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.

Keywords
Breast cancer; Screening; Net survival; Trends; Incidence

Introduction
Cancer screening is adopted widely for breast cancer prevention and control. 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.\(^1\),\(^2\) 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.\(^5\),\(^8\),\(^9\)–\(^11\) 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 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. The database has been used to study breast, pediatric, and colorectal cancers. 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. 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. Age-standardization was performed using the International Cancer Survival Standard age-weightings.

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, deidentified, 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. Cancer histology was classified and categorized using the ICD-O-2, 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). 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). 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. 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 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, 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 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 worldwide 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. Those findings may have been influenced by a lack of piece-wise linear modelling recommended by Centers for Diseases Control and Prevention guidelines, 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. 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, This
indicates that breast cancer screening in England may not be as beneficial as previously reported.\textsuperscript{9,10,28} More studies are needed to explain the novel association. Given the decrease in screening rate in the US,\textsuperscript{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,\textsuperscript{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.\textsuperscript{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 for English patients, including studies of supportive\textsuperscript{32–35} and undermined conclusions.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{6} Moreover, we used the most updated life tables for computing net survivals, which were levied on the recent methodological changes and advantages.\textsuperscript{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; although no immediate post-publication changes in the uptake of breast cancer screening were identified in the U.K. Finally, some cases might be misclassified histologically or clinically, although the cancer database has been widely used and rigorously scrutinized for quality assurance.

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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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.

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

References

[1]. Autier P, Boniol M, Middleton R, Doré JF, Héry C, Zheng T, et al. Advanced breast cancer incidence following population-based mammographic screening. Ann Oncol 2011;22(8):1726–1735. doi:10.1093/annonc/mdq633. [PubMed: 21252058]

[2]. Digital N. Proportion of women taking up breast screening invitations falls [updated Feb 28, 2019]. Available from: https://digital.nhs.uk/news/2019/proportion-of-women-taking-up-breast-screening-invitations-falls. Accessed March 5 2022.

[3]. Digital N. Breast Screening Programme, England 2017–18 [NS] [PAS] [updated Feb 28, 2019] Available from: https://digital.nhs.uk/data-and-information/publications/statistical/breast-screening-programme/england-2017-18. Accessed March 5 2022.

[4]. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet 2012;380(9855): 1778–1786. doi:10.1016/S0140-6736(12)61611-0. [PubMed: 23117178]

[5]. Nelson HD, Fu R, Cantor A, Pappas M, Daeges M, Humphrey L. Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med 2016;164(4):244–255. doi:10.7326/M15-0969. [PubMed: 26756588]

[6]. John S, Broglio J. Cancer survival in England: national estimates for patients followed up to 2017 [updated Jan 24, 2019]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/nationalestimatesforpatientsfollowedupto2017. Accessed July 2 2019.

[7]. Walters S, Benitez-Majano S, Muller P, Coleman MP, Allemani C, Butler J, et al. Is England closing the international gap in cancer survival? Br J Cancer 2015;113(5):848–860. doi:10.1038/bjc.2015.265. [PubMed: 26241817]

[8]. Gøtzsche PC. Mammography screening is harmful and should be abandoned. J R Soc Med 2015;108(9):341–345. doi:10.1177/0141076815602452. [PubMed: 26359135]

[9]. Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghatge S, et al. Benefits and Harms of Breast Cancer Screening: A Systematic Review. JAMA 2015;314(15):1615–1634. doi:10.1001/jama.2015.13183. [PubMed: 26501537]

[10]. 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(11):2205–2240. doi:10.1038/bjc.2013.177. [PubMed: 23744281]

[11]. Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of Breast Cancer Screening: Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med 2016;164(4):256–267. doi:10.7326/M15-0970. [PubMed: 26756737]

[12]. Yang M, Hu X, Bao W, Zhang X, Lin Y, Stanton S, et al. Changing trends and disparities in 5-year overall survival of women with invasive breast cancer in the United States, 1975–2015. Am J Cancer Res 2021;11(6):3201–3211. [PubMed: 34249455]

[13]. Henson KE, Ellis-Brookes L, Coupland VH, Payne E, Vernon S, Rous B, et al. Data Resource Profile: National Cancer Registration Dataset in England. Int J Epidemiol 2020;49(1):16–16h. doi:10.1093/ije/dyz076. [PubMed: 31120104]

[14]. Wallington M, Saxon EB, Bomb M, Smittenaar R, Wickenden M, McPhail S, et al. 30-day mortality after systemic anticancer treatment for breast and lung cancer in England: a population-based, observational study. Lancet Oncol 2016;17(9):1203–1216. doi:10.1016/S1470-2045(16)30383-7. [PubMed: 27599138]
[15]. McPhail S, Johnson S, Greenberg D, Peake M, Rous B. Stage at diagnosis and early mortality from cancer in England. Br J Cancer 2015;112(Suppl 1):S108–S115. doi:10.1038/bjc.2015.49. [PubMed: 25734389]

[16]. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol 2017;18(6):719–731. doi:10.1016/S1470-2045(17)30186-9. [PubMed: 28410997]

[17]. Roche L, Danieli C, Belot A, Grosclaude P, Bouvier AM, Velten M, et al. Cancer net survival on registry data: use of the new unbiased Pohar-Perme estimator and magnitude of the bias with the classical methods. Int J Cancer 2013;132(10):2359–2369. doi:10.1002/ijc.27830. [PubMed: 23961565]

[18]. Peet M, Broggio J. The impact of updating cancer survival methodologies for national estimates, 2019 [updated Jan 14, 2019]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/methodologies/theimpactofupdatingcancersurvivalmethodologiesformationalestimates2019. Accessed March 5 2022.

[19]. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. Eur J Cancer 2004;40(15):2307–2316. doi:10.1016/j.ejca.2004.07.002. [PubMed: 15454257]

[20]. UK Cancer Research. Breast cancer stages, types and grades [updated Oct 2, 2017]. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades. Accessed July 2 2019.

[21]. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al., editors. International Classification of Diseases for Oncology. 3th ed. Lyon, France. World Health Organization; 2013. Available from: https://apps.who.int/iris/bitstream/handle/10665/96612/9789241548496_eng.pdf;sequence=1. Accessed February 10, 2022.

[22]. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19(3):335–351. doi:10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z. [PubMed: 10649300]

[23]. Xu J, Lin Y, Yang M, Zhang L. Statistics and pitfalls of trend analysis in cancer research: a review focused on statistical packages. J Cancer 2020;11(10):2957–2961. doi:10.7150/jca.43521. [PubMed: 32226510]

[24]. NCI. Pairwise Comparison: National Cancer Institute. Available from: https://web.archive.org/web/20201101055109/https://surveillance.cancer.gov/help/joinpoint/setting-parameters/advanced-analysis-tools-tab/pairwise-comparison. Accessed March 5 2022.

[25]. Ingram DD, Malec DJ, Makuc DM, Kruszon-Moran D, Gindi RM, Albert M, et al. National Center for Health Statistics Guidelines for Analysis of Trends. Vital Health Stat 2 2018;(179):1–71.

[26]. Yuan X, Song F, Zhang L. Trend analysis of diabetic mortality. Lancet 2019;393(10184):1931–1932. doi:10.1016/S0140-6736(18)33051-4.

[27]. Ellis L, Woods LM, Estève J, Eloranta S, Coleman MP, Rachet B. Cancer incidence, survival and mortality: explaining the concepts. Int J Cancer 2014;135(8):1774–1782. doi:10.1002/ijc.28990. [PubMed: 24945976]

[28]. Jacklyn G, Howard K, Irwig L, Housami N, Hersch J, Barratt A. Impact of extending screening mammography to older women: Information to support informed choices. Int J Cancer 2017;141(8):1540–1550. doi:10.1002/ijc.30858. [PubMed: 28662267]

[29]. Jiang M, Hughes DR, Appleton CM, McGinty G, Duszak R Jr. Recent trends in adherence to continuous screening for breast cancer among Medicare beneficiaries. Prev Med 2015;73:47–52. doi:10.1016/j.ypmed.2014.12.031. [PubMed: 25584984]

[30]. Ryerson AB, Miller JW, Eheman CR, Leadbetter S, White MC. Recent trends in U.S. mammography use from 2000–2006: a population-based analysis. Prev Med 2008;47(5):477–482. doi:10.1016/j.ypmed.2008.06.010. [PubMed: 18602946]
[31]. Yang M, Bao W, Zhang X, Kang Y, Haffty B, Zhang L. Short-term and long-term clinical outcomes of uncommon types of invasive breast cancer. Histo-pathology 2017;71(6):874–886. doi:10.1111/his.13328.

[32]. Carney P, O’Neill C. Income inequality in uptake of voluntary versus organised breast cancer screening: evidence from the British Household Panel Survey. BMC Public Health 2018;18(1):252. doi:10.1186/s12889-018-5139-9. [PubMed: 29444642]

[33]. Jack RH, Møller H, Robson T, Davies EA. Breast cancer screening uptake among women from different ethnic groups in London: a population-based cohort study. BMJ Open 2014;4(10):e005586. doi:10.1136/bmjopen-2014-005586.

[34]. Davies EA, Renshaw C, Dixon S, Møller H, Coupland VH. Socioeconomic and ethnic inequalities in screen-detected breast cancer in London. J Public Health (Oxf) 2013;35(4):607–615. doi:10.1093/pubmed/fdt476. [PubMed: 23440707]

[35]. Renshaw C, Jack RH, Dixon S, Møller H, Davies EA. Estimating attendance for breast cancer screening in ethnic groups in London. BMC Public Health 2010;10:157. doi:10.1186/1471-2458-10-157. [PubMed: 20334699]

[36]. Jack RH, Robson T, Davies EA. The varying influence of socioeconomic deprivation on breast cancer screening uptake in London. J Public Health (Oxf) 2016;38(2):330–334. doi:10.1093/pubmed/fdv038. [PubMed: 25829530]

[37]. Maringe C, Li R, Mangtani P, Coleman MP, Rachet B. Cancer survival differences between South Asians and non-South Asians of England in 1986–2004, accounting for age at diagnosis and deprivation. Br J Cancer 2015;113(1):173–181. doi:10.1038/bjc.2015.182. [PubMed: 26079299]

[38]. Mauri D, Polyzos NP, Salanti G, Pavlidis N, Ioannidis JP. Multiple-treatments meta-analysis of chemotherapy and targeted therapies in advanced breast cancer. J Natl Cancer Inst 2008;100(24):1780–1791. doi:10.1093/jnci/djn414. [PubMed: 19066278]

[39]. Jahanzeb M Adjuvant trastuzumab therapy for HER2-positive breast cancer. Clin Breast Cancer 2008;8(4):324–333. doi:10.3816/CBC.2008.n.037. [PubMed: 18757259]

[40]. Deng F, Huang J, Yuan X, Cheng C, Zhang L. Performance and efficiency of machine learning algorithms for analyzing rectangular biomedical data. Lab Invest 2021;101(4):430–441. doi:10.1038/s41374-020-00525-x. [PubMed: 33574440]

[41]. NCCN. NCCN clinical practice guidelines in oncology: breast cancer v2.2022 [updated Dec 20, 2021]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed March 5 2022.

[42]. Steel N, Ford JA, Newton JN, Davis ACJ, Vos T, Naghavi M, et al. Changes in health in the countries of the UK and 150 English Local Authority areas 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392(10158):1647–1661. doi:10.1016/S0140-6736(18)32207-4. [PubMed: 30497795]

[43]. Zhang J, Lin Y, Zhang L. Trends in Alcoholic Fatty Liver Disease. JAMA 2019;322(10):979–980. doi:10.1001/jama.2019.10347. [PubMed: 31503302]

[44]. Taylor-Phillips S, O’ Sullivan E, Kearins O, Parsons H, Clarke A. The effects of a UK review of Breast Cancer Screening on Uptake: an observational before/after study. J Med Screen 2013;20(2):86–90. doi:10.1177/0969141313497198. [PubMed: 24009089]
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.
Table 1.
Age-standardized 5-year net survival of screened and non-screened breast cancers among women in England, 1995–2016

| Year | Non-screened | Screened | All |
|------|--------------|----------|-----|
|      | N (%) | NS, % | N (%) | NS, % | N | NS, % | p   |
| 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

| Race | Non-screened | Screened | All |
|------|--------------|----------|-----|
|      | N (%) | NS, % | N (%) | NS, % | N | NS, % | p   |
| 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

| Histology | Non-screened | Screened | All |
|-----------|--------------|----------|-----|
| 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 |

<0.001
| Tumor Stage | Non-screened | Screened | All |
|-------------|--------------|----------|-----|
|             | N (%)        | NS, %    | N (%) | NS, % | N | NS, % | p     |
| 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 | Non-screened | Screened | All |
|-------------|--------------|----------|-----|
|             | N (%)        | NS, %    | N (%) | NS, % | N | NS, % | p     |
| 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.
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 paralleism |
|-------------|------------|----------|--------------|--------------|
| All         | 1995–2007  | 7,907    | -3.5 (-4.2 to -2.8) | <0.001       |
|             | 2007–2011  | 12,991   | 5.6 (2.2 to 9.1)   |              |
| Race        |            |          |               |              |
| Black       | 1995–2011  | <15      | -1.8 (-3.3 to -0.3) | reference    |
| Other       | 1995–2008  | 3,451    | -4.1 (-6.6 to -1.5) | 0.879        |
|             | 2008–2011  | 2,259    | 12.9 (-4.2 to 33.0) |              |
| White       | 1995–2007  | 1,202    | -3.5 (-5.5 to -1.4) | 0.783        |
|             | 2007–2011  | 5,658    | 4.2 (-0.8 to 9.5)  |              |
| Histology   |            |          |               |              |
| IDC         | 1995–2007  | 2,985    | -3.3 (-4.1 to -2.5) | 0.998        |
|             | 2007–2011  | 5,894    | 5.3 (1.7 to 9.0)   |              |
| ILC         | 1995–2007  | 532      | -3.3 (-3.9 to -2.8) | reference    |
|             | 2007–2011  | 938      | 5.4 (2.9 to 8.0)   |              |
| MDLC        | 1995–2007  | 25       | -3.6 (-5.9 to -1.3) | 0.176        |
|             | 2007–2011  | 299      | 9.6 (0.9 to 18.9)  |              |
| Other       | 1995–2007  | 1,135    | -4.1 (-4.9 to -3.3) | 0.005        |
|             | 2007–2011  | 924      | 2.9 (1.0 to 4.8)   |              |
| Staging     |            |          |               |              |
| Stage 1     | 1995–2008  | 562      | -5.2 (-6.6 to -3.7) | reference    |
|             | 2008–2011  | 1,490    | 5.6 (-4.9 to 17.3) |              |
| Stage 2     | 1995–2007  | 945      | -3.1 (-4.1 to -2.1) | 0.024        |
|             | 2007–2011  | 1,798    | 4.1 (-0.4 to 8.8)  |              |
| Stage 3     | 1995–2011  | 122      | -1.8 (-2.5 to -1.1) | 0.003        |
| Stage 4     | 1995–2011  | 70       | -1.0 (-1.3 to -0.7) | 0.048        |
| Grade       |            |          |               |              |
| Grade 1     | 1995–2007  | 581      | -5.1 (-6.2 to -3.9) | reference    |
|             | 2007–2011  | 857      | 7.0 (1.1 to 13.2)  |              |
| Segment | Start year | End year | APC (95% CI) | \( p_{\text{parallelism}} \) |
|---------|------------|----------|--------------|-----------------|
| Grade 2 | 1995–2007  | 3,362 (38.4) | -4.3 (-5.1 to -3.5) | 0.018 |
|         | 2007–2011  | 5,916 (48.7) | 6.4 (2.9 to 10.1) |               |
| Grade 3 | 1995–2008  | 3,311 (58.5) | -2.1 (-2.6 to -1.6) | 0.001 |
|         | 2008–2011  | 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).
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

| Segment         | Start year, NS, % | End year, NS, % | APC (95% CI) | p parallelism | Segment          | Start year, NS, % | End year, NS, % | APC (95% CI) | p parallelism for screened vs non-screened |
|-----------------|-------------------|-----------------|--------------|--------------|-----------------|-------------------|-----------------|--------------|------------------------------------------|
| 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                                     |
|                 | 2009–2010         | 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          | 14 (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
| Segment | 1995–2006 | 1995–2011 | 2006–2011 | Grade 1 | 1995–2006 | 1995–2011 | 2008–2011 | Grade 2 | 1995–2008 | 2008–2011 | Grade 3 | 1995–2008 | 2008–2011 |
|---------|------------|------------|------------|---------|------------|------------|------------|---------|------------|------------|---------|------------|------------|
| Start year, NS, % | End year, NS, % | APC (95% CI) | p parallelism | Start year, NS, % | End year, NS, % | APC (95% CI) | p parallelism | Start year, NS, % | End year, NS, % | APC (95% CI) | p parallelism |
| Screened | 99 | 106 | 0.3 (0.0 to 0.6) | reference | 1995–2011 | 98 | 97 | 0.1 (-0.1 to 0.3) | reference | <0.001 |
| Non-screened | 2006–2011 | 106 | 98 | 101 | -0.8 (-1.3 to -0.4) | 1995–2008 | 88 | 87 | 0.1 (-0.2 to 0.4) | 0.004 | <0.001 |
| Segment | 1995–2011 | 2008–2011 | 2008–2011 | Grade 1 | 1995–2006 | 1995–2011 | 2008–2011 | Grade 2 | 1995–2008 | 2008–2011 | Grade 3 | 1995–2008 | 2008–2011 |
| Start year, NS, % | End year, NS, % | APC (95% CI) | p parallelism | Start year, NS, % | End year, NS, % | APC (95% CI) | p parallelism | Start year, NS, % | End year, NS, % | APC (95% CI) | p parallelism |
| Screened | 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 |
| Non-screened | 2006–2011 | 87 | 75 | 94 | 3.7 (2.4 to 5.0) | 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.