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

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Running title

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Abstract (250 words)

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 programmes. A case-control study was set up to assess the current impact of attendance in the English Breast Screening Programme on breast cancer mortality.

Methods Cancer registry cases who died from primary breast cancer aged 47-89 in London in 2008-2009 (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. Odds ratios (OR) were estimated using conditional logistic regression. Self-selection bias was addressed using contemporaneous attendance at the cervical screening programme. 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 36% (OR=0.64, 95%CI 0.45-0.88) after self-selection correction. Attendance in the last 3 years prior to diagnosis resulted in a 61% mortality reduction (OR=0.39, 95%CI 0.30-0.50). Lead time bias effects were negligible.

Conclusion Our results suggest that community breast screening programmes 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.

Introduction

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

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

There are two motivations for the ongoing evaluation of mammographic screening programmes, with particular reference to their effect on breast cancer mortality. The first relates to the monitoring and audit of specific programmes, 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 healthcare providers of multidisciplinary management of cancer care, including through multidisciplinary care teams (MDT) or tumor boards meetings in the US (8). These changes have led in turn to improved survival in breast cancer patients. 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 twenty-first century is therefore of value to both healthcare providers and consumers.

The case-control approach to 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),(16),(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 1980's 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;, i.e. the screen at which a case is diagnosed will be counted as screening exposure, 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 (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, i.e. 20 years after the inception of the English screening programme, to assess the on-going 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 socio-economic diversity with screening coverage consistently lower than the national average (22).

Material & 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 onwards, 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 healthcare 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 on-going evaluation of the English NHS BSP and has received all relevant approvals (details published in (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 aged 47-89 between the 1st of January 2008 and the 31st of December 2009 and as having been first diagnosed with primary breast cancer (invasive) aged 47-89 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 pseudo-diagnosis 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/pseudo-diagnosis date. For cases who had been registered on the local NHAIS system by age 47, or who had records of cervical screening prior to age 47, which could be taken to imply that they had been registered with the National Health Service (NHS), controls were selected who had either specification. For cases who had not been registered on the local NHAIS system by age 47, nor had records of cervical screening prior to age 47, 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 UK, users of the National Health Service 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 47-73 and prior to date of diagnosis/pseudo-diagnosis were included in the analysis. Mammograms performed outside of the screening programme 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 odds ratio (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 et al. (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 2-sided test (24).

Statistical methods

Regression modelling

Cases and controls were compared with respect to attendance at breast screening using conditional logistic regression. Matching factors, i.e. 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 OR (ψ) was 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 non-attenders compared to the not invited:

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

where p is the proportion of control women who attend the screening invitation. 'D_r' was estimated using the relative risk of breast cancer death in non-attenders to the cervical screening programme compared to the general population, adjusted for confounding of cervical screening attendance with breast screening attendance (see details in (25)).

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 3-category

variable in order 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/pseudo-diagnosis as their matched case.

As controls are given a pseudo-diagnosis 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 while 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 programme being a mature one, with approximately 6 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 pseudo-diagnosis 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 to 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*)

Results

Data description

1,493 breast cancer deaths were registered in London during 2008-2009; 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 (Figure 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 2 controls and 96 matched to 1 control) remained in the dataset used in the main analysis.

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

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% versus 62.8% for cases) and last (68.5% versus 61.6% for cases) invitation (Table 1b). In addition, the proportion of women who never attended screening was larger for cases (25.3% versus 18.3% for controls) and was mirrored by a larger proportion of control women having attended screening more than once (53.6% versus 46.7% for cases, Table 1b).

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%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 (corrected OR=0.88, 95%CI 0.62-1.25) compared to never being screened.

The beneficial effect of ever attending an invitation was slightly more pronounced in the more recent years, i.e. 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/pseudo-diagnosis (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, and OR=0.29, 95%CI 0.17-0.50 for diagnosis age 60-69, Table 3). Second, in those aged over 70, there was still a substantial (30%) reduction in mortality associated with last attendance being more than 5 years prior to date of diagnosis/pseudo-diagnosis (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 in order 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 10-15% increase in mortality reduction, e.g. from 0.75 down to 0.67 for attendance in the last 3 to 5 years (Table 3).

Discussion

The aim of our study was to assess the current impact of attendance at a national breast screening programme on breast cancer mortality in an urban region (London) with relatively low screening coverage compared to the national average (i.e. 65% compared to 77% national average in 2008-09 for women age 50-70,(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/pseudo-diagnosis) 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 UK, i.e. 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,(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,(31)), in five Italian regions (56% reduction in mortality for a 62% 'ever attendance' rate among controls,(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 by Otto et al. (35), i.e. 18.3% versus 18.1%); the proportion of cases who never attended was however far larger in the Netherlands (35.9% compared to 25.3% in our study), as was the proportion of screen-detected cases (29.8% versus 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, i.e. in the UK (28),(30) and in early (prior to 1990) studies set up in Utrecht, 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 70-89 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 e.g. 73 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 to well over age 70, 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 standardised management of breast cancer. It is therefore important for both healthcare providers and women invited to screening to estimate the effect of current screening programmes on risk of death from breast cancer. In this study, we assessed the effect of the NHS Breast Screening Programme on deaths from breast cancer in 2008-09. The majority of tumours 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 onwards 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 programme to include women aged 65-70 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 death in the different screening groups compared (for details, see (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 UK among women aged 40-49 (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 small geographical area; this may have increased similarities in terms of demographic and socio-economic 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 programme. 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 (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 programme provided women with a lesser benefit in the more recent years.

Overall, our results suggest that community breast screening programmes 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.

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List of abbreviations

HSCIC	Health & Social Care Information Centre
NCIN	National Cancer Intelligence Network (formerly Thames Cancer Registry)
NCDR	National Cancer Data Repository
NHAIS	National Health Applications and Infrastructure Services
NHS	National Health Service
NHS BSP	National Health Service Breast Screening Programme
NHS CSP	National Health Service Cervical Screening Programme
ONS	Office for National Statistics
OR	Odds Ratio
PRU	UK Policy Research Unit in Cancer Awareness, Screening and Early Diagnosis
RCTs	Randomised Controlled Trials

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Tables

Table 1 Patient demographics and screening history by case-control status

Table 1a. Patient demographics

		Controls (N = 1,642)	Cases (N = 869)
Breast cancer diagnosis & death			
Year of first diagnosis/pseudo-diagnosis (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/pseudo-diagnosis (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/pseudo-diagnosis 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)

Table 1b. 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 yrs (0 days – 20.0 yrs)
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 (0-60months)	770 (46.9)	385 (44.3)

Table 2 Conditional odds ratios (OR) 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)	Odds ratio (95% CI, p-value)	
			Primary analysis	+3 years exposure
Invited at least once				
Never screened	220 / 300		**1.00 (-)**	**1.00 (-)**
Number of screen ≥ 1	649 / 1342	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 / 1124	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 programme (described in (25))

[(b)] Women were assumed to have been invited at least twice to the cervical screening programme in order to derive D_r.

Table 3 Conditional odds ratios (OR) of mortality from primary breast cancer according to time since last breast screen: correction for lead time (exposure opportunity) bias

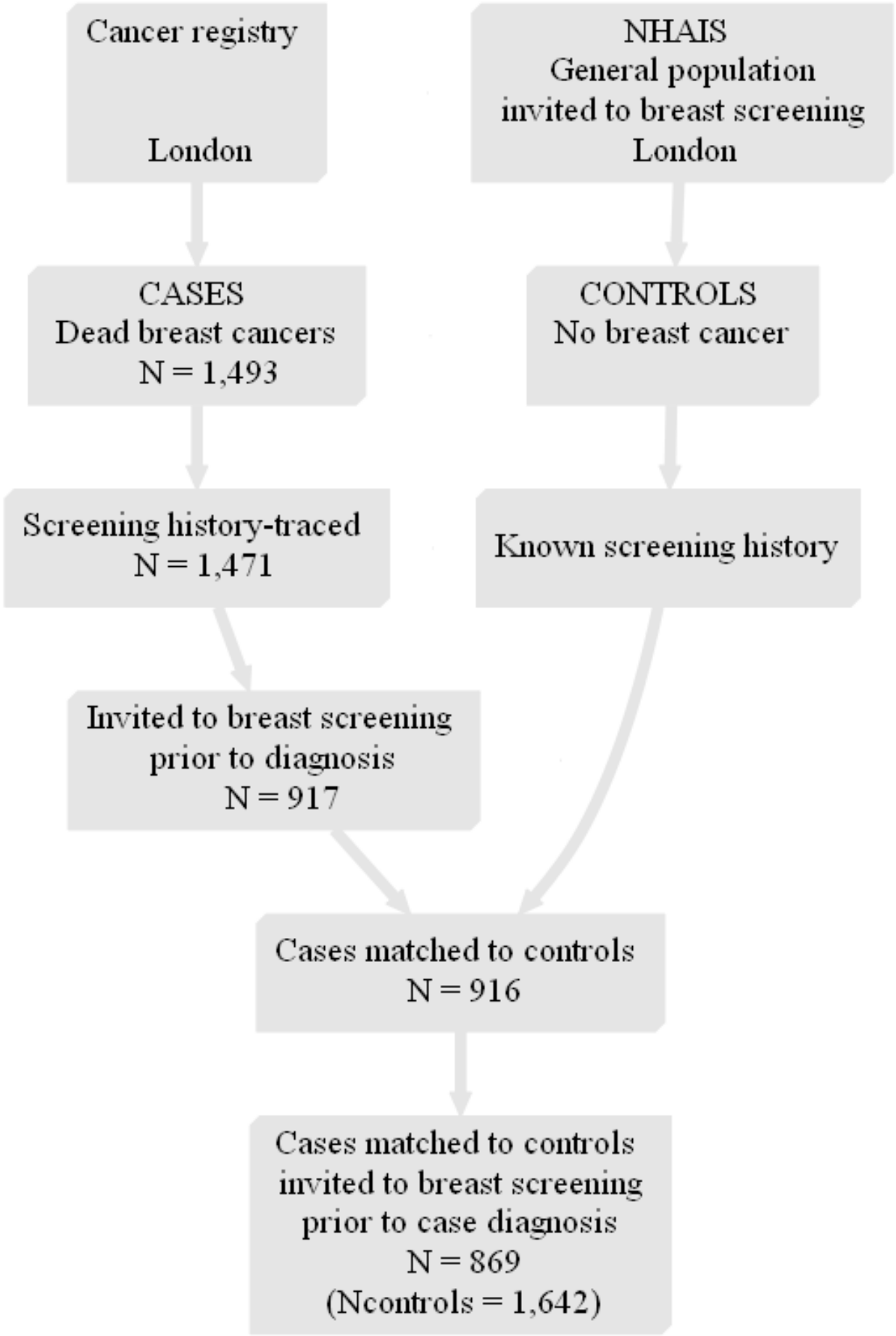
Analyses were adjusted for attendance at cervical screening[(a)].

Age at case first diagnosis	Time since last breast screen	Cases / Controls	Odds Ratio (95% CI, p-value)	
			Primary analysis	+ 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 1b.

List of Figures

Figure 1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General population
invited to breast screening
London
CASES
Dead breast cancers
N = 1,493
CONTROLS
No breast cancer
Screening history-traced
N = 1,471
Known screening history
Invited to breast screening
prior to diagnosis
N = 917
Cases matched to controls
N = 916
Cases matched to controls
invited to breast screening
prior to case diagnosis
N = 869
(Ncontrols = 1,642)