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Research Article

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Impact of Screening on Breast Cancer Mortality: The UK Program 20 Years On

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Abstract

Background: With changes in diagnosis, treatment, and management of breast cancer since the mammography screening trials, there is a need to evaluate contemporary breast screening programs. A case–control study was set up to assess the current impact of attendance in the English Breast Screening Program on breast cancer mortality.

Methods: Cancer registry cases who died from primary breast cancer ages 47 to 89 years in London in 2008 to 2009 (869 women) were matched to 1 or 2 general population controls (1,642 women) with no diagnosis of breast cancer at the time of the case's diagnosis, who were alive at the case's death. Cases and controls were matched for date of birth and screening area, and had been invited to breast screening at least once prior to the case's diagnosis. ORs were estimated using conditional logistic regression. Self-selection bias was addressed using contemporaneous attendance at the cervical screening program. Sensitivity analyses were undertaken to assess the likely effect of lead time bias.

Results: Attendance at breast screening resulted in a breast cancer mortality reduction of 39% [OR, 0.61; 95% confidence interval (CI), 0.44–0.85] after self-selection correction. Attendance in the last 3 years prior to diagnosis resulted in a 60% mortality reduction (OR, 0.40; 95% CI, 0.31–0.51). Lead time bias effects were negligible.

Conclusion: Our results suggest that community breast screening programs provide their expected benefit in terms of reducing the risk of breast cancer death among women participating.

Impact: Mammography is an important tool for reducing breast cancer mortality and its impact could be increased by encouraging regular attendance. *Cancer Epidemiol Biomarkers Prev; 25(3); 455–62. ©2015 AACR.*

See related article by Massat et al., p. 479

Introduction

Following results of two randomized controlled trials (RCT) of population mammographic screening (1, 2), the UK National Health Service Breast Screening Program (NHS BSP) was implemented in 1988 inviting women ages 50 to 64 years to attend mammographic screening every 3 years. In 2001, this was extended to include women ages 65 to 70 years, and the impact of expanding it to invite women ages 47 to 73 years is currently being trialed (3, 4).

Breast cancer remains the most commonly diagnosed cancer among women in the United Kingdom, accounting for a third of all female cancer cases, and the second most common cause of female cancer-related death (5).

There are two motivations for the ongoing evaluation of mammographic screening programs, with particular reference to their effect on breast cancer mortality. The first relates to the monitoring and audit of specific programs, to ensure that they are delivering their clinical aim, and to improve quality where they are not. The second more general reason is that, as has been argued in a number of high profile publications (6, 7), the RCTs of mammography screening took place several decades ago, before the epoch of effective adjuvant systemic therapies and the introduction by many health care providers of multidisciplinary management of cancer care, including through multidisciplinary care teams (MDT) or tumor boards meetings in the United States (8). These changes have led, in turn, to improved survival in patients with breast cancer. Thus, there remains the question of whether the intervention of early detection is still necessary when prognosis has improved for breast cancers of all stages (9, 10). In addition, there have been changes to the mammography screening test since the RCTs, such as the introduction of two-view mammography (11), and to referral policies and practices with respect to breast symptoms (12). An estimate of the effect of breast cancer screening on mortality from the disease in the 21st century is therefore of value to both health care providers and consumers.

The case–control approach to the evaluation of cervical screening has been particularly productive (13, 14). In breast cancer screening, estimates from case–control studies have been shown to be in reasonable agreement with RCT estimates, providing adequate adjustment/correction is made (15–17). Case–control studies of the effect of screening on breast cancer mortality are potentially prone to self-selection bias whereby women who choose not to comply are generally thought to have a higher underlying risk of breast cancer death, as had been observed in the analysis of the 1980s trial data (18, 19). Case–control studies of the effect of screening on breast cancer mortality also suffer from lead time, the amount of time by which the date of diagnosis of the case has been advanced by screening, that is, the screen at which a case is diagnosed will be counted as screening exposure,

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whereas a screen which occurred after the case diagnosis (but prior to the date on which it would have been diagnosed symptomatically) for a matched control will not. This may confer a bias against screening due to the lesser opportunity for screening among healthy women (controls).

Using the case–control design, attendance at breast screening has been reported to halve breast cancer mortality risk across Europe and Australia after correcting for self-selection (reviewed in refs. 7, 20, 21).

In this article, we report the results from a case–control study which included primary breast cancer deaths that occurred in 2008 and 2009, that is, 20 years after the inception of the English screening program, to assess the ongoing impact of the NHS BSP on breast cancer mortality. The study was set up in the London region (England), which has a dynamic population with a high degree of cultural, ethnic, and socioeconomic diversity with screening coverage consistently lower than the national average (22).

Materials and Methods

Study design

A case–control study nested with the NHS BSP was set up. We targeted women residing in the London region, who had been invited to participate in the NHS BSP from 1988 onward, and who had not expressed dissent to their records being used for evaluation purposes. In England, patients have the opportunity to specify that their primary health care data cannot be shared with third parties for the purposes of audit, research, or commerce. Patients who made such a stipulation were excluded from this study.

This study is part of a protocol for the ongoing evaluation of the English NHS BSP and has received all relevant approvals (details published in ref. 23).

All women registered as having primary breast cancer as the leading cause of death on their death certificate (rather than as contributing to death or with no specified leading cause), as having died ages 47 to 89 years between the 1st of January 2008 and the 31st of December 2009, and as having been first diagnosed with primary breast cancer (invasive) ages 47 to 89 years and since 1990 were selected as cases.

Each case was matched to one or two general population controls sampled from the National Health Applications and Infrastructure Services (NHAIS) system of the Health & Social Care Information Centre (HSCIC) national database: each control was alive at the case's date of death and had not been diagnosed with breast cancer prior to the case's date of first diagnosis, to allow for equal screening opportunity. The controls were matched to cases according to date of birth, within 6 months in either direction, to account for the increased incidence of breast cancer with age, and were registered in the same NHAIS area (English geographical screening entity), within London, as the case, at the case's date of first diagnosis.

Controls were given a pseudodiagnosis equal to the date of first diagnosis of their matched case.

All cases and controls had been invited to take part in the NHS BSP at least once prior to their first diagnosis/pseudodiagnosis date. For cases who had been registered on the local NHAIS system by age 47 years, or who had records of cervical screening prior to age 47 years, which could be taken to imply that they had been registered with the NHS, controls were selected who had either specification. For cases who had not been registered on the local NHAIS system by age 47 years, nor had records of cervical screening prior to age 47 years, controls were selected who had received a first invitation to breast screening within 6 months either side of the case's date of first invitation to breast screening. This strategy ensured that both cases and controls received similar number of invitations.

Data collection

Cause of death was obtained from the Office for National Statistics (ONS) and linked to the primary breast cancer occurrences data extracted from the National Cancer Data Repository (NCDR) by the National Cancer Intelligence Network (NCIN) London.

Screening history data were traced on the NHAIS system and linked to breast cancer data. In the United Kingdom, users of the NHS have a unique NHS number. We ensured accurate linkage using this number in addition to the woman's date of birth. Only breast screens with corresponding invitation dates sent at ages 47 to 73 years and prior to date of diagnosis/pseudodiagnosis were included in the analysis. Mammograms performed outside of the screening program are not registered in this database.

All data were processed in accordance with NHS Information Governance guidelines (NHS IG Toolkit, https://www.igt.hscic.gov.uk/).

Power calculation

The OR for breast cancer mortality associated with ever attending breast screening was assumed to be equal to the meta-analysis estimate of 0.70 obtained by Broeders and colleagues (7). With two controls per case, and an estimated number of discordant pairs of 33%, 800 cancer deaths, and 1,600 general population controls would provide over 90% power to detect such an effect size at the 5% significance level using a two-sided test (24).

Statistical analysis

Regression modeling. Cases and controls were compared with respect to attendance at breast screening using conditional logistic regression. Matching factors, that is, date of birth and NHAIS area registration, were controlled for in the design. Various measures of exposure to mammographic screening were assessed, including ever being screened, time since last screen, and number of screens attended. The extent of self-selection and lead time (exposure opportunity) biases were investigated.

Self-selection. The ORs (ψ) obtained using conditional logistic regression were corrected for self-selection bias using the formula derived by Duffy et al. (19) where a correction factor "D_r" is defined as the relative risk of breast cancer death for nonattenders compared to those not invited, and "ψ" is the corrected OR:

$$\psi' = \psi.p.D_r/(1-(1-p).D_r),$$

where p is the proportion of control women who attend the screening invitation. "D_r" was estimated using the relative risk of breast cancer–related death in nonattenders to the cervical screening program compared with the general population, adjusted for confounding of cervical screening attendance with breast screening attendance (see details in ref. 25).

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For analyses of time since last screen stratified by age at first diagnosis, the logistic regression was adjusted for contemporary attendance at cervical screening prior to diagnosis using a three-category variable to partially account for self-selection: "Never screened," "Formerly screened (> 60 months)," and "Currently screened (0–60 months)."

Lead time (exposure opportunity) Although we adopted a selection strategy which allowed for similar opportunity in terms of invitation to breast screening, controls assigned to screen-detected cases may not have had an equal opportunity to attend the last invitation prior to date of diagnosis/pseudodiagnosis as their matched case.

As controls are given a pseudodiagnosis date equal to that of their matched case diagnosis and as screening history is only considered up to that date, the fact that cases have necessarily a diagnosis of breast cancer whereas controls do not, induces an artificially higher retrospective probability of screening exposure in the cases, and results in a bias against screening (26). This bias can be assumed to be minimal when assessing the effect of ever having been screened, due to the program being a mature one, with approximately six incidence screens (over 20 years).

However, when assessing the effect of number of screens or time since last screen, this bias cannot be ignored. To compensate for the lead time owing to cancer screen detection among cases, a sensitivity analysis was performed where the pseudodiagnosis date of the controls matched to each screen-detected case was postponed by 1 year to allow the control women to be screened for a duration comparable with the preclinical detectable phase/clinical lead time (27), and by 3 years to allow for an extra screening round (4).

All statistical analyses were performed using the statistical softwares STATA version 12.1 (www.stata.com) and R version 2.13.0 (The R Foundation for Statistical Computing, www.r-project.org/foundation).

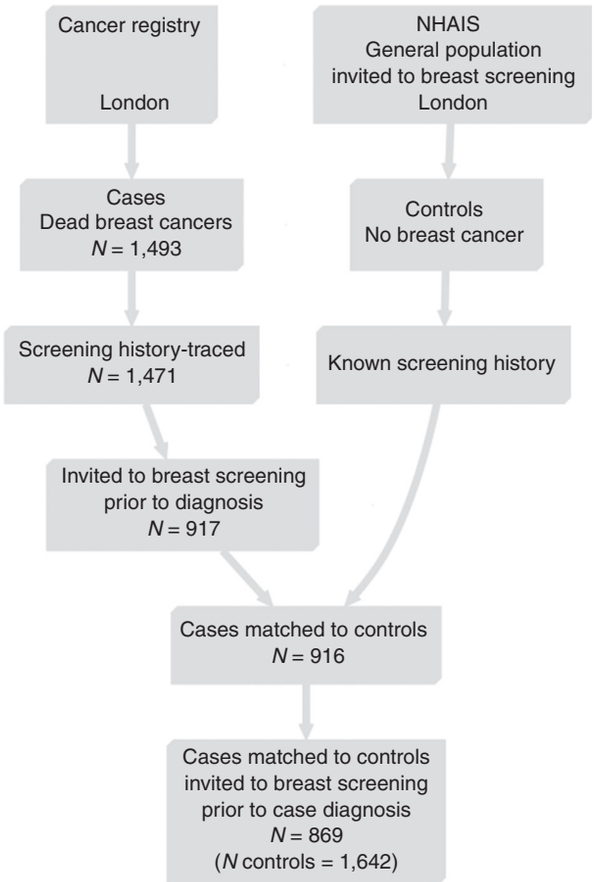

Figure 1.
Overview of the case–control study dataset.

Results

Data description

A total of 1,493 breast cancer deaths were registered in London during 2008 to 2009; of these, 1,471 were traced in the NHAIS database. Sixty-two percent of these women (917 cases) had breast screening registration records prior to first diagnosis and 916 were matched to at least one control who had not been diagnosed with breast cancer at the date of first diagnosis of their matched case (Fig. 1). Forty-seven matched sets were excluded because either the case or both controls had not been invited to the NHS BSP at least once prior to the case's date of first diagnosis, or because the date of first invitation for both controls fell more than 4 years distant from the case first invitation. Therefore, 869 cases and 1,642 controls (773 cases matched to two controls and 96 matched to one control) remained in the dataset used in the main analysis.

Over 80% of women in our dataset selected were diagnosed from the year 2000 onward (Table 1). The cases' median age at diagnosis was 63.1 years and median age at death 69.1 years.

Median age at first NHS BSP invitation was 52.6 for both cases and controls, and both groups received a median number of invitations to breast screening of 3. Among participants in breast screening, median ages at first (53.9 for controls and 54.4 for cases) and last (60.7 for controls and 60.8 for cases) breast screens were similar, although proportionally more controls attended their first (70.5% vs. 62.8% for cases) and last (68.5% vs. 61.6% for cases) invitation (Table 1). In addition, the proportion of women who never attended screening was larger for cases (25.3% vs. 18.3% for controls) and was mirrored by a larger proportion of control women having attended screening more than once (53.6% vs. 46.7% for cases, Table 1).

Effect of attendance at screening after adjusting for self-selection bias and underlying attendance rate

Breast cancer mortality was 35% lower among attenders at breast screening compared with those who never attended [OR, 0.65; 95% confidence interval (CI), 0.53–0.80; Table 2]. Correcting for self-selection bias had little impact on the overall OR [corrected OR, 0.61; 95% CI, 0.44–0.85 based on a correction factor D_r of 0.95; 95% CI, 0.74–1.23 and an attendance rate p of 81.7%, (25)]. Attendance at last invitation was associated with significant but lower mortality reduction (corrected OR, 0.74; 95% CI, 0.62–0.90; Table 2), as this population of attenders was enriched in screen-detected fatal cancers.

Among women who had been invited at least twice, attending breast screening more than once conferred greater benefit (corrected OR, 0.66; 95% CI, 0.45–0.98) than attending once only

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Table 1. Patient demographics and screening history by case–control status

Patient demographics		
	Controls (*N* = 1,642)	**Cases (*N* = 869)**
Breast cancer diagnosis and death		
Year of first diagnosis/pseudodiagnosis (Count, %)		
1990–1994	57 (3.5)	31 (3.6)
1995–1999	216 (13.2)	113 (13.0)
2000–2004	483 (29.4)	256 (29.5)
2005–2009	886 (54.0)	469 (54.0)
Age category at first diagnosis/pseudodiagnosis (Count, %)		
47–54	260 (15.8)	133 (15.3)
55–59	377 (23.0)	196 (22.6)
60–64	296 (18.0)	157 (18.1)
65–69	267 (16.3)	145 (16.7)
70–74	244 (14.9)	129 (14.8)
75–89	198 (12.1)	109 (12.5)
Median age at first diagnosis/pseudodiagnosis in years (range)	63.0 (48.0–87.8)	63.1 (48.0–87.8)
Median age at death in years (range)	NA	69.1 (51.6–88.0)

Patient screening history		
	Controls (*N* = 1,642)	**Cases (*N* = 869)**
Breast screening history		
Number of screening invitations (Count, %)		
1	407 (24.8)	239 (27.5)
2	398 (24.2)	192 (22.1)
3	360 (21.9)	173 (19.9)
4	235 (14.3)	135 (15.5)
5+	242 (14.7)	130 (15.0)
Median number of screening invitations (range)	3.0 (1–9)	3.0 (1–8)
Median age at first screening invitation in years (range)	52.6 (47.3–71.9)	52.6 (47.0–72.1)
Attendance at first screening invitation		
Did not attend	485 (29.5)	323 (37.2)
Attended	1,157 (70.5)	546 (62.8)
Median age at last screening invitation in years (range)	61.2 (47.3–73.8)	61.2 (47.3–73.9)
Attendance at last screening invitation		
Did not attend	518 (31.6)	334 (38.4)
Attended	1,124 (68.5)	535 (61.6)
Number of screens (Count, %)		
0 (Never screened)	300 (18.3)	220 (25.3)
1	462 (28.1)	243 (28.0)
1+	880 (53.6)	406 (46.7)
Median number of screens (range)	2.0 (0–7)	1.0 (0–8)
Median time since last screen (range)–*among compliers*	2.3 yrs (0 days–19.7 yrs)	2.4 years (0 days–20.0 years)
Median age at first screen in years (range)–*among compliers*	53.9 (47.6–72.2)	54.4 (47.3–71.0)
Median age at last screen in years (range)–*among compliers*	60.7 (47.6–73.9)	60.8 (49.1–73.9)
Cervical screening history		
Attendance at cervical screening (Count, %)		
Never screened	355 (21.6)	200 (23.0)
Formerly screened (>60 months)	517 (31.5)	284 (32.7)
Currently screened (0–60 months)	770 (46.9)	385 (44.3)

(corrected OR, 0.88; 95% CI, 0.62–1.25; Table 2) compared with never being screened.

The beneficial effect of ever attending an invitation was slightly more pronounced in the more recent years, that is, among cases diagnosed since 2000 (corrected OR, 0.54; 95% CI, 0.36–0.81).

Effect of time since last attendance at breast screening according to age at first diagnosis

Overall, the breast cancer mortality reduction decreased with time since last screen, from a 66% reduction (OR, 0.34; 95% CI, 0.25–0.46) for last attendance in the 2 years prior to date of diagnosis/pseudodiagnosis (excluding the first 3 months to account for most of the screen-detected cancers) to a 20% reduction for last attendance more than 5 years prior to diagnosis (OR, 0.80; 95% CI, 0.60–1.06; Table 3). This decreasing trend was seen for all age categories investigated.

Attendance within the last 3 years resulted in a 60% reduction in mortality (OR, 0.40; 95% CI, 0.31–0.51; Table 3) with an even greater benefit observed in the older age group (70+; OR, 0.33; 95% CI, 0.14–0.73; Table 3). Adjustment for attendance at cervical screening, as a means of addressing self-selection, had little effect on the ORs (data not shown).

There were only two notable differences in effect with respect to age. First, for attendance within the last 2 years, the reduction in mortality was less pronounced among women diagnosed at a younger age (OR, 0.42; 95% CI, 0.29–0.62 for diagnosis age 47–59 years; and OR, 0.29; 95% CI, 0.17–0.50 for diagnosis age 60—69 years; Table 3). Second, in those ages over 70 years, there was still a substantial (30%) reduction in

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Table 2. Conditional ORs of mortality from primary breast cancer for attendance at breast screening

Exposure to screening	Cases/controls	Self-selection bias correction factor D_r[a] (95% CI)	OR (95% CI, *P* value) Primary analysis	OR (95% CI, *P* value) + 3 years exposure
Invited at least once				
Never screened	220/300		1.00 (—)	1.00 (—)
Number of screen ≥ 1	649/1,342	None	0.65 (0.53–0.80, <0.001)	0.62 (0.50–0.76, <0.001)
		$D_r = 0.95$ (0.74–1.23)	0.61 (0.44–0.85, 0.004)	0.59 (0.42–0.82, 0.002)
Did not attend last invitation	334/518		1.00 (—)	1.00 (—)
Attended last invitation	535/1,124	None	0.73 (0.62–0.88, 0.001)	0.72 (0.60–0.86, <0.001)
		$D_r = 1.01$ (0.93–1.11)	0.74 (0.62–0.90, 0.002)	0.73 (0.60–0.90, 0.003)
Invited at least twice				
Never screened	121/178		1.00 (—)	1.00 (—)
Number of screen = 1	103/177	None	0.83 (0.59–1.18, 0.3)	0.83 (0.59–1.17, 0.3)
		$D_r = 1.03$ (0.94–1.13)[b]	0.88 (0.62–1.25, 0.5)	0.88 (0.62–1.25, 0.5)
Number of screen > 1	406/880	None	0.62 (0.47–0.82, 0.001)	0.66 (0.51 - 0.87, 0.003)
		$D_r = 1.06$ (0.81–1.39)[b]	0.66 (0.45–0.98, 0.04)	0.71 (0.49–1.03, 0.07)

[a]Self-selection correction of OR using data on attendance at the cervical screening program (described in ref. 25).
[b]Women were assumed to have been invited at least twice to the cervical screening program to derive D_r.

mortality associated with last attendance being more than 5 years prior to date of diagnosis/pseudodiagnosis (OR, 0.70; 95% CI, 0.47–1.04).

Sensitivity analyses were performed which allowed for the controls of screen-detected cases to have the opportunity to be screened in the 3 years following the case's date of first diagnosis to account for any exposure opportunity bias (an additional 252 invitations were received by the controls and 179 were attended). Extending the period of screening opportunity for the controls only impacted the ORs among younger women in terms of benefit of attendance at screening beyond 3 years prior to diagnosis, showing a 10% to 15% increase in mortality reduction, for example, from 0.75 down to 0.67 for attendance in the last 3 to 5 years (Table 3).

Table 3. Conditional ORs of mortality from primary breast cancer according to time since last breast screen: correction for lead time (exposure opportunity) bias (analyses were adjusted for attendance at cervical screening[a])

Age at case first diagnosis	Time since last breast screen	Cases/controls	OR (95% CI, *P* value) Primary analysis	OR (95% CI, *P* value) + 3 years exposure
47–89				
	Never screened	**220/300**	**1.00 (—)**	**1.00 (—)**
	Screened 3–36 months	215/716	0.40 (0.31–0.51, <0.001)	0.39 (0.30–0.50, <0.001)
	Screened >60 months	212/381	0.80 (0.60–1.06, 0.1)	0.78 (0.59–1.04, 0.08)
	Screened 36–60 months	61/138	0.62 (0.42–0.91, 0.02)	0.60 (0.41–0.88, 0.009)
	Screened 24–36 months	88/240	0.48 (0.35–0.67, <0.001)	0.47 (0.34–0.65, <0.001)
	Screened 3–24 months	127/476	0.34 (0.25–0.46, <0.001)	0.33 (0.25–0.45, <0.001)
	Screened ≤3 months	161/107	2.66 (1.84–3.87, <0.001)	2.54 (1.74–3.70, <0.001)
47–59				
	Never screened	**98/138**	**1.00 (—)**	**1.00 (—)**
	Screened 3–36 months	107/365	0.45 (0.32–0.65, <0.001)	0.42 (0.29–0.61, <0.001)
	Screened >60 months	12/20	0.75 (0.34–1.66, 0.5)	0.64 (0.30–1.40, 0.3)
	Screened 36–60 months	19/41	0.75 (0.40–1.40, 0.4)	0.67 (0.36–1.25, 0.2)
	Screened 24–36 months	34/99	0.54 (0.33–0.89, 0.02)	0.50 (0.30–0.82, 0.006)
	Screened 3–24 months	73/266	0.42 (0.29–0.62, <0.001)	0.40 (0.27–0.60, <0.001)
	Screened ≤3 months	93/73	2.48 (1.52–4.04, <0.001)	2.42 (1.47–4.01, 0.001)
60–69				
	Never screened	**57/77**	**1.00 (—)**	**1.00 (—)**
	Screened 3-36 months	96/306	0.35 (0.22–0.57, <0.001)	0.35 (0.22–0.57, <0.001)
	Screened >60 months	52/74	0.97 (0.54–1.72, 0.9)	0.98 (0.55–1.76, 0.96)
	Screened 36–60 months	34/77	0.59 (0.32–1.08, 0.09)	0.59 (0.32–1.08, 0.08)
	Screened 24–36 months	46/119	0.46 (0.26–0.80, 0.006)	0.46 (0.26–0.80, 0.006)
	Screened 3–24 months	50/187	0.29 (0.17–0.50, <0.001)	0.29 (0.17–0.50, <0.001)
	Screened ≤3 months	63/29	3.86 (1.95–7.64, <0.001)	3.47 (1.75–6.88, 0.001)
70–89				
	Never screened	**65/85**	**1.00 (—)**	**1.00 (—)**
	Screened 3–36 months	12/45	0.33 (0.14–0.73, 0.006)	0.33 (0.14–0.73, 0.006)
	Screened >60 months	148/287	0.70 (0.47–1.04, 0.07)	0.70 (0.47–1.04, 0.07)
	Screened 36–60 months	8/20	0.54 (0.21–1.35, 0.2)	0.54 (0.21–1.35, 0.2)
	Screened 24–36 months	8/22	0.46 (0.18–1.16, 0.1)	0.46 (0.18–1.16, 0.1)
	Screened 3–24 months	4/23	0.18 (0.05–0.65, 0.009)	0.18 (0.05–0.65, 0.009)
	Screened ≤3 months	5/5	1.58 (0.33–7.56, 0.6)	1.58 (0.33–7.56, 0.6)

[a]Self-selection adjustment using and attendance at cervical screening. See categorization in Table 1.

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Discussion

The aim of our study was to assess the current impact of attendance at a national breast screening program on breast cancer mortality in an urban region (London) with relatively low screening coverage compared with the national average (i.e., 65% compared with 77% national average in 2008–09 for women ages 50–70; ref. 22).

We found that attending breast screening at least once reduced the mortality risk by 35% (for a 81.7% "ever attendance" rate among controls), and that this estimate was not affected by self-selection. Attending in the last 3 years (prior to the case's date of diagnosis/pseudodiagnosis) resulted in around 60% reduction in mortality. The benefit of attending screening was slightly larger in cancers diagnosed since 2000.

Our unadjusted estimate of mortality risk reduction for ever attending breast screening was very close to a previous case–control study undertaken in another region of the United Kingdom, that is, a 38% crude reduction in Wales for a 77% "ever attendance" rate among controls (28). Our estimate was also very similar to the estimate obtained for a case–control study run in the London region 20 years prior: a 33% crude reduction was observed for a 72% "ever attendance" rate among controls (29). The much larger crude reduction observed in the UK East Anglia region (65% reduction for a 89% "ever attendance" rate among controls; ref. 30) is likely to have been due to the short survival of the selected cases (diagnosis and death during the same time period).

Our unadjusted estimate of mortality risk reduction for ever attending breast screening was also lower than the unadjusted estimate obtained in Iceland (41% reduction for a 62% "ever attendance" rate among controls; ref. 31), in five Italian regions (56% reduction in mortality for a 62% "ever attendance" rate among controls; ref. 32), and in two Australian regions [41% reduction for a 62% "ever attendance" rate among controls, (33) and 49% reduction for a 56% "ever attendance" rate among controls, (20)].

Attendance at breast screening in the 3 years prior to case diagnosis (screen-detected cancers excluded) led to a 60% reduction in mortality: this estimate is not widely at variance with results obtained for recent attendance in a number of Dutch regional studies. They observed between 30% and up to 70% reduction in seven different regions (21, 34, 35): in the most urban region with relative lowest attendance rate (SBBZWN), the unadjusted reduction was 56%, an estimate indeed very close to our estimate of effect of attendance in the 3 years prior to case diagnosis. The proportion of controls who had never responded to an invitation in our study was very similar to the proportion observed by Otto and colleagues (35), that is, 18.3% vs. 18.1%; the proportion of cases who never attended was, however, far larger in the Netherlands (35.9% compared with 25.3% in our study), as was the proportion of screen-detected cases (29.8% vs. 18.5%).

In agreement with our results, other case–control studies have reported increased benefit with number of screens, and decreased benefit with increasing time since last breast screen, that is, in the United Kingdom (28, 30) and in early (prior to 1990) studies set up in Utrecht, the Netherlands (36, 37).

The increased benefit of attendance at breast screening with age at first diagnosis was observed previously (20, 33, 35). Our estimate for the 70 to 89 years age group may be subject to strong self-selection bias, as after 70 years old, one would have to self-refer to be screened. This fact may also be reflected in the difference seen between the OR of attendance at last invitation and the OR of attendance in the last 3 years, as women diagnosed over the age of, for example, 73 years may not have been invited in the last 3 years. It is worth noting that our estimated mortality reductions did not vary substantially by age, suggesting that from age 47 years to well over the age 70 years, there is a similar relative benefit from mammography screening.

The breast cancer mortality reductions observed in association with screening in the RCTs of mammography may not automatically apply in our current epoch of effective adjuvant systemic therapy and standardized management of breast cancer. It is therefore important for both health care providers and women invited to screening to estimate the effect of current screening programs on risk of death from breast cancer. In this study, we assessed the effect of the NHS Breast Screening Program on deaths from breast cancer in 2008 to 2009. The majority of tumors were diagnosed since the year 2000, unequivocally in this adjuvant therapy epoch.

The fact that we observed a slightly larger effect of screening from 2000 onward may be a consequence of the roll-out for the adoption of two-view mammography in all breast screening units at every attendance from 2000 (11), or of the extension of the program to include women ages 65 to 70 from 2001 (3). In addition, changes in breast cancer management, such as the introduction of new referral and practice guidelines with respect to breast symptoms and the implementation of MDTs alongside screening in more recent years may be a contributory factor (12, 38).

We felt that an approach which uses contemporary data was desirable to estimate the degree and effect of self-selection in our study population. We chose to use a new approach based on contemporary attendance at cervical screening to estimate the underlying risk of breast cancer–related death in the different screening groups compared (for details, see ref. 25). Our results suggest that self-selection bias in the London region is limited (close to 1.0) when assessing the effect of screening on breast cancer mortality among the general population. This observation is in agreement with findings by other authors who used contemporary data, including in the United Kingdom among women ages 40 to 49 years (39). Cases and controls were drawn from the same cohort of women invited to screening and their screening histories were retrieved from the same database; in addition, they were selected from within the same geographical screening area; this may have increased similarities in terms of demographic and socioeconomic characteristics, consequently accounting for some of the self-selection.

In our study, cases and controls were not matched on the number of invitations to breast screening they received, and the screening database does not record round of invitation. Sensitivity analyses did not expose residual opportunity bias for controls, suggesting the design adequately ensured equal screening opportunity among controls. In the extension of this case-control evaluation to the rest of England, we will be selecting controls who receive their first invitation within 6 months of the case's date of first invitation.

We report on the findings of the largest case–control study assessing the impact of participation in the English national breast screening program. Cases and controls were drawn from the same

underlying cohort of the women invited to screening in the most populated region of the country.

In this urban population, attendance at breast screening led to a decrease in breast cancer mortality of 35% which is higher than the reported 20% reduction observed in the RCTs of mammographic screening, but lower than the approximate 50% reductions reported using various case–control designs in other regions of Europe and Australia with different population characteristics (reviewed in refs. 7, 20, 21). Self-selection was observed to be minimal.

Our results provide evidence of a clear beneficial effect of the NHS BSP on the risk of mortality from breast cancer in an area of England known to have low coverage. We found no evidence suggesting that attendance at this mature screening program provided women with a lesser benefit in the more recent years.

Overall, our results suggest that community breast screening programs provide their expected benefit in terms of reducing the risk of breast cancer death among women participating. Mammography is an important tool for reducing breast cancer mortality and its impact could be increased by encouraging regular attendance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: N.J. Massat, P.D. Sasieni, S.W. Duffy
Development of methodology: N.J. Massat, P.D. Sasieni, S.W. Duffy
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Parmar
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N.J. Massat, A. Dibden, J. Cuzick, P.D. Sasieni, S.W. Duffy
Writing, review, and/or revision of the manuscript: N.J. Massat, A. Dibden, J. Cuzick, P.D. Sasieni, S.W. Duffy
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D. Parmar
Study supervision: P.D. Sasieni, S.W. Duffy

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