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Original Article

Changing Trends in the Proportional Incidence and Five-year Net Survival of Screened and Non-screened Breast Cancers among Women During 1995–2011 in England

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Abstract

Background and objectives: Uptake of breast cancer screening has been decreasing in England since 2007. However, the associated factors are unclear. On the other hand, survival among breast cancer patients have recently increased. We conducted a quasi-experimental analysis to test whether the trend-change in proportional incidence of non-screened cancers coincided with that in five-year net-survival. ***Methods:*** We extracted population-based proportional incidence and age-standardized five-year net-survival data from Public Health England that included English women with invasive breast cancer diagnosed during 1995–2011 (linked to death certificates, followed through 2016). Piece-wise log-linear models with change-point/joinpoint were used to estimate temporal trends. ***Results:*** Among 254,063 women in England with invasive breast cancer diagnosed during 1995–2011, there was downward-to-upward trend-change in proportional incidence of non-screened breast cancers (annual percent change [APC]=5.6 after 2007 versus APC=−3.5 before 2007, $p<0.001$) in diagnosis-year 2007, when a steeper upward-trend in age-standardized five-year net survival started (APC=5.7 after 2007/2008 versus APC=0.3 before 2007/2008, $p<0.001$). Net-survival difference of screened versus non-screened cancers also significantly narrowed (18% in 2007/2008 versus 5% in 2011). Similar associations were found in all strata of race, cancer stage, grade, and histology, except in Black patients or patients with stage I, stage III, or grade I cancer. ***Conclusions:*** There was a downward-to-upward trend-change in proportional incidence of non-screened breast cancers in 2007 that coincided with a steeper upward-trend in age-standardized five-year net survival among English women in 2007. Survival benefits of breast cancer screening decreased during 2007–2011. The data support reduction of breast cancer screening in some patients, but future validation studies are warranted.

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Introduction

Cancer screening is adopted widely for breast cancer prevention and control.[1] However, the use of breast cancer screening has been decreasing among women in England since 2007, from 73.2% among women aged 50–70 years in 2007–2008 to 70.5% in 2017–2018.[2,3] Given the widely accepted benefits of cancer screening in 2009 and 2012,[4,5] a decrease in screening may increase the proportional incidence of non-screened breast cancers and suppress improvement of patient survival. However, the long-term trends in proportional incidence of screened and non-screened breast cancers are largely unknown, despite an overall upward trend of breast cancer incidence in England.[6,7]

The benefits and harms of breast cancer screening are controversial, although the benefits appear to outweigh the harms.[5,8–11] Thus, the recent decrease in breast cancer screening in England may be linked to different changes in breast cancer survival of non-screened and screened patients. However, the trends in net survival of screened and non-screened invasive breast cancers are unclear among women in England, while the overall net survival of patients has increased 2007–2011.[6,7] A similar upward trend in survival of breast cancer was also observed in U.S. women.[12] Therefore, using data from Public Health England (PHE), we estimated five-year net survival trends of the breast cancers diagnosed during 1995–2011. We also conducted a quasi-experimental analysis to examine whether the trend-change

Keywords: Breast cancer; Screening; Net survival; Trends; Incidence.
Abbreviations: IDC, invasive ductal carcinoma; ICD-O-2, International Classification of Diseases for Oncology, Second Edition; ICD-10, International Classification of Diseases 10th Revision; ILC, invasive lobular carcinoma; MDLC, mixed invasive ductal and lobular carcinoma; PHE, Public Health England.
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in proportional incidence of non-screened invasive breast cancers is associated with the trend-change in age-standardized five-year net survival of these cancers among women in England. Subgroup analyses by cancer stage, histology, cancer grade, and patient race were also performed. This quasi-experimental analysis may help better understand the benefits of breast cancer screening during 1995–2011.

Methods and materials

We requested the aggregated data of proportional incidence and age-standardized five-year net survival of invasive breast cancers by various factors, which were prepared for and calculated using Stata (version 15, StataCorp LLC, TX, USA), and released by the National Cancer Registration and Analysis Service within PHE.[6,13] The database has been used to study breast, pediatric, and colorectal cancers.[14–16] Invasive breast cancer was defined according to the International Classification of Diseases 10th Revision (ICD-10) and by morphology and behavior codes in the International Classification of Diseases for Oncology, Second Edition (ICD-O-2). Screened cancers were defined as invasive breast cancers in the PHE database that were detected during a breast cancer screening on an English woman. Non-screened cancers were defined as invasive breast cancers in the PHE database that were not detected during a breast cancer screening on an English woman. The breast cancer patients with no breast screening information were excluded. The net survival is a ratio calculated by dividing the overall/observed survival of breast cancer patients over that of the general population using the Pohar-Perme estimator.[17] The overall/observed survivals were estimated using the latest death certificate data that contained the vital status of the subjects in 2016. Thus, the last follow-up date was the end of 2016. The net survival used here was adjusted for the survival of breast cancer patients with that of the general population using an updated, smoothed life table.[18] Age-standardization was performed using the International Cancer Survival Standard age-weightings.[19] We included all qualified invasive breast cancers (site and morphology, Primary site-labeled: breast) in England diagnosed during 1995–2011 (released in February 2019). The exclusion criteria were as follows: death certificate only, autopsy only, or alive with no survival time; exclusion to match the expected survival table with regards to age value not found in the table, invalid year, and values not found for other variables. Since we used an existing, de-identified, publicly available dataset, no Institutional Review Board review was required for the study.

We classified the cancer stage using a tumor, node, and metastasis (TNM)-based staging system defined by Cancer Research UK.[20] Cancer histology was classified and categorized using the ICD-O-2,[21] according to the pathology diagnosis in medical charts. We grouped the tumors into invasive ductal carcinoma (IDC, ICD-O-2 8500/3), invasive lobular carcinoma (ILC, ICD-O-2 8520/3), mixed invasive ductal and lobular carcinoma (MDLC, ICD-O-2 8522/3), and non-ductal non-lobular carcinomas (all other codes) for the primary analyses. We stratified the proportional incidence and age-standardized five-year net-survivals by diagnosis year, race, histology, cancer stage, and cancer grade among women with screened or non-screened breast cancer. We calculated proportional incidence using stratum's incident case number divided by the number of all strata's incident cases.

Statistical analysis

In the quasi-experimental analysis, we identified and compared the changing points of the trends in proportional incidence and age-standardized five-year net survival, respectively, using piece-wise log-linear models in the Joinpoint program (Version 4.6.0.0., Statistical Research and Applications Branch, National Cancer Institute, Bethesda, MD, USA).[22,23] We employed the following setups for analyses: standard errors (provided) option for Heteroscedastic Errors Option (Weighted Least Squares); grid search method with 2 as the minimal number of observations from a joinpoint to either end of the data (excluding the first or last joinpoint if it fell on an observation), and the minimal number of observations between two joinpoints (excluding any joinpoint if it fell on an observation).[22,24] The model selection for the best-fit joinpoint was based on permutation tests with an overall significance level at 0.05. We also compared the trends/slopes among the strata using the pairwise comparison function of the Joinpoint program.[24] On very rare occasions (< 1%), age-standardized net-survivals were unavailable due to missing data, and those data points were omitted in the analysis. All *p* values were 2-sided, and were considered statistically significant when <0.05.

Results

Trends in the proportional incidence of invasive breast cancer among women in England diagnosed during 1995–2011

Among the 254,063 women in England with invasive breast cancer diagnosed during 1995–2011 (183,018 [72.0%] IDC; 30,323 [11.9%] ILC; 9,324 [3.7%] MDLC; and 31,398 [12.4%] others), 122,870 (48.8%) were screened cancers overall (Table 1). The proportional incidence of screened breast cancer (versus non-screened) was significantly different by diagnosis year, race, histology, stage, and tumor grade (Table 1). We found a joinpoint in the proportional incidence of non-screened breast cancer in 2007, which differed before and after the jointpoint year by histology, stage, and cancer grade, but not race (Table 2). Compared with grade 1, grades 2 and 3 had different trend-changes. Compared with stage 1, stages 2, 3, and 4 also had different trend-changes. Interestingly, other types of invasive breast cancers had trend-changes different from those of ILC ($p_{parallelism}$=0.005), while IDC and MDLC did not. The same joinpoint of 2007 was also identified in the trend of proportional incidence of non-screened breast cancer (Fig. 1). The APC was −3.5 (−4.2 to −2.8) during 1995–2007 and 5.6 (2.2 to 9.1) during 2007–2011, respectively (p<0.001).

Trends in the age-standardized five-year net-survival of screened and non-screened breast cancers diagnosed among women in England during 1995–2011 (followed through 2016)

The age-standardized five-year net survival of screened cancer was higher than that of non-screened cancer, while the difference significantly decreased for the cancers diagnosed during 2007–2011 (19% difference for cancers diagnosed in 1995 versus 18% and 5% for those diagnosed in 2007/2008 and 2011, respectively, $p_{parallelism}$ <0.001; Table 3). The age-standardized five-year net survival of screened cancer showed a downward trend in other types of screened breast cancers diagnosed during 2006–2011 (APC=−2.5 [−5.0 to 0.0]), but an upward trend in that of non-screened breast cancers (APC=5.2 [3.8 to 6.7]). Moreover, all strata of race, stage, grade, and subtypes of breast cancer showed different trends or trend-changes of screened and non-screened cancers. There were upward trends in the age-standardized

Table 1. Age-standardized 5-year net survival of screened and non-screened breast cancers among women in England, 1995–2016

	Non-screened		Screened		All		*p*
	N (%)	NS, %	N (%)	NS, %	N	NS, %	
Year							<0.001
1995	4,665 (62.7)	77	2,771 (37.3)	96	7,436	84	
1996	5,175 (62.4)	77	3,122 (37.6)	93	8,297	83	
1997	7,036 (65.3)	77	3,744 (34.7)	98	10,780	84	
1998	6,484 (61.4)	78	4,071 (38.6)	100	10,555	86	
1999	6,156 (57.4)	79	4,563 (42.6)	99	10,719	88	
2000	5,794 (53.8)	78	4,966 (46.2)	101	10,760	88	
2001	5,781 (52.0)	80	5,331 (48.0)	96	11,112	88	
2002	5,894 (50.7)	78	5,726 (49.3)	100	11,620	89	
2003	6,585 (49.7)	79	6,671 (50.3)	99	13,256	89	
2004	7,132 (47.8)	79	7,778 (52.2)	99	14,910	89	
2005	7,191 (45.5)	79	8,599 (54.5)	100	15,790	90	
2006	8,597 (46.2)	77	9,996 (53.8)	101	18,593	89	
2007	7,907 (43.0)	81	10,479 (57.0)	99	18,386	91	
2008	8,965 (44.4)	81	11,241 (55.6)	99	20,206	91	
2009	9,310 (46.3)	86	10,795 (53.7)	102	20,105	94	
2010	12,779 (53.3)	88	11,202 (46.7)	101	23,981	94	
2011	12,991 (52.4)	95	11,815 (47.6)	100	24,806	97	
Race							<0.001
Black	973 (64.6)	81	533 (35.4)	89	1,506	85	
Other	54,387 (50.9)	76	52,543 (49.1)	97	106,930	86	
White	73,068 (51.2)	87	69,727 (48.8)	101	142,795	93	
Histology							<0.001
IDC	91,671 (50.1)	84	91,347 (49.9)	99	183,018	91	
ILC	15,960 (52.6)	86	14,363 (47.4)	98	30,323	92	
MDLC	3,867 (41.5)	86	5,457 (58.5)	97	9,324	92	
Other	18,540 (59.1)	70	12,858 (41.0)	97	31,398	80	
Tumor Stage*							<0.001
Stage 1	25,857 (36.2)	97	45,636 (63.8)	102	71,493	99	
Stage 2	29,271 (61.7)	87	18,162 (38.3)	95	47,433	90	
Stage 3	6,119 (75.3)	68	2,009 (24.7)	88	8,128	73	
Stage 4	4,193 (85.0)	31	743 (15.1)	72	4,936	38	
Tumor grade*							<0.001
Grade 1	16,078 (32.4)	96	33,603 (67.6)	103	49,681	99	
Grade 2	52,877 (47.1)	90	59,422 (52.9)	100	112,299	95	
Grade 3	44,455 (64.9)	75	24,069 (35.1)	92	68,524	81	
Total							
	13,038 (51.2)	82	122,870 (48.8)	99	254,062	90	

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MDLC, mixed ductal and lobular carcinoma; NS, age-standardized five-year net survival; *P*, chi-square test for the within group differences; *data were missing in some years.

five-year net-survival of screened and non-screened breast cancers diagnosed among women in England, while a steeper upward trend was seen for the cancers diagnosed after 2007/2008 (2007 and 2008 had the same survivals; Fig. 1). This joinpoint appeared to coincide with the joinpoint of proportional incidence of non-screened breast cancers. For both screened and non-screened breast cancers, the trends of age-standardized five-year net-survival differed by race,

Table 2. Trends in proportion of non-screened breast cancers in all breast cancers diagnosed during 1995–2011 among women in England

	Segment	Start year		End year		APC (95% CI)	$p_{parallelism}$
		n	(%)	n	(%)		
All	1995–2007	4,665	(62.7)	7,907	(43.0)	−3.5 (−4.2 to −2.8)	<0.001
	2007–2011	7,907	(43.0)	12,991	(52.4)	5.6 (2.2 to 9.1)	
Race							
Black	1995–2011	<15	(72.7)	100	(62.9)	−1.8 (−3.3 to −0.3)	reference
Other	1995–2008	3,451	(63.1)	2,259	(40.0)	−4.1 (−6.6 to −1.5)	0.879
	2008–2011	2,259	(40.0)	4,644	(53.2)	12.9 (−4.2 to 33.0)	
White	1995–2007	1,202	(59.0)	5,658	(45.8)	−3.5 (−5.5 to −1.4)	0.783
	2007–2011	5,658	(45.8)	8,247	(51.8)	4.2 (−0.8 to 9.5)	
Histology							
IDC	1995–2007	2,985	(60.2)	5,894	(42.7)	−3.3 (−4.1 to −2.5)	0.998
	2007–2011	5,894	(42.7)	9,651	(51.6)	5.3 (1.7 to 9.0)	
ILC	1995–2007	532	(63.1)	938	(43.2)	−3.3 (−3.9 to −2.8)	reference
	2007–2011	938	(43.2)	1,731	(54.5)	5.4 (2.9 to 8.0)	
MDLC	1995–2007	25	(30.5)	299	(35.1)	−3.6 (−5.9 to −1.3)	0.176
	2007–2011	299	(35.1)	319	(47.6)	9.6 (0.9 to 18.9)	
Other	1995–2007	1,135	(72.2)	924	(51.0)	−4.1 (−4.9 to −3.3)	0.005
	2007–2011	924	(51.0)	1,483	(57.9)	2.9 (1.0 to 4.8)	
Staging							
Stage 1	1995–2008	562	(49.1)	1,490	(27.1)	−5.2 (−6.6 to −3.7)	reference
	2008–2011	1,490	(27.1)	2,745	(31.4)	5.6 (−4.9 to 17.3)	
Stage 2	1995–2007	945	(73.3)	1,798	(54.4)	−3.1 (−4.1 to −2.1)	0.024
	2007–2011	1,798	(54.4)	3,321	(59.5)	4.1 (−0.4 to 8.8)	
Stage 3	1995–2011	122	(88.6)	852	(70.1)	−1.8 (−2.5 to −1.1)	0.003
Stage 4	1995–2011	70	(90.1)	701	(77.9)	−1.0 (−1.3 to −0.7)	0.048
Grade							
Grade 1	1995–2007	581	(42.0)	857	(24.9)	−5.1 (−6.2 to −3.9)	reference
	2007–2011	857	(24.9)	1,332	(31.6)	7.0 (1.1 to 13.2)	
Grade 2	1995–2007	1,520	(59.8)	3,362	(38.4)	−4.3 (−5.1 to −3.5)	0.018
	2007–2011	3,362	(38.4)	5,916	(48.7)	6.4 (2.9 to 10.1)	
Grade 3	1995–2008	1,235	(73.9)	3,311	(58.5)	−2.1 (−2.6 to −1.6)	0.001
	2008–2011	3,311	(58.5)	4,935	(66.7)	5.7 (1.9 to 9.5)	

APC, annual percentage change; CI, confidence intervals; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MDLC, mixed ductal and lobular carcinoma; *p*, *p*-values of parallelism test for the within group differences (< 0.05 indicates different slopes/trends compared with the reference).

histology, stage, and tumor grade (Table 3). Compared with screened breast cancers, non-screened breast cancers also showed different trends in the age-standardized five-year net-survival by these factors, although some strata did not show a trend difference, such as White race and stage 2 cancer ($p_{parallelism}$=0.454 and 0.053, respectively; Table 3).

Discussion

Among the 254,063 women in England with invasive breast cancer diagnosed during 1995–2011, the proportional incidence of non-screened invasive breast cancer had a downward trend in the cases diagnosed during 1995–2007, but an upward trend in those diagnosed during 2007–2011. Interestingly, the trend-changes in proportional incidence of non-screened invasive breast cancer differed by histology, cancer stage, and grade, but not by race. The difference in age-standardized five-year net survival of screened versus non-screened cancers significantly decreased for cancers diagnosed during 2007–2011. The downward-to-upward trend-change in proportional incidence of non-screened breast cancers in 2007 coincided with a steeper upward trend in age-standardized five-year net survival of non-screened invasive breast cancer, suggesting a possible association of the two trend-changes. Similar associations were found in all strata of race, cancer stage, cancer grade, and histology. The associations slightly differed by cancer characteristics

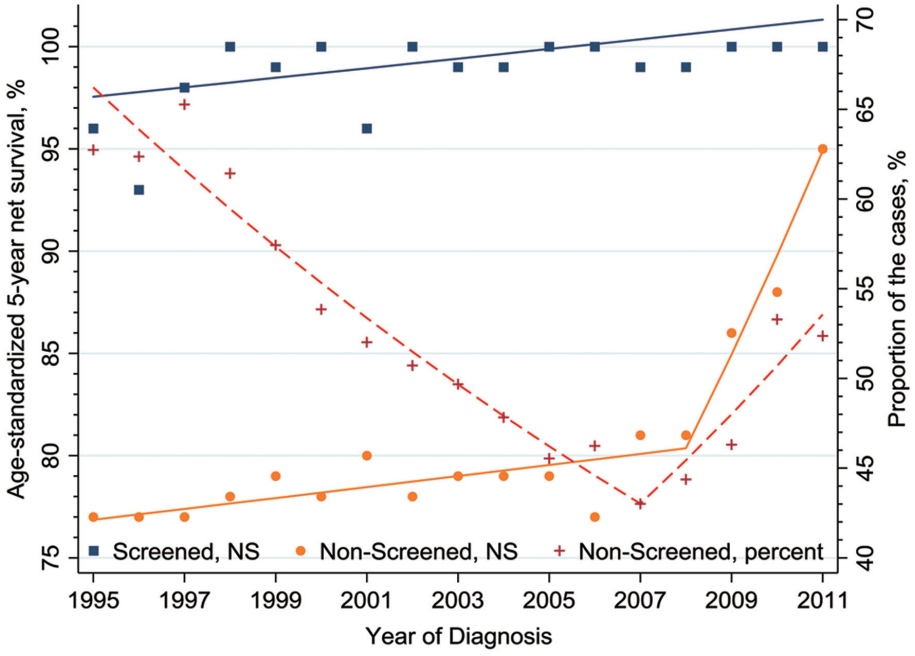

Fig. 1. Trends in proportion and age-standardized five-year net survival of screened and non-screened breast cancers diagnosed during 1995–2011 among women in England (followed through 2016). There was a downward trend in the proportional incident of non-screened breast cancers (red crosses; annual percentage change [APC], 95% confidence intervals [CI]=−3.5 (−4.2 to −2.8), $p<0.001$) during the diagnosis years of 1995–2007, followed by an upward trend after 2007 (APC, 95% CI=5.6 (2.2 to 9.1), $p=0.003$). Screened breast cancers had an upward trend in age-standardized five-year net-survival (blue squares; APC, 95% CI=0.4 (1.0 to 2.9), $p=0.01$), while non-screened breast cancers had an upward trend during the diagnosis years of 1995–2008 (yellow circles; APC, 95% CI=0.6 [1.0 to 3.1], $p=0.009$), followed by an even steeper upward trend after 2008 (APC, 95% CI=7.1 [1.0 to 9.2], $p<0.001$). Dots show individual data points; lines show piece-wise log-linear trends of the best-fit model that were identified using the Joinpoint program. The jointpoint of the trends in the proportion of cancers and in the age-standardized five-year net-survival were similar (2007 and 2008, respectively) among women with non-screened invasive breast cancers.

and patient race. However, the age-standardized five-year net survival of non-screened breast cancers remained lower compared to screened cancers during 1995–2011.

We provide early evidence on the 16-year trend of proportional incidence of screened and non-screened breast cancers among women in England. In contrast to our finding, a world-wide population study showed no decrease in incidence of advanced breast cancer following sustained implementation of breast cancer screening from the 1980s to the 2000s, including no significant trends in Scotland.[1] Those findings may have been influenced by a lack of piecewise linear modelling recommended by Centers for Diseases Control and Prevention guidelines,[25,26] no data after 2007, and differences between Scotland and England. The study on Scottish women also primarily defines advanced breast cancer by cancer size, whereas we used clinical cancer staging, which is more widely used and adopted by PHE.[6] The proportional incidence used here was adjusted for incidence of all breast cancers, and in our view is more reliable than unadjusted incidence. We showed a downward trend in the proportional incidence of early-stage screened breast cancer since the beginning of the decrease in use of breast cancer screening in 2007. Thus, it is possible that the recent decrease in screening is associated with a decrease in proportional incidence of early-stage breast cancer and increase in that of late-stage breast cancer.

The quasi-experimental analysis reveals a novel association of trend-changes in proportional incidence of non-screened breast cancers with trend-changes in the five-year net survival of non-screened breast cancers. Despite the increase in proportional incidence of advanced non-screened breast cancers, our data show that a downward-to-upward trend-change in proportional incidence of non-screened breast cancers coincided with a steeper upward trend in net survival of non-screened breast cancers after 2007. This finding is somewhat surprising, but consistent with an upward survival trend in England and the US.[7,12,27] This indicates that breast cancer screening in England may not be as beneficial as previously reported.[9,10,28] More studies are needed to explain the novel association. Given the decrease in screening rate in the US,[29,30] it would be of interest to investigate whether the decrease in breast cancer screening is associated with an upward trend in relative/net survival in the US. Unfortunately, no US population data are available on screened versus non-screened breast cancers.

We also explored the factors associated with increasing proportional incidence and age-standardized five-year net survival of non-screened breast cancers, respectively, as well as the factors linked to these trend-changes. First, we show a steeper upward trend in age-standardized five-year net survival in all strata of race, cancer stage, grade, and histology among patients with non-screened breast cancers after 2007. Therefore, the overall increasing survival of breast cancer patients, as reported before,[7,12,27] appears disproportionally linked to the non-screened breast cancers of advanced stage, higher grade, and common histologic types. Second, we found downward trends in age-standardized five-year net survival of some screened cancers, which were grade I and other histologic types. The downward trend in these screened breast cancers is concerning and warrants more investigation, but the finding is consistent with a worse overall survival of other/uncommon type of breast cancers in the US.[12,31] Third, Black patients in this study did not appear to have an increasing proportional incidence of non-screened breast cancers, nor (subsequent) a steeper upward trend in net survival after 2007. However, the role of socioeconomic disparity/inequality in the screening use and survival of breast cancer remains controversial

Table 3. Trends in age-standardized five-year net survival of screened and non-screened breast cancers diagnosed during 1995–2011 among women in England

	Screened					Non-screened					$p_{parallelism}$ for screened vs non-screened
	Segment	Start year, NS, %	End Year, NS, %	APC (95% CI)	$p_{parallelism}$	Segment	Start year, NS, %	End Year, NS, %	APC (95% CI)	$p_{parallelism}$	
All	1995–2011	96	100	0.1 (0.4 to 1.0)		1995–2008	77	81	0.3 (0.1 to 0.6)		<0.001
						2008–2011	81	95	5.7 (4.3 to 7.1)		
Race											
White	1995–2011	100	101	0.0 (−0.1 to 0.1)	reference	1995–2008	96	82	−1.5 (−2.1 to −0.9)	reference	0.494
						2008–2011	82	97	6.4 (2.7 to 10.1)		
Black*	1998–2010	97	90	0.7 (0.1 to 1.4)	0.082		51	99	2.0 (1.2 to 2.8)	0.015	0.004
Other	1995–2011	93	98	0.4 (0.2 to 0.7)	0.001	1995–2008	72	74	0.3 (−0.4 to 1.0)	<0.001	0.004
						2008–2011	74	93	5.9 (3.6 to 8.3)		
Histology											
IDC	1995–2011	96	101	0.3 (0.2 to 0.5)	reference	1995–2008	80	83	0.2 (−0.1 to 0.4)	reference	<0.001
						2008–2011	83	96	5.3 (3.8 to 6.9)		
ILC	1995–2011	85	101	0.3 (0.1 to 0.5)	0.626	1995–2007	87	82	−0.6 (−1.5 to 0.3)	0.203	<0.001
						2007–2011	82	98	4.7 (2.5 to 7.0)		
MDLC	1995–2011	97	101	0.3 (0.1 to 0.5)	0.89	1995–2008	86	76	0.0 (−0.9 to 0.9)	0.858	0.012
						2008–2011	76	99	5.1 (2.0 to 8.3)		
Other	1995–2006	86	106	1.5 (0.8 to 2.1)	0.009	1995–2006	65	63	0.2 (−0.6 to 0.9)	0.003	0.009
	2006–2011	100	97	−2.5 (−5.0 to 0.0)		2006–2011	63	86	5.2 (3.8 to 6.7)		
Staging											
Stage 1	1995–2009	96	104	0.2 (−0.1 to 0.6)	reference	1995–2011	96	100	0.3 (0.1 to 0.5)	reference	0.002
	2009–2011	104	100	−2.0 (−4.7 to 0.8)							
Stage 2	1995–2011	62	101	0.6 (0.4 to 0.9)	0.014	1995–2006	80	83	0.8 (0.3 to 1.4)	0.006	0.053
						2006–2011	83	99	2.9 (2.0 to 3.7)		
Stage 3	1995–1998	7	89	347.0 (−67.1 to 5,981.0)	<0.001	1995–2011	41	98	5.6 (4.4 to 6.8)	<0.001	<0.001
	1998–2011	89	101	1.4 (0.5 to 2.4)							
Stage 4	1995–2011	26	94	5.2 (2.2 to 8.2)	<0.001	1995–2007	16	17	−4.1 (−15.5 to 8.8)	<0.001	0.009
						2007–2011	17	68	40.5 (11.2 to 77.6)		
Grade											
Grade 1	1995–2006	99	106	0.3 (0.0 to 0.6)	reference	1995–2011	98	97	0.1 (−0.1 to 0.3)	reference	<0.001
	2006–2011	106	101	−0.8 (−1.3 to −0.4)							
Grade 2	1995–2011	98	101	0.3 (0.2 to 0.5)	0.005	1995–2008	88	87	0.1 (−0.2 to 0.4)	0.004	<0.001
						2008–2011	87	98	3.7 (2.4 to 5.0)		
Grade 3	1995–2011	87	99	0.8 (0.5 to 1.2)	<0.001	1995–2008	65	75	1.1 (0.8 to 1.5)	<0.001	<0.001
						2008–2011	75	94	8.0 (6.3 to 9.8)		

APC, annual percentage change; CI, confidence intervals; NS, age-standardized five-year net survival; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MDLC, mixed ductal and lobular carcinoma; NA, not available; *p*, *p*-values of parallelism test for the within group differences (< 0.05 indicates different slopes/trends compared with the reference); *data missing in some years.

for English patients, including studies of supportive[32–35] and undermined conclusions.[36,37] More research is required to understand the role of socioeconomic disparity. Finally, the trend-changes in proportional incidence and age-standardized five-year net survival of non-screened breast cancers coincided in the year of 2007, as shown by our quasi-experimental analysis. The underlying cause may be the increasing use of adjuvant trastuzumab therapy for human epidermal growth factor receptor 2 (HER2)-positive breast cancer after trastuzumab's approval by the US Food and Drug Administration in November 2006.[38,39] The 2006 approval expanded the indication of trastuzumab from metastatic breast cancers to primary breast cancers. Indeed, HER2 has since become a critical prognostic factor and treatment target of breast cancer.[12,31,40,41] We also showed similar, or identical in some cases, five-year net survivals of non-screened and screened invasive breast cancers, that may indirectly support and promote reduction of breast cancer screening in some populations. However, additional studies are required to evaluate the risk and benefits of reducing breast cancer screening in some patients.

This study has several strengths. Age-standardization is critical for long-term trend analysis.[26,42,43] Our findings on age-standardized net survival are consistent with the recent data of net survival of invasive and *in-situ* breast cancers reported by PHE.[6] Moreover, we used the most updated life tables for computing net survivals, which were levied on the recent methodological changes and advantages.[18] Specifically, the updated life tables have better coding, enhancement to inclusion and cohort-selection criteria, and correction to capturing dates of death. In addition, subgroup analyses by race, histology, stage, and grade help better understand trends among the strata of these variables. However, future multi-variable studies are needed to adjust for these variables if possible. Furthermore, this population-based, large-scale study had sufficient statistical power and few biases, despite its limitations. Finally, the quasi-experimental design, although not as rigorous as randomized clinical trials, provides solid evidence on the association of trend-changes in non-screened breast cancer proportional incidence with those in their net survivals.

This study has several limitations. First, survival analysis on the effects of cancer screening may have resulted in lead-time and length-time biases. However, this quasi-experimental analysis was focused on the association of trend-changes in the proportional incidence and net survival of non-screened breast cancers and should be less susceptible to these biases. Moreover, given additional survival benefits of screened cancers linked to these biases, the decrease in net-survival benefits of screened cancers would be more profound should these biases be eliminated. Second, several prognostic factors of breast cancer and socioeconomic factors were not available for analysis, including statuses of estrogen and progesterone receptors and patient income levels. Third, age was not analyzed as an exposure. Our reasoning is that, given age-standardized data, the influence of age on the trend analysis would be minimal, if even present. Fourth, due to the minimal follow-up time of 5 years for five-year survival, we could not analyze the trends after the publication of 2012 independent review on breast cancer screening;[4] although no immediate post-publication changes in the uptake of breast cancer screening were identified in the U.K.[44] Finally, some cases might be misclassified histologically or clinically , although the cancer database has been widely used,[15,16,42] and rigorously scrutinized for quality assurance.[6]

Conclusions

The downward-to-upward trend-change in proportional incidence of non-screened breast cancers occurred in 2007 and is associated with a steeper upward-trend in age-standardized five-year net survival among English women in the same year. Survival benefits of breast cancer screening also appeared to decrease during 2007–2011. The data support reduction of breast cancer screening in some patients, but future validation studies are warranted.

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Conflict of interest

One of the authors, LZ, has been a deputy Editor-in-Chief of *Journal of Clinical and Translational Pathology* since May 2021.The other authors have nothing to disclose.

Author contributions

LZ was responsible for study concept and design. JJ was responsible for data acquisition of data. LZ and JJ were responsible for analysis and interpretation of data. JJ drafted the manuscript. LZ and JJ provided critical revision of the manuscript for important intellectual content. LZ provided administrative, technical, or material support, as well as study supervision. Authors' contributions: HW, JB, and LZ designed the study. HW, KW, and JB extracted the data, HW, SEL, and LZ analyzed the data. HW and LZ wrote the first draft of the manuscript, and all authors edited and approved the final manuscript.

Data sharing statement

The data were confidential and obtained with review and approval from the Public Health England. Interested parties can request the data following the same protocol.

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