screening is observed in women with fatty breasts (OR 0.59, 95% CI 0.44–0.79) than in women with dense breasts (OR 0.87, 95% CI 0.52–1.45) (Table 2).

Sensitivity analysis. A sensitivity analysis was performed to assess the robustness of our analysis, given the uncertainty in our breast density prevalence estimates for the control group. The effect of screening in different breast density strata (i.e., fatty/dense) was explored using different assumptions on the prevalence of dense breasts in participants and non-participants in the control group. In Table 4, the grey area highlights estimates where there was a stronger screening effect in women with fatty breasts than in women with dense breasts. In most of our scenarios, the mortality reduction is smaller in the group with dense breasts than in the group with fatty breasts. Take, for example, the scenario based on a prevalence of 30% in control women who participated in screening and a prevalence of 25% in women who did not participate in screening. The ORs would then be 0.85 and 0.61 in the women with dense breasts and in women with fatty breasts, respectively. Under the assumption that the prevalence of dense breasts is similar in participants and non-participants, there would be no mortality reduction (OR 1.02) in women with dense breasts and a 43% (OR 0.57) reduction in women with fatty breasts. The 95% CI slightly depends on the prevalence estimates. At 10% prevalence of

dense breasts in the control group (both participants and non-participants), the 95% CI would be (0.58–1.81) and (0.42–0.76) in the group with dense breasts and the group with fatty breasts, respectively. At 65% prevalence, the interval in the group with dense breasts is smaller (0.64–1.64), whereas the effect on the CI in the group with fatty breasts is limited (0.41–0.78).

Discussion

Women who participated in screening in the 4-year period before (pseudo-)diagnosis had a 33% lower risk of breast cancer death than those who did not participate. High breast density is associated with lower programme sensitivity (57.8% vs 75.7%) of mammographic screening and mostly a lower PPV (41.4% vs 49.8%) throughout the study period, which is expected to decrease the effect of screening on breast cancer mortality. The analyses on screening effectiveness across breast density strata support the hypothesis of a differential effect (estimated mortality reduction: 41% fatty and 13% dense breasts), although prevalence estimates have been shown to affect the absolute difference.

The effect of breast density on screening sensitivity has been studied previously with film-screen mammography.[24–29] Digital mammography is expected to perform better in women with dense breasts than screen-film mammography. The preliminary results from a study by Wanders *et al.* showed that sensitivity indeed improved, but there was still a difference in sensitivity estimates between women with dense breasts and women with fatty breasts.[30] Kerlikowske *et al.* reported a similar gradient in sensitivity across breast density levels.[31] Literature estimates of PPV, negative predictive value, and specificity are generally lower in women with increased breast density.[24] We found that the positive predictive value tended to be lower in women with dense breasts (41.4%) than with fatty breasts (49.8%), although this varied over time. Breast density is also likely to explain at least part of the changes in screening test performance with age, based on the knowledge that there is an inverse association between age and breast density.

As a result of the decreased screening performance in women with dense breasts, more breast tumours would be missed during screening. These may be detected at a later screening round or turn up as symptomatic interval tumours. A high breast density indeed appears to be associated with an increased risk of interval cancer.[31–34] Among the interval cases in our population, a relatively large proportion of the women had a dense breast pattern. Due to the late detection, tumours that occur in dense breasts are expected to have reached a more advanced stage at diagnosis. Studies have shown that a high breast density is associated with larger tumour size and potentially lymph node involvement.[15] Our results also suggested a greater tumour size at detection. No strong association has been observed between breast density and other prognostic tumour characteristics, which implies that a high breast density is not associated with the occurrence of more aggressive tumours. For example, most previous studies did not observe an association between breast density and receptor (ER/PR) status.[35,36] Ambiguous results have been published on the association between breast density and breast cancer survival, which suggest that an effect on survival could be explained by the time of diagnosis.[37–42]

The overall (i.e., not stratified on breast density) screening effect has been studied in case–control studies, with the average mortality reduction being estimated at 31% for women invited to screening.[43] The effect in women actually participating in screening is larger (48% after correction for self-selection bias). The effect in different breast density strata has not been presented before. It is challenging to assess this effect, because we need an estimate of breast density for the entire invited population. This includes women who are free of breast cancer and did not participate in breast cancer screening. These women may have never had a mammogram, hence making it difficult to determine mammographic density. In this study, the analyses were based on assumptions regarding prevalence of breast density in the control group. A population measure was thus used to predict breast density at the individual level.

Sensitivity analyses were performed to study the effect of different breast density prevalence estimates on the ORs. Not all scenarios were equally realistic: we included prevalence estimates up to 65%. We found that in the absence of self-selection bias on breast density, i.e., the density prevalence is the same among screened and non-screened controls, the level of effect modification does not depend on the overall breast density prevalence in the control group. This is the diagonal line in Table 4: at all prevalence estimates, the OR is 1.02 in the dense group and 0.57 in the fatty group. Because most women do not know their breast density, breast density is not assumed to directly influence screening participation. However, other risk factors that are associated with breast density may affect the decision to participate. We found that the participants were somewhat younger (median age participating controls: 59 years; median age non-participating controls: 63 years), which could lead to a higher prevalence of dense breasts. Based on the age distribution, 23% of the participants would have dense breasts, compared with 19% of the non-participants. We would, however, like to note that these estimates were based on a model developed in subpopulation that may not be a completely representative sample of the entire study population. This subpopulation only consisted of women who participated in the first few years of the screening programme. This is the reason that the sensitivity analyses were included.

Having a family history of breast cancer is also known to increase breast density and has been suggested to increase screening participation.[44,45] Screening participation is also higher in women with a high socio-economic status,[46–48] which appears to be associated with dense breasts as well.[49,50] On the other hand, women with more dense tissue may also

experience more discomfort or pain during mammography, which could decrease participation rates for subsequent screening exams. In our dataset, however, the participation rate for women with dense breasts was actually slightly higher than in the low density group when we looked at the subsequent screens for a sample of women who participated in the first screening round (81% vs 75%, respectively). Body mass index (BMI) is strongly associated with breast density as well. A recent study in Denmark by Hellmann *et al.* showed that non-attendance in the Danish programme was higher in both underweight (<18.5 kg/m^2; 23.0%) and overweight (25.0–29.9 kg/m^2; 19.1%) women compared to women with a normal weight (18.5–24.9 kg/m^2; 12.0%).[51] This indicates that both extremely dense breasts (underweight women) and very fatty breasts (overweight women) would occur more frequently among non-participants.

A previous study by Paap *et al.* showed that, overall, little self-selection bias is present in the Dutch screening population.[52] Assuming that the prevalence of a high breast density is similar or only slightly (+5%) higher in participants in the control group compared to non-participants, the screening effect would be smaller for women with a high breast density compared to women with a low breast density. From the sensitivity analyses, we can conclude that only under quite extreme conditions, with high density patterns occurring much more frequently in screening participants (>+10%), the benefit of screening would be greater in women with dense breasts. It is realistic to expect that the prevalence is lower in the controls than in the cases (overall prevalence estimate of 30%), given that breast density is a risk factor for breast cancer.

Our study has shown that the lack of information on non-participants constitutes a challenge in determining the screening effect in different risk factor strata, such as for breast density. An additional limitation of our study was that density was only measured once via visual assessment, and clinical mammograms were included in these measurements. This may have led to some misclassification. Furthermore, we only had data from analogous mammograms, with multiple readers. In future studies, automated density measurements can be used for digital mammograms, which limit the problems with intra- and inter-observer variability. The limited information on non-participants, however, will remain an issue in estimating the screening effect in these studies.

Nevertheless, both our results and recent literature seem to indicate that breast density is an important factor to consider when individualizing screening. Women with high breast density still appear to benefit from participating in screening, but this benefit would be smaller than in women with fatty breasts. Furthermore, the disadvantages or harms of screening (*e.g.*, false-positive recall) may be greater in women with dense breasts. The balance between harms and benefits could potentially be increased by offering additional imaging to women with high breast density. Recent research has, however, shown that choices on additional screening should be based on a combination of risk factors, rather than breast density alone.[31]

In conclusion, screening performance differs across breast density levels, which appears to be true for the screening effect as well. A high breast density decreases screening performance and appears to be associated with a smaller mortality reduction. Breast density is thus a likely candidate for risk-stratified screening. More research is, however, needed to learn about the association between breast density and screening harms to gain insight into the screening balance.

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Conflict of Interest

The authors declare no conflict of interest.

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