Explaining the better prognosis of screening-exposed breast cancers: influence of tumour characteristics and treatment

Running title
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List of Authors
Nathalie J Massat[1],

Peter D Sasieni[1],

Daniela Tataru[2],

Dharmishta Parmar[1],

Jack Cuzick[1],

and Stephen W Duffy[1].

Affiliations
[1] Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, England

[2] National Cancer Intelligence Network (NCIN), Public Health England, London, England

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Corresponding author
Stephen W. Duffy, Professor of Cancer Screening, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse square, London, EC1M 6BQ, UK

Tel: +44 (0)20 7882 3535

Email: s.w.duffy@qmul.ac.uk

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Abstract (237 words)

Background In England, population mammographic screening has been offered to women for over 20 years. Overall decrease in breast cancer mortality rates and improvements in cancer awareness and organisation of medical care over this period call for a more current evaluation of the mediators behind the better prognosis of screening-exposed breast cancers.

Methods A case-control study was conducted within the English National Breast Screening Programme. Women who died from primary breast cancer in 2008-09 were matched (by year of birth, screening invitation and area) to controls that received a diagnosis of invasive breast cancer at the time of the case diagnosis but survived the case death. Data were analysed by unconditional logistic regression with adjustment for matching factors.

Results The unadjusted odds ratio (OR) for dying from breast cancer associated with ever having attended breast screening was 0.44 (95%CI 0.33-0.58). After adjustment for lead time, overdiagnosis, and self-selection, the OR increased to 0.69 (95%CI 0.50-0.94). Adjusting for tumour size, lymph node status, stage, grade, histopathology and laterality accounted for all the screening effect (OR=1.00, 95%CI 0.71-1.40). Further adjustment for treatment factors only had a minimal impact on the OR (OR=1.02, 95%CI 0.72-1.45).

Conclusions Our results suggest that earlier diagnosis, as reflected by tumour characteristics, remains the major mediator of the improvement in breast cancer survival due to participation in mammographic screening.

Impact Mammographic screening continues to prevent breast cancer deaths in the epoch of adjuvant systemic therapy.

Introduction

Since the late 1970s, UK breast cancer mortality rates have been rising in all age groups alongside incidence rates until around 1990 when mortality rates started falling, including for women outside the screening age range (1),(2). This steady decrease is believed to be the result of (1) the implementation and improvement of the national screening programme , and (2) improvements in cancer staging and treatment including the use of adjuvant systemic therapies (3),(4),(5),(6). In addition, the inception of a screening service may have resulted in increased breast awareness (earlier response to self-detected breast symptoms) and coincided with better organisation of cancer care, including the implementation of multidisciplinary care in 1996 (7), possibly resulting in more effective treatment (8). The Cancer Intervention and Surveillance Modeling Network (CISNET) collaborators estimated that screening service delivery and advances in adjuvant treatment made similar large contributions to decreased mortality in the US (9). In Sweden, the majority of recent reductions in mortality in the screening age range were estimated to be due to screening (10).

Screening is concerned with the detection of disease at an early detectable stage and can only reduce the rate of death when followed by effective treatment. The expectation is that treatment will be more effective if begun earlier in the disease process. If improvements in treatment are such that better survival is achieved regardless of disease stage at diagnosis, then identifying cancer in early stages becomes less critical, rendering breast screening less relevant. Screening may also lead to overdiagnosis, the detection and treatment of tumours which would not have come to clinical attention during the woman's lifetime had screening not taken place (11).

In England, population mammographic screening has been offered to women for over 20 years. It is therefore important to assess the role of screening on fatality from breast cancer in the context of

potential risks as well as benefits, and its current contribution to survival from breast cancer, independent of treatment.

Here, we report on the results from a case-control study with an innovative design which allows us to compare cases who died from invasive primary breast cancer with controls who received a similar diagnosis but who survived the disease up to, and beyond the case's death, with respect to attendance at breast screening prior to diagnosis. The impact of disease attributes and cancer treatment on the relative effect of attendance at breast screening was investigated.

The purpose of this study was *not* to estimate the impact of screening on breast cancer mortality but to investigate sources of the difference in survival conferred by screening, with corrections for lead time, overdiagnosis and self-selection bias. The impact of screening on breast cancer mortality was assessed in a companion study (12).

Material & Methods

Study design

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. All women who died of primary breast cancer (as stated in part 1 of the death certificate) aged 47-89 between the 1st of January 2008 and the 31st of December 2009 and who had been first diagnosed with primary breast cancer (invasive) aged 47-89 and since 1990 were selected as cases. Cases identified as "Death Certificate Only" were excluded. Each case was matched to one control who was alive at the case date of death, was born within 4 months either side of the case date of birth, and was registered in the same cancer network as the case, at the case date of first diagnosis. The control had had a first diagnosis of primary breast cancer (invasive) within 6 months

prior to and including the case date of first diagnosis. All cases and controls had been invited to take part in the NHS BSP at least once prior the date of their first diagnosis.

Power calculation

The odds ratio (OR) for breast cancer death associated with ever attending breast screening was postulated to be equal to (or less than) the estimated 0.65 based on matched comparisons of breast cancer deaths with general population controls (13). With one control per case, 650 fatal cancers would provide 80% power to detect such an effect size at the 5% significance level using a 2-sided test (14).

Data collection

Tumour characteristics and treatment data were extracted from the National Cancer Data Repository (NCDR) by the National Cancer Intelligence Network (NCIN) London. Area-based deprivation quintiles based on the 2010 Income Domain of the English Indices of Multiple Deprivation (IMD) were also obtained (15).

Screening history data were traced on the National Health Applications and Infrastructure Services (NHAIS) system of the HSCIC database. Only breast screens with invitation dates which occurred after the 1st of January 1988, within age range 47-73 at invitation and prior to and including date of first diagnosis were included in the analysis. For cervical screening (used in adjustment for self-selection bias - see below), only screen dates which occurred after the 1st of January 1998, within age range 20-70 at screen and prior to and including date of first diagnosis were included in the analysis (cervical screening invitation data are not available on the NHAIS system).

Statistical methods

Regression modelling & adjustment for mediators of screening effect

Unusually, for a matched case-control study, the primary analysis had to be by unconditional logistic regression, with broad adjustment for the matching factors (cancer network registration and age at first diagnosis, and year of first diagnosis), as the correction for overdiagnosis (see below) entailed removal of large numbers of controls which would have lost the case information in a conditional analysis. After adjustment for overdiagnosis/lead time and self-selection bias, we adjusted for tumour characteristics (histopathological size, lymph node status, tumour stage as classified by the registry and dichotomized to localised (1) or extending beyond the organ (2-4), histological grade (Bloom-Scarff-Richardson (BRS)), histological type, and laterality), and for treatment - whether a woman received surgery (mastectomy or Breast Conservative Surgery (BCS)), radiotherapy, chemotherapy and/or endocrine therapy within 6 months of first diagnosis.

Unknown tumour characteristics and treatment data were treated as separate categories. A sensitivity analysis was performed where relative effects of chemotherapy, radiotherapy and endocrine therapy compared to no treatment, from randomized trials, were included as offsets in the regression, based on data from the Early Breast Cancer Trialists' Collaborative Group (16). For each treatment (except surgery), offsets were set to 1 if the treatment was not received and to the relevant ratio if treatment was received, i.e. 0.79 (95%CI 0.72-0.85) for polychemotherapy (anthracycline-based regimen) (17); 0.83 (95%CI 0.73–0.95), 0.79 (95%CI 0.65–0.95) and 0.82 (95%CI 0.75–0.90) for radiotherapy of node-negative, node-positive, and node status unknown cancers respectively (18); and 0.76 (95%CI 0.70-0.82) for endocrine therapy (19).

Collinearity between treatment and tumour characteristics was assessed using the inflation observed in the estimated standard errors of the regression coefficients and was judged to be negligible (20).

Lead time, overdiagnosis & length bias

Lead-time, the amount of time by which the date of diagnosis has been advanced by screening as opposed to symptomatic detection, increases the apparent follow-up time of screen-detected cancers (defined in this study as cancers diagnosed in women having had their last breast screen within 90 of first diagnosis). This confers a survival bias *in favour* of screening.

The individual lead time (t) for the preclinical but screen-detectable phase was estimated for each screen-detected cancer assuming an exponential distribution with mean $1/\lambda$, where for the rate of transition to symptomatic disease (λ), we used 0.25 (mean sojourn time = 4 years) as estimated by Tabar and coll. (21).

For a screen-detected breast cancer patient who did not die of breast cancer (i.e. screen-detected controls), we sampled an unconditional random variable from the exponential distribution:

$$t = -\log(1 - Uniform[0,1])/\lambda\ .$$

Overdiagnosis corresponds to the detection (and associated treatment) of tumours, which would not have come to clinical attention during the woman's lifetime had screening not taken place. In our study design, the potential for overdiagnosis only applies to controls as by definition, cases were diagnosed with progressive (fatal) disease, and may confer a bias *in favour* of screening.

Overdiagnosis can therefore be seen as an extreme form of lead-time bias among screen-detected cancers, in which the lead time exceeds the future life time. In our analysis, we adjusted for overdiagnosis by excluding control women with estimated lead time extending beyond the case's date of death, and consequently we had to perform adjusted unconditional logistic regression analyses to avoid losing the corresponding case information. This is a highly conservative correction for overdiagnosis, since a control's lead time exceeding the corresponding case's time to death does not necessarily imply that the latter would exceed that control's time to death.

Self-selection

Self-selection, the voluntary compliance with the invitation to screening may bias the estimates of the effect of screening as factors related to both the decision to attend screening and the underlying risk of getting and/or dying from breast cancer may confound the relationship between exposure to screening and disease outcome.

The OR (ψ) was corrected for self-selection bias using the formula derived by Duffy et al. (22) 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 (23)).

For ever attendance at breast screening, a sensitivity analysis was also performed where the OR was calculated for women attenders among the invited compared to women who would have attended if invited (see details in (23)).

For analyses of time since last screen, the logistic regression was adjusted for deprivation, thought to be the major driver of self-selection bias in this context, and 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)".

All statistical analyses were performed using the statistical software R version 2.13.0 (The R Foundation for Statistical Computing, http://www.r-project.org/foundation).

Ethics

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 elsewhere (24)).

Results

Data description

1,493 breast cancer deaths were registered in London during 2008-09, and 1,192 of these were able to be matched to diseased controls and traced for screening history (Figure 1). Among these 1,192 pairs, 22 were excluded due to a first diagnosis being an in situ disease (8 controls & 14 cases) and 491 for not having been invited to the NHS BSP at least once prior to their first diagnosis (391 controls & 417 cases), leaving 679 pairs in the dataset for the main analysis.

Over 80% of women in our dataset selected were diagnosed from the year 2000 onwards (Table 1a). As per study design, cases and controls had the same median age at diagnosis (63 years old). Median age at death for the cases was 68 years old.

Median age at first NHS BSP invitation was 52 years for both groups. Among compliers with breast screening, median age at first breast screen was very similar (53 years old), while the proportion of women who never attended screening was larger for cases than for controls (26.4% versus 13.7%), and was mirrored by a larger proportion of control women having attended screening more than once (61.9% versus 48.2%). In addition, time since last breast screen was over a year longer for the case population (1.2 versus 2.4 years) and the number of screen-detected cancers, defined as cancers diagnosed in women having had their last breast screen within 90 of first diagnosis, was

higher among controls than cases (37.1% versus 18.7%). Controls also attended their last or penultimate invitation in larger proportion (41.7% versus 33.3%, and 57.7% versus 47.3%, respectively, Table 1b).

Impact of lead time, overdiagnosis and self-selection on the relative effect of exposure to breast screening

When assessing the effect of having attended at least one breast screen prior to first diagnosis on case fatality from breast cancer, the conditional OR (cOR) and the unconditional OR (uOR) adjusted for matching factors were found to be very similar (cOR=0.42, 95%CI 0.30-0.56 and uOR=0.44, 95%CI 0.33-0.58, respectively, Table 2).

To account for overdiagnosis, the unconditional analysis was repeated after excluding screen-detected controls with an estimated lead time extending beyond the date of death of their matched case (uOR=0.55, 95%CI 0.42-0.73, Table 2).

The treatment profile of early stage (localised) screen-detected cancers among women diagnosed age 47-74, potentially associated with overdiagnosis/overtreatment, was found to be less aggressive than that of symptomatic cancers (Table 3): only 9% of screen-detected women received chemotherapy and (an additional) 12% had mastectomy. The corresponding figures for symptomatic cancers were 19% and 29%.

Adjustment for deprivation had minimal impact on the relative effect of screening (uOR=0.56, 95%CI 0.42-0.75). Regular attendance at cervical screening (as measured by attendance in the last 5 years compared to never screened), but not deprivation, was an inverse predictor of primary breast cancer outcome (uOR= 0.75, 95%CI 0.54-1.03, p=0.08). Adjusting for self-selection using a 'D_r' estimated based on attendance at the cervical screening programme (D_r=1.19, 95%CI 1.05-1.36, see details in (23)) increased the uOR to 0.69 (95% CI 0.50-0.94, Table 2). This estimate was very close to a

sensitivity estimate of the OR calculated using women attenders among the invited compared to women who would have attended if invited (0.71, 95%CI 0.52-0.97, see details in (23)).

After excluding screen-detected cancers from the analysis, the unconditional OR was 0.60 (95%CI 0.45-0.81); it increased to 0.81 (95%CI 0.59-1.12) after adjustment for deprivation and correction for self-selection which was found to be larger in this subgroup of screen-exposed symptomatic women compared to the never screened (D_r=1.24, 95%CI 1.09-1.40, , see details in (23) and Table 2).

The risk of fatality reversed slightly with time since last screen compared to no screening with a conditional OR of 0.68 (95%CI 0.47-0.98) for last attendance over 5 years prior to first diagnosis, down to 0.59 (95%CI 0.39-0.89) for time since last screen of between 3 months and 2 years (Table 4). The better prognosis observed for screen-detected cancers in this analysis is strongly affected by overdiagnosis, lead time and length biases, so no inferences are made from this estimate.

Impact of disease attributes and cancer treatment on the relative effect of exposure to breast screening

Tumour size, tumour stage and surgery were the most single influential factors on the OR of the effect of screening: from uOR=0.56 (95%CI 0.42-0.75) after adjustment for overdiagnosis/lead time and deprivation, to uOR=0.70 (95%CI 0.52-0.94), uOR=0.63 (95%CI 0.47-0.85), and uOR=0.68 (95%CI 0.51-0.92), respectively.

The model was adjusted for tumour characteristics at diagnosis, which included tumour size, lymph node status, extension beyond organ (registry-based measure of stage), histological grade, histological type, and laterality (Table 1c): the unconditional OR of attending at least one routine breast screen prior to first diagnosis increased from 0.69 (95% CI 0.50-0.94, after correction for self-selection) to 1.00 (95%CI 0.71-1.40, Table 2), the tumour characteristics accounting entirely for the effect of screening.

Additional adjustment for treatment factors (surgery, radiotherapy, chemotherapy and endocrine therapy) had little impact on the OR (uOR=1.02, 95%CI 0.72-1.45). Using treatment effect estimates based on RCT data resulted in similar adjustment in the OR (uOR=1.04, 95%CI 0.73-1.49, Table 2).

Similar observations were made regarding the mediation, through disease attributes and treatment, of the effect of ever attending breast screening for symptomatic cancers (Table 2), and in terms of time since last screen in all cancers (Table 4).

Discussion

We estimated the impact of breast screening attendance on breast cancer fatality and investigated the current mediators of that effect. The study was carried out using an innovative case-control design in an urban region (London) with relatively low rates of participation in screening.

Attendance in the NHS BSP reduced fatality risk was by 45% after accounting for overdiagnosis and lead time in screen-detected cancers, and by 34% after additionally accounting for deprivation and self-selection. We found the major intermediaries between screening and survival to be the traditional tumour characteristics, in particular smaller size and extension beyond the breast, rather than differential treatment, in agreement with previously findings (25),(26),(27),(28),(29). We also observed increased fatality in left-sided or bilateral tumours. Reduction in size and likelihood of spread beyond the organ are considered a necessary effect of a screening programme (5). Our results are in agreement with recent reports comparing parallel cohorts in Denmark and Norway, which observed a residual effect of screening after introduction of multidisciplinary medical care in breast cancer management (30),(31).

After adjusting for these disease attributes, and for treatment (in addition to overdiagnosis and lead time), most of the screening effect (screen and interval detection) was accounted for, leaving little scope for other factors to explain the better prognosis of screening.

A beneficial effect of attendance at breast screening was also observed among screen-exposed women diagnosed with symptomatic cancers (40% for interval detection) compared to never screened, although this effect was no longer significant at the 5% level after correcting for self-selection (19% reduction). The residual benefit of screening was also explained by the characteristics of their tumour as previously noted by Day et al. (32). Interval tumours have previously been found to be smaller (and more likely to be estrogen receptor-positive) and associated with better survival than tumours in the unscreened population (33),(34),(35). We and others have noted that the survival benefit in interval cancers diminishes with time since last screen (36),(37), suggesting that the effect of attendance at breast screening is not entirely due to self-selection, while others have not (36).

Women who participated in the screening programme but whose cancer was not screen-detected may have developed increased self-awareness as a consequence of the information provided during the screening process: Tyndel et al. (38), have reported that women who had a recall had become more aware of their risk of developing breast cancer.

Deprivation is believed to be the main confounding factor between the decision to attend screening and cancer survival: in England, deprivation is associated with lower attendance at breast screening after adjustment for other socio-demographic factors, such as urbanisation and the percentage of ethnic minorities (39), and cancer survival is lowest in the most deprived areas (40). Deprivation adjustment had no impact on the OR pertaining to attendance at breast screening in spite of having been shown to impact both attendance at breast screening and survival from breast cancer (41), possibly because cases and controls were matched for diagnosis in the same cancer network,

imposing a degree of residential proximity. A similar observation was made for the case-control nested within the UK Age Trial which assessed the effect of the NHS BSP in a cohort of women age 40-49 (42).

To address self-selection , 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 (23). Our results suggest that self-selection bias among this group of women at higher risk of breast cancer is larger than among the general population (12).

Screening is likely to pick up cancers with best and worst prognosis. The fact that the effect of screening is minimal once the regression has been adjusted for tumour characteristics suggests that screening downstage tumours. Further investigation into the impact of tumour characteristics and treatment was limited by the absence of information on receptor status and other biological attributes (43), or type of endocrine therapy. Recent studies have questioned the relevance of tumour staging in treatment decisions, while histological and molecular characterisation of tumours and surrounding tissues have been shown to predict clinical outcomes (44),(45),(46),(47).

There has been limited scope for the clear distinction of fast- versus slow-growing or steady-state tumours (48),(49), and correspondingly, it has been considered necessary to intervene once a tumour has been diagnosed. Both invasive and in situ lesions have been found to have the potential to recur and metastasize, or to remain symptomless (indolent disease) (50),(51). An estimated 7% (range 3-15%) of 40–80 year-old women of various ethnical backgrounds are found to have undiagnosed, mainly in situ, breast cancer at autopsy (reviewed in (52)). Given the upper limit provided by the autopsy results, and the limitations of mammographic detection - an average of 1.16 cm threshold for women aged 50 to 69 (53) -, we believe that our approach which excluded approximately 15% of screen-detected controls accounted adequately for overdiagnosis & lead time.

In addition, our data suggest that the treatment associated with potential overdiagnosis, i.e. among screen-detected women diagnosed with early stage cancers after attending an invitation, tend to be less aggressive compared to the treatment received by early stage cancers detected symptomatically, i.e. they rarely - if ever - includes mastectomy or chemotherapy.

In 2013, the UK Independent Review panel of mammographic screening felt that the benefits of screening and those of improved treatments could reasonably be considered independent (6). If the recent improvements in treatment indeed rendered early detection redundant or less effective, we might have expected to see attenuation of the screening effect on fatality by adjustment for treatment factors. This was not the case. We found that most of the improved fatality associated with screening exposure was due to tumour characteristics, in common with earlier studies (25),(26),(27),(28),(29).

It is worth observing that effects of treatment in a non-randomised setting are themselves subject to selection bias, in that those given the most aggressive treatments tend to be those cases at most risk of poor outcome (54),(55). This was the case in this study with chemotherapy (data not shown). Accordingly, additionally to conventional adjustment, we also adjusted for the effects of therapies as found in meta-analyses of the randomised trials (16). The results were the same, in that the major mediating factors for the lower fatality of screening-exposed cases were the tumour characteristics rather than treatment.

In this study, over 80% of the women included received cancer treatment spanning over the last decade (2000-2009). In addition, the study design was such that epoch of diagnosis was confounded with the survival of the cases. It was therefore not possible to assess any change over time in the relative contribution of treatment o the screening effect, and hence the extents to which time trends in mortality are due to screening or treatment?

Extension of this case-control study design to other regions of England will provide insight into regional self-selection factors. In addition, one of the companion case-control studies, designed alongside this one, will allow us to quantify the rate of overdiagnosis within the current English Breast Screening Programme. In the meantime, our results suggest a substantial reduction in case fatality in screening-exposed breast cancer cases. This is largely attributable to more favourable tumour characteristics, consistent with the effect of early detection.

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List of abbreviations

BCS	Breast Conservative Surgery
BRS	Bloom-Scarff-Richardson
cOR	Conditional Odds Ratio
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
HSCIC	Health & Social Care Information Centre
IMD	Index of Multiple Deprivation
NCIN	National Cancer Intelligence Network (formerly Thames Cancer Registry)
NCDR	National Cancer Data Repository
NHAIS	National Health Applications and Infrastructure Services
NHS BSP	National Health Service Breast Screening Programme
NHS CSP	National Health Service Cervical Screening Programme
OR	Odds Ratio
PRU	UK Policy Research Unit in Cancer Awareness, Screening and Early Diagnosis
RCTs	Randomised Controlled Trials
uOR	Unconditional Odds Ratio

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Tables

Table 1 Patient demographics, screening history, tumour characteristics and treatment by case-control status

Table 1a Patient demographics

		Controls	Cases
Breast cancer diagnosis & death			
Year of diagnosis (Count, %)			
	1991-1994	13 (1.9)	13 (1.9)
	1995-1999	69 (10.2)	69 (10.2)
	2000-2004	207 (30.5)	196 (28.9)
	2005-2009	390 (57.4)	401 (59.1)
Age at diagnosis (Count, %)			
	47 - 55	103 (15.2)	103 (15.2)
	55 – 59	158 (23.3)	155 22.8)
	60 – 64	128 (18.9)	128 (18.9)
	65 - 69	109 (16.1)	110 (16.2)
	70 – 74	112 (16.5)	109 (16.1)
	75 - 89	69 (10.2)	74 10.9)
Median age at diagnosis in years (range)		63.0 (49.9 – 82.5)	63.2 (50.2 – 82.6)
Age category at death (Count, %)			
	47 - 55	_	24 (3.5)
	55 – 59	_	95 (14.0)
	60 – 64	_	144 (21.2)
	65 - 69	_	127 (18.7)
	70 – 74	_	135 (19.9)
	75 - 89	_	154 (22.7)
Median age at death in years (range)		NA[(a)]	68.2 (51.6 – 84.2)

[(a)] 102 out of 679 controls (15%) died between the date of death of their matched case and the censor date of 28th February 2013, among whom 58 died of breast cancer (8.5% of total).

Table 1b Patient screening history

	Controls	Cases
Breast screening history		
Number of screening invitations (Count, %)		
1	136 (20.0)	164 (24.2)
2	155 (22.8)	157 (23.1)
2+	388 (57.2)	358 (52.7)
Median number of screening invitations (range)	3.0 (1 – 8)	3.0 (1 - 8)
Attendance at first invitation		
Did not attend	93 (13.7)	179 (26.4)
Attended	586 (86.3)	500 (73.6)
Attendance at penultimate invitation		
Did not attend	287 (42.3)	358 (52.7)
Attended	392 (57.7)	321 (47.3)
Attendance at last invitation		
Did not attend	396 (58.3)	453 (67.7)
Attended	283 (41.7)	226 (33.3)
Median age at first screening invitation in years (range)	52.4 (47.3 – 73.1)	52.4 (47.5 – 70.3)
Number of screens (Count, %)		
0 (Never screened)	93 (13.7)	179 (26.4)
1	167 (24.6)	173 (25.5)
1+	419 (61.7)	327 (48.1)
Median number of screens (range)	2.0 (0 – 7)	1.0 (0 – 8)
Time since last screen in months (Count, %)		
Never screened	93 (13.7)	179 (26.4)
>72 months	130 (19.1)	147 (21.6)
48-72 months	40 (5.9)	38 (5.6)
24-48 months	82 (12.1)	97 (14.3)
3-24 months	82 (12.1)	91 (13.4)
≤ 3 months	252 (37.1)	127 (18.7)
Median time since last screen in years (range) – *among compliers*	1.2 (0 days – 18.2 years)	2.4 (0 days – 19.2 years)
Median age at first screen in years (range) – *among compliers*	53.5 (47.3 – 73.5)	53.8 (47.7 – 70.3)
Median age at last screen in years (range) – *among compliers*	61.3 (49.9 – 73.7)	61.1 (49.1 – 72.6)
Self-selection variables		
Deprivation quintile[(b)] (Count, %)		
Least deprived Q1	99 (14.6)	93 (13.7)
Q2	107 (15.8)	102 (15.1)
Q3	132 (19.5)	122 (18.0)
Q4	161 (23.8)	172 (25.4)
Most deprived Q5	177 (26.2)	188 (27.8)
Attendance at cervical screening (Count, %)		
Never screened	116 (17.1)	149 (21.9)
Formerly screened (>60 months)	214 (31.5)	229 (33.7)
Currently screened (0-60months)	349 (51.4)	301 (44.3)

[(b)] Index of Multiple Deprivation (IMD) Income domain quintile

Table 1c Patient treatment and tumour characteristics

		Controls	Cases
Treatment			
Any treatment			
	No / NK	65 (9.6)	139 (20.5)
	Yes	614 (90.4)	540 (79.5)
Surgery			
	No / NK	124 (18.3)	300 (44.2)
	BCS	363 (53.5)	185 (27.2)
	Mastectomy	192 (28.3)	194 (28.6)
Radiotherapy			
	No / NK	398 (58.6)	502 (73.9)
	Yes	281 (41.4)	177 (26.1)
Chemotherapy			
	No / NK	533 (78.5)	399 (58.8)
	Yes	146 (21.5)	280 (41.2)
Endocrine therapy			
	No / NK	409 (60.2)	501 (73.8)
	Yes	270 (39.8)	178 (26.2)
Tumour characteristic			
Size (mm)			
	≤20	265 (39.0)	104 (15.3)
	>20	206 (30.3)	217 (32.0)
	NK	208 (30.6)	358 (52.7)
Number of affected regional lymph nodes			
	0	423 (62.3)	270 (39.8)
	1-3	107 (15.8)	115 (16.9)
	4+	57 (8.4)	126 (18.6)
	NK	92 (13.5)	168 (24.7)
Stage			
	Early/Localised to breast	282 (41.5)	113 (16.6)
	Advanced/Spread beyond breast	168 (24.7)	375 (55.2)
	NK	229 (33.7)	191 (28.1)
Histological grade (BRS)			
	1	129 (19.0)	31 (4.6)
	2	252 (37.1)	195 (28.7)
	3	158 (23.3)	232 (34.2)
	NK	140 (20.6)	221 (32.5)
Histological type			
	Ductal	530 (78.1)	553 (81.4)
	Lobular	97 (14.3)	96 (14.1)
	Other	52 (7.7)	30 (4.4)
Tumour laterality			
	Right	329 (48.5)	277 (40.8)
	Left (or bilateral)	338 (49.8)	352 (51.8)
	NK	12 (1.8)	50 (7.4)

NK: Not Known; BCS, Breast Conservation Surgery; BRS: Bloom-Scarff-Richardson

Table 2 Impact of disease attributes and cancer treatment on the relative effect of exposure to breast screening according to ever attendance and attendance at last invitation.

Treatment variables included surgery, radiotherapy, chemotherapy and endocrine therapy; tumour characteristics included size, lymph node status, stage, histological grade, histological type, and laterality.

Exposure to screening	Correction/adjustment	OR (95% CI, p-value)
Never screened		**1.00 (-)**
Screen-exposed (all)	None (conditional analysis, N pairs = 679)	0.42 (0.31 - 0.56, <0.001)
	Unconditional analyses	
	None (matching factors only)	0.44 (0.33 – 0.58, <0.001)
	OD/LT[(a)]	0.55 (0.42 – 0.73, <0.001)
	OD/LT + Deprivation[(b)]	0.56 (0.42 - 0.75, 0.001)
	OD/LT + Deprivation + SS[(c)] D_r = 1.19 (1.05 – 1.36)	0.69 (0.50 – 0.94, 0.02)
	OD/LT + Deprivation + Tumour characteristics + SS	1.00 (0.71 – 1.40, 0.9)
	OD/LT + Deprivation + Tumour characteristics + Treatment + SS	1.02 (0.72 - 1.45, 0.9)
	OD/LT + Deprivation + Tumour characteristics + *RCT treatments as offsets* + SS	1.04 (0.73 – 1.49, 0.8)
Never screened		**1.00 (-)**
Screen-exposed, symptomatic only	None (conditional analysis, N pairs = 362)	0.56 (0.38 – 0.80, 0.002)
	Unconditional analyses	
	None (matching factors only)	0.60 (0.45 – 0.81, <0.001)
	OD/LT[(a)]	NA
	Deprivation[(b)]	0.61 (0.46 – 0.83, 0.001)
	Deprivation + SS[(c)] D_r = 1.24 (1.09 – 1.40)	0.81 (0.59 – 1.12, 0.2)
	Deprivation + Tumour characteristics + SS	1.01 (0.71 – 1.44, 0.9)
	Deprivation + Tumour characteristics + Treatment + SS	1.01 (0.70 – 1.45, 0.9)
	Deprivation + Tumour characteristics + *RCT treatments as offsets* + SS	1.06 (0.74 – 1.52, 0.7)

[(a)] Exclusion of screen-detected controls with lead time extending beyond the matched case date of death.
[(b)] Self-selection adjustment using deprivation quintile (see categorization in Table 1b).
[(c)] Self-selection correction of OR using data on attendance at the cervical screening programme (described in (23))
NA: Not Applicable; OD/LT: overdiagnosis & lead time adjustment; SS: self-selection

Table 3 Treatment profile of early stage (localised to breast) cancers received by control women diagnosed with screened-detected versus symptomatic cancers (age at diagnosis 47-74)

Surgery	Chemotherapy	Other therapy	Controls (count, %)	
			Screen-detected N = 113	All symptomatic[(a)] N = 132
No	No	None	1 (0.9)	4 (3.0)
		Endocrine	1 (0.9)	4 (3.0)
		Radio ±Endocrine	3 (2.7)	2 (1.5)
BCS	No	None ±Endocrine	23 (20.4)	18 (13.6)
		Radio ±Endocrine	61 (54.0)	42 (31.8)
Mastectomy	No	None ±Endocrine	12 (10.6)	31 (23.5)
		Radio ±Endocrine	2 (1.8)	7 (5.3)
Any surgery	Yes	Any	10 (8.8)	24 (18.2)

[(a)] Screen-exposed and never screened symptomatic cancers.

Table 4 Impact of disease attributes and cancer treatment on the relative effect of exposure to breast screening according to time since last breast screen

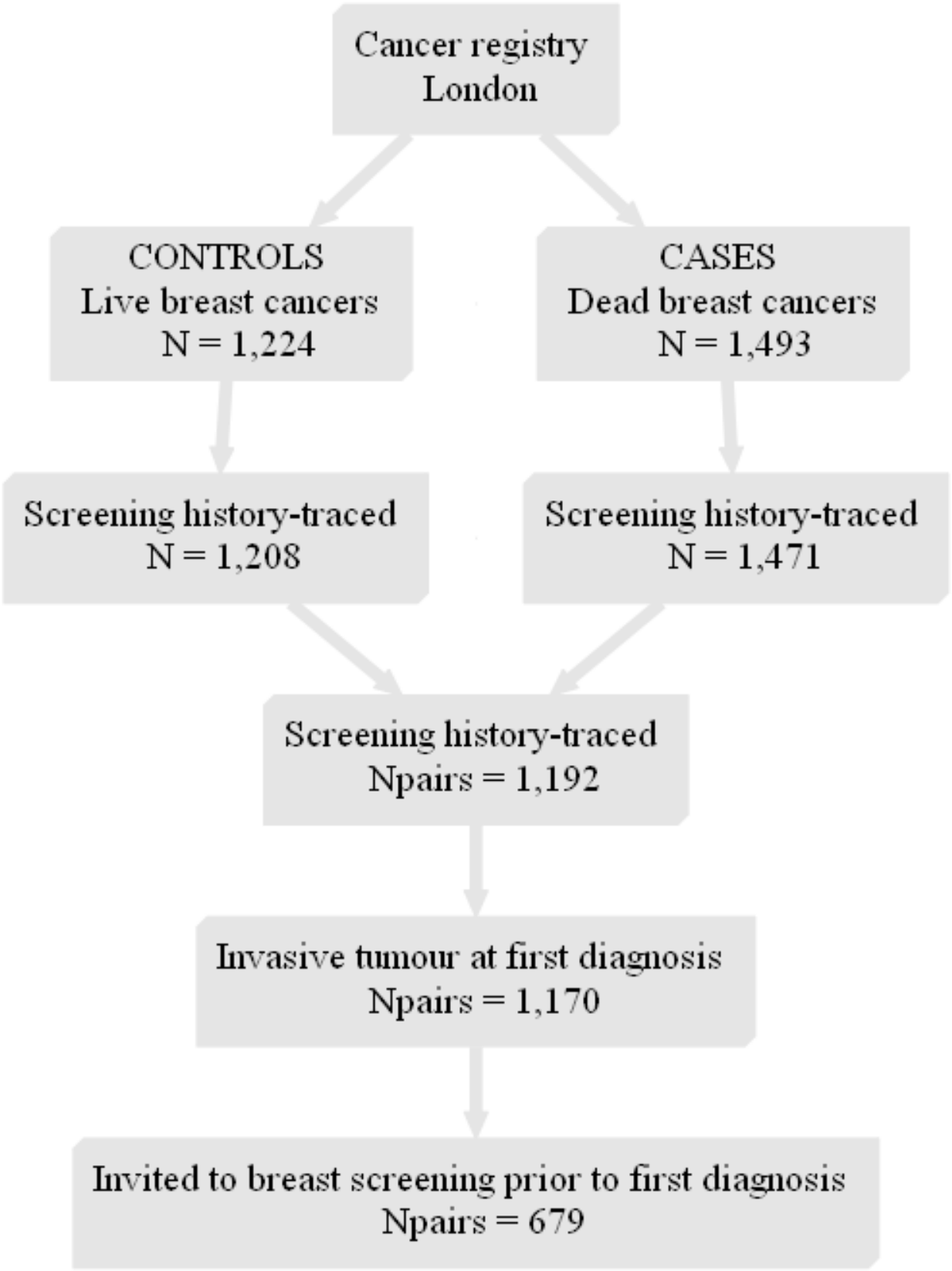
Treatment variables included surgery, radiotherapy, chemotherapy and endocrine therapy; tumour characteristics included size, lymph node status, stage, histological grade, histological type, and laterality.

Time since last breast screen	Adjustment	OR (95% CI, p-value)
Never screened	_	**1.00 (-)**
Screened 3-36 months	Deprivation + Attendance at cervical screening	0.60 (0.42 – 0.85, 0.004)
Screened >60 months	Deprivation + Attendance at cervical screening[(a)]	0.68 (0.47 – 0.98, 0.04)
Screened 36-60 months	Deprivation + Attendance at cervical screening	0.63 (0.37 – 1.05, 0.07)
Screened 24-36 months	Deprivation + Attendance at cervical screening	0.61 (0.39 – 0.93, 0.02)
Screened 3-24 months	Deprivation + Attendance at cervical screening	0.59 (0.39 – 0.89, 0.01)
Screened ≤3 months[(a)]	*Deprivation + Attendance at cervical screening*	*0.26 (0.18 – 0.37, <0.001)*
Screened 3-36 months	Deprivation + Attendance at cervical screening + Tumour characteristics	0.73 (0.50 – 1.08, 0.1)
Screened >60 months	Deprivation + Attendance at cervical screening + Tumour characteristics	0.82 (0.55 – 1.25, 0.4)
Screened 36-60 months	Deprivation + Attendance at cervical screening + Tumour characteristics	0.85 (0.48 – 1.50, 0.6)
Screened 24-36 months	Deprivation + Attendance at cervical screening + Tumour characteristics	0.75 (0.47 – 1.21, 0.2)
Screened 3-24 months	Deprivation + Attendance at cervical screening + Tumour characteristics	0.72 (0.46 – 1.13, 0.2)
Screened ≤3 months	*Deprivation + Attendance at cervical screening + Tumour characteristics*	*0.59 (0.39 – 0.88, 0.01)*
Screened 3-36 months	Deprivation + Attendance at cervical screening + Tumour characteristics + Treatment	0.74 (0.50 – 1.10, 0.1)
Screened >60 months	Deprivation + Attendance at cervical screening + Tumour characteristics + Treatment	0.81 (0.53 – 1.24, 0.3)
Screened 36-60 months	Deprivation + Attendance at cervical screening + Tumour characteristics + Treatment	0.90 (0.50 – 1.24, 0.7)
Screened 24-36 months	Deprivation + Attendance at cervical screening + Tumour characteristics + Treatment	0.76 (0.47 – 1.24, 0.3)
Screened 3-24 months	Deprivation + Attendance at cervical screening + Tumour characteristics + Treatment	0.73 (0.46 – 1.16, 0.2)
Screened ≤3 months	*Deprivation + Attendance at cervical screening + Tumour characteristics + Treatment*	*0.64 (0.42 – 0.97, 0.03)*

[(a)] Self-selection adjustment using deprivation quintile and attendance at cervical screening. See categorization in Table 1b.

List of Figures

Figure 1


Cancer registry
London
CONTROLS
Live breast cancers
N = 1,224
CASES
Dead breast cancers
N = 1,493
Screening history-traced
N = 1,208
Screening history-traced
N = 1,471
Screening history-traced
Npairs = 1,192
Invasive tumour at first diagnosis
Npairs = 1,170
Invited to breast screening prior to first diagnosis
Npairs = 679