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Research Article

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Explaining the Better Prognosis of Screening-Exposed Breast Cancers: Influence of Tumor Characteristics and Treatment

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Abstract

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 organization 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 Program. Women who died from primary breast cancer in 2008 to 2009 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 analyzed by unconditional logistic regression with adjustment for matching factors.

Results: The unadjusted OR for dying from breast cancer associated with ever having attended breast screening was 0.44 [95% confidence interval (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 tumor 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 tumor 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–related deaths in the epoch of adjuvant systemic therapy.

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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 (i) the implementation and improvement of the national screening program, and (ii) improvements in cancer staging and treatment including the use of adjuvant systemic therapies (3–6). 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 organization 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 collaborators estimated that screening service delivery and advances in adjuvant treatment made similar large contributions to decreased mortality in the United States (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 tumors 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.

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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).

Materials and Methods

Study design

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. All women who died of primary breast cancer (as stated in part 1 of the death certificate) ages 47 to 89 between January 1, 2008 and December 31, 2009 and who had been first diagnosed with primary breast cancer (invasive) ages 47 to 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 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 to the date of their first diagnosis.

Power calculation

The 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 two-sided test (14).

Data collection

Tumor 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 Health & Social Care Information Center (HSCIC) database. Only breast screens with invitation dates which occurred after January 1, 1988, within age range 47 to 73 years 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 January 1, 1998, within age range 20 to 70 years 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 analysis

Regression modeling and 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 tumor characteristics (histopathologic size, lymph node status, tumor stage as classified by the registry and dichotomized to localized (1) or extending beyond the organ (2–4), histologic grade [Bloom-Scarff-Richardson (BRS), histologic 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 tumor characteristics and treatment data were treated as separate categories. A sensitivity analysis was performed where relative effects of chemotherapy, radiotherapy, and endocrine therapy compared with 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, that is, 0.79 (95% CI, 0.72–0.85) for polychemotherapy (anthracycline-based regimen; ref. 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 tumor characteristics was assessed using the inflation observed in the estimated SEs of the regression coefficients and was judged to be negligible (20).

Lead time, overdiagnosis, and 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 days of first diagnosis). This confers a survival bias in favor 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 $\frac{1}{\lambda}$, where for the rate of transition to symptomatic disease (λ), we used 0.25 (mean sojourn time = 4 years) as estimated by Tabar and colleagues (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 tumors, 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 favor of screening.

Overdiagnosis can therefore be seen as an extreme form of lead-time bias among screen-detected cancers, in which the lead time

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exceeds the future lifetime. 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, because 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 and colleagues (22) where a correction factor "D_r" is defined as the relative risk of breast cancer death for nonattenders compared with 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 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. 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 three-category variable 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 ongoing evaluation of the English NHS BSP and has received all relevant approvals (details published elsewhere; ref. 24).

Results

Data description

A total of 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 (Fig. 1). Among these 1,192 pairs, 22 were excluded due to a first diagnosis being an *in situ* disease (8 controls and 14 cases) and 491 for not having been invited to the NHS BSP at least once prior to their first diagnosis (391 controls and 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 onward (Table 1). 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.

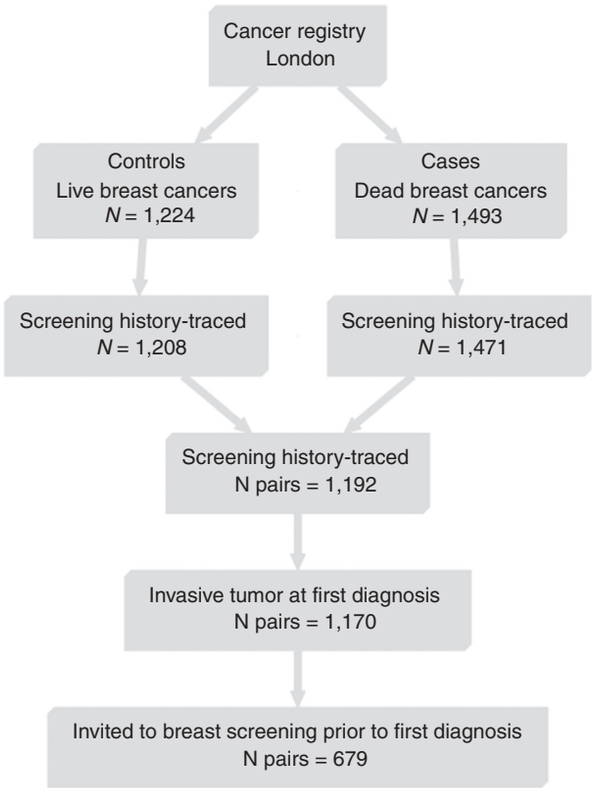

Figure 1.
Overview of the case-control study dataset.

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), whereas the proportion of women who never attended screening was larger for cases than for controls (26.4% vs. 13.7%), and was mirrored by a larger proportion of control women having attended screening more than once (61.7% vs. 48.1%). In addition, time since last breast screen was over a year longer for the case population (1.2 vs. 2.4 years) and the number of screen-detected cancers, defined as cancers diagnosed in women having had their last breast screen within 90 days of first diagnosis, was higher among controls than cases (37.1% vs. 18.7%). Controls also attended their last or penultimate invitation in larger proportion (41.7% vs. 33.3%, and 57.7% vs. 47.3%, respectively; Table 1).

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, 0.31–0.56 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).

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Table 1. Patient demographics, screening history, tumor characteristics, and treatment by case–control status

Patient demographics		
	Controls	**Cases**
Breast cancer diagnosis and death		
Year of diagnosi s (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)

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 (0–60 months)	349 (51.4)	301 (44.3)

(Continued on the following page)

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Table 1. (Cont'd)

Patient treatment and tumor 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)
Tumor 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/localized 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)
Histologic 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)
Histologic type		
Ductal	530 (78.1)	553 (81.4)
Lobular	97 (14.3)	96 (14.1)
Other	52 (7.7)	30 (4.4)
Tumor laterality		
Right	329 (48.5)	277 (40.8)
Left (or bilateral)	338 (49.8)	352 (51.8)
NK	12 (1.8)	50 (7.4)

Abbreviation: NK, not known.

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

[b]Index of multiple deprivation (IMD) income domain quintile.

The treatment profile of early stage (localized) screen-detected cancers among women diagnosed ages 47 to 74 years, 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 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 with 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 on the basis of attendance at the cervical screening program ($D_r = 1.19$; 95% CI, 1.05–1.36; see details in ref. 23) increased the uOR to 0.69 (95% CI, 0.50–0.94, Table 2).

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 with the never screened ($D_r = 1.24$; 95% CI, 1.09–1.40, see details in ref. 23 and Table 2).

The risk of fatality reversed slightly with time since last screen compared with 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

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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

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 + Tumor characteristics + SS	1.00 (0.71–1.40, 0.9)
	OD/LT + Deprivation + Tumor characteristics + Treatment + SS	1.02 (0.72–1.45, 0.9)
	OD/LT + Deprivation + Tumor 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 + Tumor characteristics + SS	1.01 (0.71–1.44, 0.9)
	Deprivation + Tumor characteristics + Treatment + SS	1.01 (0.70–1.45, 0.9)
	Deprivation + Tumor characteristics + *RCT treatments as offsets* + SS	1.06 (0.74–1.52, 0.7)

NOTE: Treatment variables included surgery, radiotherapy, chemotherapy, and endocrine therapy; tumor characteristics included size, lymph node status, stage, histologic grade, histologic type, and laterality.
Abbreviations: NA, not applicable; OD/LT, overdiagnosis and lead-time adjustment; SS, self-selection.
[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 1).
[c]Self-selection correction of OR using data on attendance at the cervical screening program (described in ref. 23).

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

Tumor size, tumor 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 tumor characteristics at diagnosis, which included tumor size, lymph node status, extension beyond organ (registry-based measure of stage), histologic grade, histologic type, and laterality (Table 1): 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 tumor 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 by 45% after accounting for overdiagnosis and lead time in screen-detected cancers, and by 34% after additionally accounting for deprivation

Table 3. Treatment profile of early-stage (localized) breast cancers received by control women diagnosed with screened–detected versus symptomatic cancers (age at diagnosis, 47–74 years)

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.

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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

Time since last breast screen	Adjustment	OR (95% CI, *P* value)
Never screened	_	**1.00 (—)**
Screened 3–36 months	Deprivation + attendance at cervical screening[a]	0.60 (0.42–0.85, 0.004)
Screened >60 months	Deprivation + attendance at cervical screening	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 + tumor characteristics	0.73 (0.50–1.08, 0.1)
Screened >60 months	Deprivation + attendance at cervical screening + tumor characteristics	0.82 (0.55–1.25, 0.4)
Screened 36–60 months	Deprivation + attendance at cervical screening + tumor characteristics	0.85 (0.48–1.50, 0.6)
Screened 24–36 months	Deprivation + attendance at cervical screening + tumor characteristics	0.75 (0.47–1.21, 0.2)
Screened 3–24 months	Deprivation + attendance at cervical screening + tumor characteristics	0.72 (0.46–1.13, 0.2)
Screened ≤3 months	*Deprivation + attendance at cervical screening + tumor characteristics*	*0.59 (0.39–0.88, 0.01)*
Screened 3–36 months	Deprivation + attendance at cervical screening + tumor characteristics + treatment	0.74 (0.50–1.10, 0.1)
Screened >60 months	Deprivation + attendance at cervical screening + tumor characteristics + treatment	0.81 (0.53–1.24, 0.3)
Screened 36–60 months	Deprivation + attendance at cervical screening + tumor characteristics + Treatment	0.90 (0.50–1.24, 0.7)
Screened 24–36 months	Deprivation + attendance at cervical screening + tumor characteristics + treatment	0.76 (0.47–1.24, 0.3)
Screened 3–24 months	Deprivation + attendance at cervical screening + tumor characteristics + treatment	0.73 (0.46–1.16, 0.2)
Screened ≤3 months	*Deprivation + attendance at cervical screening + tumor characteristics + treatment*	*0.64 (0.42–0.97, 0.03)*

NOTE: Treatment variables included surgery, radiotherapy, chemotherapy, and endocrine therapy; tumor characteristics included size, lymph node status, stage, histologic grade, histologic type, and laterality.

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

and self-selection. We found the major intermediaries between screening and survival to be the traditional tumor characteristics, in particular smaller size and extension beyond the breast, rather than differential treatment, in agreement with previously findings (25–29). We also observed increased fatality in left-sided or bilateral tumors. Reduction in size and likelihood of spread beyond the organ are considered a necessary effect of a screening program (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 with 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 tumor as previously noted by Day and colleagues (32). Interval tumors have previously been found to be smaller (and more likely to be estrogen receptor-positive) and associated with better survival than tumors in the unscreened population (33–35). 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, whereas others have not (36).

Women who participated in the screening program 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 and colleagues (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 sociodemographic factors, such as urbanization 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 matched case–control study nested within the UK Age Trial which assessed the effect of the NHS BSP in a cohort of women ages 40 to 49 years (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 tumor characteristics suggests that screening downstages tumors. Further investigation into the impact of tumor 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 tumor staging in treatment decisions, whereas histologic and molecular characterization of tumors and surrounding tissues have been shown to predict clinical outcomes (44–47).

There has been limited scope for the clear distinction of fast- versus slow-growing or steady-state tumors (48, 49), and correspondingly, it has been considered necessary to intervene once a tumor 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; refs. 50, 51). An estimated 7% (range 3%–15%) of 40- to 80-year-old women of various ethnical backgrounds are found to have undiagnosed, mainly *in*

situ, breast cancer at autopsy (reviewed in ref. 52). Given the upper limit provided by the autopsy results, and the limitations of mammographic detection, an average of 1.16 cm-diameter threshold for women ages 50 to 69 years (53), we believe that our approach which excluded approximately 15% of screen-detected controls accounted adequately for overdiagnosis and lead time.

In addition, our data suggest that the treatments associated with potential overdiagnosis, that is, among screen-detected women diagnosed with early-stage cancers after attending an invitation, tend to be less aggressive compared with the treatment received by early-stage cancers detected symptomatically, that is, they rarely, if ever, include 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 tumor characteristics, in common with earlier studies (25–29).

It is worth observing that effects of treatment in a nonrandomized 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, in addition to conventional adjustment, we also adjusted for the effects of therapies as found in meta-analyses of the randomized trials (16). The results were the same, in that the major mediating factors for the lower fatality of screening-exposed cases were the tumor 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 on the screening effect, and hence on the extent 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 Program. In the meantime, our results suggest a substantial reduction in case fatality in screening-exposed breast cancer cases. This is largely attributable to more favorable tumor characteristics, consistent with the effect of early detection.

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
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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, P.D. Sasieni, J. Cuzick, S.W. Duffy
Writing, review, and/or revision of the manuscript: N.J. Massat, P.D. Sasieni, D. Tataru, J. Cuzick, S.W. Duffy
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D. Tataru, D. Parmar
Other (data extraction and preparation, and guidance on treatment and tumor characteristics data): D. Tataru

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References

1. Darby S, Davies C, McGale P. The early breast cancer trialists' collaborative group: a brief history of results to date. In: Davison AC, Dodge Y, Wermuth N (eds). Celebrating Statistics. Oxford: Oxford University Press; 2005, p. 185–98.
2. Cancer Research UK (CRUK). Breast cancer statistics 2011. 2014; Available from http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast.
3. Tataru D, Robinson D, Møller H, Davies E. Trends in the treatment of breast cancer in Southeast England following the introduction of national guidelines. J Public Health 2006;28:215–7.
4. Ravnsbæk Jensen A, Husted Madsen A, Overgaard J. Trends in breast cancer during three decades in Denmark: Stage at diagnosis, surgical management and survival. Acta Oncologica 2008;47:537–44.
5. Hofvind S, Sørum R, Thoresen S. Incidence and tumor characteristics of breast cancer diagnosed before and after implementation of a population-based screening-program. Acta Oncologica 2008;47:225–31.
6. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. Br J Cancer 2013;108:2205–40.
7. National Institute for Health & Care Excellence (NICE). Improving outcomes in breast cancer (CSGBC). NICE guidelines; 1996. Available from: https://www.nice.org.uk/guidance/csgbc
8. van Hoeve J, de Munck L, Otter R, de Vries J, Siesling S. Quality improvement by implementing an integrated oncological care pathway for breast cancer patients. Breast 2014;23:364–70.
9. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Eng J Med 2005;353:1784–92.
10. Tabar L, Yen M-F, Vitak B, Chen H-HT, Smith RA, Duffy SW. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet 2003;361:1405–10.
11. Marcus PM. Estimating overdiagnosis in lung cancer screening. JAMA Int Med 2014;174:1198.
12. Massat NJ, Dibden A, Parmar D, Cuzick J, Sasieni PD, Duffy SW. Impact of screening on breast cancer mortality: the UK program 20 years on. Cancer Epidemiol Biomarkers Prev 2016;25:455–62.

13. Broeders M, Moss S, Nystrom L, Njor S, Jonsson H, Paap E, et al. The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies. J Med Screen 2012;19(Suppl 1):14–25.
14. Machin D, Campbell M, Fayers P, Pinol A. Sample size tables for clinical studies. Oxford, United Kingdom: Blackwell; 1997.
15. UK Department for Communities and Local Government. English indices of deprivation 2010; Statistics 2011. Available from www.gov.uk/government/statistics/english-indices-of-deprivation-2010.
16. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Recent results from EBCTCG: follow-up to 2006; 2015. Available from http://www.ctsu.ox.ac.uk/~ebctcg/.
17. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. Lancet 2012;379:432–44.
18. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet 2011;378:1707–16.
19. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–717.
20. Lesaffre E, Marx BD. Collinearity in generalized linear regression. Commun Stat 1993;22:1933–52.
21. Tabar L, Vitak B, Chen HH, Duffy SW, Yen MF, Chiang CF, et al. The Swedish Two-County Trial twenty years later. Updated mortality results and new insights from long-term follow-up. Radiol Clin North Am 2000;38:625–51.
22. Duffy SW, Cuzick J, Tabar L, Vitak B, Hsiu-Hsi Chen T, Yen M-F, et al. Correcting for non-compliance bias in case–control studies to evaluate cancer screening programmes. J Royal Stat Soc: Series C 2002;51:235–43.
23. Massat NJ, Sasieni PD, Duffy SW. A new approach to estimate the underlying risk of outcome in studies of cancer screening. Submitted to Statistical Methods in Medical Research.
24. Massat NJ, Sasieni PD, Parmar D, Duffy SW. An ongoing case-control study to evaluate the NHS breast screening programme. BMC Cancer 2013;13:596.
25. Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O. Update of the Swedish two-county program of mammographic screening for breast cancer. Radiol Clin North Am 1992;30:187–210.
26. Michaelson JS, Silverstein M, Sgroi D, Cheongsiatmoy JA, Taghian A, Powell S, et al. The effect of tumor size and lymph node status on breast carcinoma lethality. Cancer 2003;98:2133–43.
27. Paci E, Ponti A, Zappa M, Patriarca S, Falini P, Delmastro G, et al. Early diagnosis, not differential treatment, explains better survival in service screening. Eur J Cancer 2005;41:2728–34.
28. Dawson SJ, Duffy SW, Blows FM, Driver KE, Provenzano E, LeQuesne J, et al. Molecular characteristics of screen-detected vs symptomatic breast cancers and their impact on survival. Br J Cancer 2009;101:1338–44.
29. Obi N, Waldmann A, Schäfer F, Schreer I, Katalinic A. Impact of the Quality assured Mamma Diagnostic (QuaMaDi) programme on survival of breast cancer patients. Cancer Epidemiology 2011;35:286–92.
30. Kalager M, Haldorsen T, Bretthauer M, Hoff G, Thoresen SO, Adami H-O. Improved breast cancer survival following introduction of an organized mammography screening program among both screened and unscreened women: a population-based cohort study. Breast Cancer Res 2009;11:R44.
31. Njor SH, Schwartz W, Blichert-Toft M, Lynge E. Decline in breast cancer mortality: How much is attributable to screening? J Med Screen 2014;22:20–7.
32. Day N, Duffy S. Trial design based on surrogate endpoints: application to a trial of different breast screening frequencies. J R Stat Soc A 1996;159:49–60.
33. Duffy SW, Tabar L, Fagerberg G, Gad A, Gröntoft O, South MC, et al. Breast screening, prognostic factors and survival–results from the Swedish two county study. Br J Cancer 1991;64:1133–8.
34. Lawrence G, O'Sullivan E, Kearins O, Tappenden N, Martin K, Wallis M. Screening histories of invasive breast cancers diagnosed 1989–2006 in the West Midlands, UK: variation with time and impact on 10-year survival. J Med Screen 2009;16:186–92.
35. Nagtegaal ID, Allgood PC, Duffy SW, Kearins O, Sullivan EO, Tappenden N, et al. Prognosis and pathology of screen-detected carcinomas. Cancer 2011;117:1360–8.
36. Coldman AJ, Phillips N. Breast cancer survival and prognosis by screening history. Br J Cancer 2014;110:556–9.
37. Porter GJ, Evans AJ, Burrell HC, Lee AH, Ellis IO, Chakrabarti J. Interval breast cancers: prognostic features and survival by subtype and time since screening. J Med Screen 2006;13:115–22.
38. Tyndel S, Austoker J, Henderson BJ, Brain K, Bankhead C, Clements A, et al. What Is the psychological impact of mammographic screening on younger women with a family history of breast cancer? Findings from a prospective cohort study by the PIMMS management group. J Clin Oncol 2007;25:3823–30.
39. Massat NJ, Douglas E, Waller J, Wardle J, Duffy SW. Variation in cervical and breast cancer screening coverage in England: a cross-sectional analysis to characterise districts with atypical behaviour. BMJ Open 2015;5:e007735.
40. Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. Br J Cancer 2004;90:1367–73.
41. Aarts MJ, Voogd AC, Duijm LE, Coebergh JW, Louwman WJ. Socioeconomic inequalities in attending the mass screening for breast cancer in the south of the Netherlands–associations with stage at diagnosis and survival. Breast Cancer Res Treat 2011;128:517–25.
42. van der Waal D, Broeders MJM, Verbeek ALM, Duffy SW, Moss SM. Case-control Studies on the Effectiveness of Breast Cancer Screening: Insights from the UK Age Trial. Epidemiology 2015;26:590–6.
43. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: How special are they? Mol Oncol 2010;4:192–208.
44. Yerushalmi R, Hayes MM, Gelmon KA. Breast carcinoma—rare types: review of the literature. Ann Oncol 2009;20:1763–70.
45. Jung HA, Park YH, Kim M, Kim S, Chang WJ, Choi MK, et al. Prognostic relevance of biological subtype overrides that of TNM staging in breast cancer: discordance between stage and biology. Tumour Biol 2014;36:1073–9.
46. Sawaki M, Idota A, Ichikawa M, Gondo N, Horio A, Kondo N, et al. Impact of intrinsic subtype on predicting axillary lymph node metastasis in breast cancer. Oncol Lett 2014;8:1707–12.
47. Casbas-Hernandez P, Sun X, Roman-Perez E, D'Arcy M, Sandhu R, Hishida A, et al. Tumor Intrinsic Subtype Is Reflected in Cancer-Adjacent Tissue. Cancer Epidemiol Biomark Prev 2015;24:406–14.
48. Pinder S, Ellis I. The diagnosis and management of pre-invasive breast disease: Ductal carcinoma in situ (DCIS) and atypical ductal hyperplasia (ADH) - current definitions and classification. Breast Cancer Res 2003;5:254–7.
49. Di Bonito M, Cantile M, De Cecio R, Liguori G, Botti G. Prognostic value of molecular markers and cytogenetic alterations that characterize breast cancer precursor lesions (Review). Oncol Lett 2013;6:1181–3.
50. Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 2010;12:21–9.
51. Sanders ME, Schuyler PA, Simpson JF, Page DL, Dupont WD. Continued observation of the natural history of low-grade ductal carcinoma in situ reaffirms proclivity for local recurrence even after more than 30 years of follow-up. Mod Pathol 2014;28:662–9.
52. Santen RJ, Song Y, Yue W, Wang J-P, Heitjan DF. Effects of menopausal hormonal therapy on occult breast tumors. J Steroid Biochem Mol Biol 2013;137:150–6.
53. Bailey SL, Sigal BM, Plevritis SK. A simulation model investigating the impact of tumor volume doubling time and mammographic tumor detectability on screening outcomes in women aged 40–49 Years. J Natl Cancer Inst 2010;102:1263–71.
54. Kwon T, Jeong I, Lee J, Lee C, You D, Hong B, et al. Adjuvant chemotherapy after radical cystectomy for bladder cancer: a comparative study using inverse-probability-of-treatment weighting. J Cancer Res Clin Oncol 2015;141:169–76.
55. Schmoor C, Caputo A, Schumacher M. Evidence from nonrandomized studies: a case study on the estimation of causal effects. Am J Epidemiol 2008;167:1120–9.

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