Breast cancer incidence and survival in Scotland by socio-economic deprivation and tumour subtype

Ines Mesa Eguiagaray (✉ ieguiaga@ed.ac.uk)
Usher Institute, College of Medicine and Veterinary Medicine, University of Edinburgh, UK
https://orcid.org/0000-0002-6784-2419

Sarah H Wild
Usher Institute, College of Medicine and Veterinary Medicine, University of Edinburgh, UK

Sheila M Bird
Cambridge University's MRC Biostatistics Unit, Cambridge, UK

Linda J Williams
Usher Institute, College of Medicine and Veterinary Medicine, University of Edinburgh, UK

David H Brewster
Usher Institute, College of Medicine and Veterinary Medicine, University of Edinburgh, UK

Peter S Hall
Cancer Research UK Edinburgh Centre, Institute of Genetics and Cancer, University of Edinburgh,UK

Jonine D Figueroa
Usher Institute, College of Medicine and Veterinary Medicine, University of Edinburgh, UK

Research Article

Keywords: breast cancer, incidence, mortality, subtypes, socio-economic status

Posted Date: February 1st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1296798/v1

Abstract

Background:

Women from socio-economically deprived areas are less likely to develop and then to survive breast cancer (BC). It is unknown whether the associations between deprivation and BC incidence and survival differ by tumour subtypes.

Methods:

Data consisted of 62,378 women diagnosed with invasive BC between 2000 and 2016 in Scotland. Incidence rates and time trends were calculated for oestrogen receptor positive (ER+) and negative (ER-) tumours and stratified by quintiles of an area-based measure of socio-economic status and screening status. We calculated hazard ratios for BC death by molecular subtype adjusted for screening status and other confounders (aHR) for the most versus the least deprived quintile.

Results:

In Scotland, screen detected ER+ tumour incidence increased over time, particularly in the least deprived quintile (AAPC=2.9% [1.2, 4.7]) with no marked differences observed for non-screen detected ER+ tumours or ER- tumours by deprivation. BC mortality was higher in the most compared to the least deprived quintile irrespective of ER status (aHR =1.29 [1.18, 1.41] for ER+ and 1.27 [1.09, 1.47] for ER- tumours). Deprivation was also associated with significantly higher mortality for luminal A and HER2 enriched tumours (aHR =1.46 [1.13, 1.88] and 2.10 [1.23, 3.59] respectively) but the association was not statistically significant for luminal B and TNBC tumours.

Conclusions:

Deprivation is associated with differential breast cancer incidence trends for screen-detected ER+ tumours and with higher mortality for select tumour subtypes. Further research is required to confirm these findings and monitor inequalities in BC by tumour subtypes.

Background

Breast cancer (BC) survival has improved markedly over the last 30 years due to the introduction of mammographic screening and improvements in treatment, including targeted therapies for hormone sensitive tumours [1]. However socio-economic inequalities in BC survival persist in Scotland [2] and many other countries [3-6]. It is well established that BC incidence and survival differ significantly by molecular subtype [7-12]. Examining whether there are differences by deprivation for different subtypes could inform approaches to reducing inequalities through primary and secondary prevention.

Disparities by socio-economic status (SES) in BC incidence are complex and involve risk factor differences including race/ethnicity, access to healthcare and differences in the predisposition to

different tumour types. The prognostic disparity by SES has been attributed to patient and clinic factors, including differences in the incidence of tumours characterized by pathologically and biologically aggressive phenotypes, the prevalence of obesity and other comorbid conditions, health-risk behaviours, access to treatment, and quality of care received [13-15].

Several studies have shown that women living in more deprived areas are more likely than those living in less deprived areas to be diagnosed with oestrogen receptor negative (ER-) and triple negative (ER-, progesterone receptor negative (PR-), and human epidermal growth factor receptor-2 negative (HER2-)) breast cancers (TNBC) [16-18]. Race/ethnic differences in incidence of hormone negative and more aggressive breast cancer subtypes have been observed in the US where it can be difficult to separate racial and socio-economic disparities [19-21]. TNBC tumours are associated with early recurrence and poor survival due to lack of specific targets for commonly used adjuvant therapies [22]. It remains unclear whether differences in TNBC incidence by SES explains the observed worse prognosis of BC patients living in areas with greater socio-economic deprivation.

Greater understanding of the role of socio-economic deprivation on the incidence and survival of different subtypes of BC could inform the development of interventions aiming to reduce disparities and improve BC prognosis. Within the high-quality Scottish cancer registry, we previously showed distinct temporal trends in cancer incidence by ER status [23]. Specifically, we reported that ER+ tumour incidence increased by an average of 0.4%/year, but that the increasing incidence was limited to women aged 50–69 years who are eligible for routine screening, where we reported increases in age-standardised incidence between 1997 and 2011 (1.6%/year, 95% CI: 1.2–2.1). ER- tumour incidence decreased for all age groups by 2.5%/year (95% CI: −3.9 to −1.1%) over the study period. Here we aimed to determine whether incidence and survival by BC subtype differed by an area-based measure of SES.

Methods

Study population

All adult women (20 years or older) diagnosed with a primary invasive BC (ICD10 C50) in Scotland between 2000 and 2016 were identified from the Scottish Cancer Registry. A single invasive BC record for each woman was selected as previously described [23]. The incidence cohort was further restricted for the survival analyses: women aged more than 99 years, with missing vital status or diagnosed with BC only from death certificates were excluded from the analysis (**Figure 1**). Women who had the same date of incidence and death were also excluded. The total number of excluded cases was 361 (0.6% of the total) and the final population for the survival analysis consisted of 62,012 women whose breast cancer was diagnosed between 2000 and 2016 (**Figure 1**).

Molecular subtypes definition

ER status has been recorded in the Scottish cancer registry since 1997 for all invasive tumours diagnosed histologically, through biopsy, surgical excision or histology of nodes or metastases. The method used to

assign ER status (positive or negative) to a tumour was the Allred score system and is assigned following immunohistochemical (IHC) staining for the proportion of cells that stain positively and the intensity of staining [24]. Progesterone receptor status (PR) and HER2 status were available from 2009 and were also measured using IHC. The fluorescence in-situ hybridisation (FISH) test was carried out to confirm the result for HER2 status if IHC result was borderline. ER, PR and HER2 combinations were used as a proxy for the classification of molecular BC through genetic profiling known as intrinsic molecular subtypes of BC [25]. The molecular subtypes were defined according to the St Gallen 2011 consensus: ER+ and/or PR+ and HER2- tumours were defined as luminal A, ER+ and/or PR+ and HER2+ as luminal B, ER- and PR- and HER2+ as HER2 enriched and ER- and PR- and HER2- as TNBCs. The Ki-67 a marker for tumour proliferation is not currently recorded in the Scottish cancer registry, which is why grade was used to further differentiate luminal A and luminal B tumours with luminal A tumours of high grade (poorly differentiated) reclassified as luminal B tumours.

Deprivation definition

The Scottish Index of Multiple Deprivation (SIMD) was used as an area-based measure of SES. SIMD is based on seven domains: income, employment, health, education, crime, access to services and housing that are used to rank the 6,976 data zones in Scotland from the most deprived to the least deprived area. SIMD is often expressed in quintiles and we compared women in the most deprived fifth of areas (quintile 1) with women in the least deprived fifth of areas (quintile 5) of Scotland. SIMD was available for all women within the cancer registry with a Scottish postcode. Several SIMD versions (SIMD 2004, 2006, 2009, 2012 and 2016) were available for our study period from 2000 to 2016. The most appropriate SIMD version for each year of diagnosis was selected as recommended in the deprivation guidance for analysts [26] and a unique quintile was used for each woman.

Survival outcome

Breast cancer specific survival (BCSS) was the primary outcome of the survival analysis. BC deaths were derived using only the underlying (primary) cause of death as derived from death records linked to the cancer registry [27]. Date of incidence in the Scottish Registry is normally recorded as the date of first consultation or admission at the hospital for that cancer. This date is a definite point in time that can be verified from the records and is the most consistent and reliable date to use [28]. Duration of follow-up was defined as time from date of diagnosis of BC to the first of: date of death, 31st December 2017 for women still alive at the end of the study period or embarkation date if women moved outside Scotland (within the UK). The 31st of December 2017 was selected as the end of follow-up as the data were obtained in April of 2018. Complete incidence data for the year 2016 would be expected by the end of 2017 in accordance with the United Kingdom and Ireland Association of Cancer Registries (UKIACR) guidelines. The approach taken for this analysis is similar to that described by Skyrud et al. [29] in that only ICD9 174 and ICD10 C50 codes from primary cause of death were used to derive BC specific death. Other primary causes of death were regarded as censored observations for the calculation of BC specific survival.

Statistical analysis

Incidence

Age standardised incidence of BC was computed for all women living in the most and least deprived quintiles of Scotland by ER status. Counts of BC by ER status and SIMD based on a single incident BC per woman for each age and year of diagnosis were used as the numerator. The population estimates used as the denominator were mid-year population estimates for each age group (in 5-years age groups), year of diagnosis and SIMD quintile obtained from the National Records of Scotland [30]. These estimates are derived from decennial census data with adjustment for population changes in intervening years and for under-numeration (estimated coverage was 94% in the 2011 Census) [31]. Incidence was standardised using the direct method to the European standard population (2013) in 5-year age groups. Further, incidence rates by ER status and SIMD were calculated for women of approximate screening age (50 to 69 years) and stratified by method of detection (screen vs non-screen detected tumours). Graphs of incidence trends were smoothed using a three-year moving average, with incidence year in the graphs representing the middle year for each three-year period (for example, year 2001 in the graph represents the average of years 2000 to 2002). The average annual percentage change (AAPC) for each ER status and the two extreme quintiles of deprivation (most and least deprived areas) was computed overall and stratified by method of detection and is presented in the graphs with 95% CI [32].

Survival Analyses

Non-parametric Kaplan-Meier estimates [33] were used to estimate breast cancer specific survival (BCSS) by ER status and the IHC defined molecular subtypes for women by deprivation quintile who had been followed up for at least 5 years. Comparisons between those in the most and least deprived areas are reported here. Five-year survival was chosen as primary endpoint as it is often used for population cancer statistics and recommended as a quality performance indicator by NHS Scotland [34]. Cox proportional hazards models [35] were fitted to investigate the association between living in the most and least deprived areas of deprivation (main exposures) and BC death among Scottish women with BC. Models were fitted on complete cases and adjusted for covariates separately for each ER status or molecular subtype to adjust for non-proportional hazards between subtypes. Covariates in the models were: year of diagnosis, age at diagnosis, NHS Scottish region, tumour characteristics (grade, TNM stage, and method of detection), treatment regimens (surgery, radiotherapy, chemotherapy and hormone therapy) and comorbidities measured using the Charlson index of comorbidity based on hospital admission data derived from the Scottish Morbidity Records dataset [36].

Results

Incidence

Among the 62,373 BC cases diagnosed between 2000 and 2016, 18% were in the most deprived quintile and 21% were in the least deprived quintile, **Table 1**. The proportion of ER- cases declined over time but

was slightly higher amongst women from the most deprived quintile with the highest proportion observed in 2000-2003 (21% vs 17% in the least deprived quintile). Women diagnosed with ER+ tumours in the least deprived areas had slightly higher frequency of lower stage tumours (40% vs 34% stage I) but proportions of high grade tumours (27% vs 28% for grade III) were similar to those in women from the most deprived quintile. Differences in tumour characteristics were less marked for ER- tumours, although women from the most deprived quintile had slightly lower frequencies of stage I and slightly higher frequencies of stages II and III than women in the least deprived quintile. The proportion of screen detected tumours was higher in the least deprived quintile than in the most deprived quintile for both ER+ (34% vs 28%) and ER- tumours (19% vs 15%). There were clear treatment differences between the subtypes and lower proportions of women had surgery, radiotherapy and chemotherapy in the most deprived areas of Scotland compared to the least deprived areas regardless of ER status. In contrast, proportions of women who received hormone therapy were very similar across deprivation quintiles.

Figure 2 presents temporal trends in the incidence rates from 2000-2016 by deprivation status. ER+ tumours incidence was higher than ER- tumours incidence for all deprivation quintiles. Incidence of ER+ tumours was similar for least and most deprived quintiles with no clear increasing trend (AAPC = 0.7% (95% CI: -0.2 to 1.7) for least deprived and -0.1% (95% CI: -1.1 to 0.8) for most deprived). From 2009 ER+ incidence appears to slightly increase more markedly for the least deprived quintile. For ER- tumours, incidence has remained approximately constant over time with around 40 cases per 100,000 women in the most deprived quintile; and around 30 per 100,000 women in the least deprived quintile.

Figure 3 shows that increasing incidence rates were observed for ER+ screen detected tumours in women of screening age (50 to 69 years) regardless of deprivation, although the magnitude was higher for least deprived women. The incidence pattern for this subgroup was similar to that for the whole of Scotland, with steady increases (AAPC=2.9% [1.2, 4.7]) until early 2010s when they levelled off. In contrast, we observe no marked differences in the incidence or time trends of non-screen detected ER+ tumours by deprivation. Incidence of ER- tumours was slightly higher for non-screen detected tumours than for screen detected tumours with no clear differences in incidence or time trends observed by deprivation.

Survival

Of the 62,012 women included in the survival analysis, 50,420 (81%) were followed-up for 5 years or longer. In Scotland, higher proportions of women diagnosed with BC between 2000 and 2016 were alive at the end of the follow-up (2017) in the least deprived areas than in the most deprived areas, regardless of tumour subtype (**Table 1**). However, proportions of BC specific deaths were similar across deprivation quintiles. Among women diagnosed with an ER+ tumour who died during the study period, 66% died from BC in the least deprived areas compared to 64% in the most deprived areas. Proportions of deaths attributed to BC were higher for women with ER- tumours but did not differ by deprivation quintile, accounting for 82% of all deaths in the least deprived and 81% in the most deprived (**Table 1**).

Breast cancer specific survival at 5 years was highest amongst women living in the least deprived fifth of areas of Scotland diagnosed with luminal A or ER+ tumours (90.6 and 87.4% respectively) (**Table 2**). In

contrast, women with more aggressive subtypes (ER-, HER2 enriched and TNBC) living in the most deprived fifth of areas had the lowest BC specific survival at 5 years with 65.1, 64.5 and 69.7% respectively. Women living in the most deprived areas had lower survival than women living in the least deprived areas for all subtypes, this difference was particularly high for women diagnosed with an ER- tumour particularly if the cancer overexpressed HER2 (**Table 2**).

Breast cancer specific mortality for the most compared to the least deprived was similar by ER status, HR of 1.29 (95% CI: 1.18 to 1.41) and 1.27 (95% CI: 1.09 to 1.47) for ER+ and ER- tumours respectively (**Figure 4**) after adjusting for individual and tumour characteristics, treatments and comorbidities. Deprivation showed differential associations with BC specific mortality when using St Gallen's molecularly defined subtypes. The highest relative risk of BC death was observed for women with the least common subtype, HER2 enriched, for whom HR was 2.1 (95% CI: 1.23 to 3.59) for those living in the most deprived areas compared to women living in the least deprived areas of Scotland. Women with luminal A tumours in the most deprived areas were 46% more likely to die of BC compared to women in the least deprived areas (**Figure 4**). For women with luminal B and TNBC there was no evidence that deprivation was associated with BC death after adjustment for other tumour characteristics, treatments and comorbidities.

Discussion

We previously reported increasing incidence of ER+ tumours and decreasing incidence of ER- tumours across Scotland between 1997 and 2016 and identified that screening was a major contributor to rising incidence of ER+ tumours [23]. Here we observed that although trends over time were similar to those previously reported regardless of deprivation, incidence increased mainly amongst women living in least deprived areas of Scotland with screen detected ER+ tumours (AAPC of 2.9%).Absolute incidence for ER+ screen detected tumours was also higher among the least deprived compared to the most deprived (with approximately 50 more cases per 100,000 women at the peak in 2011. Screening uptake might partially account for the differences in BC incidence observed between most and least deprived areas. Uptake of BC screening in the most deprived areas of Scotland was 59.5 % in 2016-2019 and 79.7% in the least deprived areas [37].

We found lower point estimates and no statistically significant association between deprivation and BC survival among women with the rarer subtypes of TNBC or luminal B tumours. Previous studies from Scotland and other countries have found an association between SES (at both individual and neighbourhood level) and BC mortality, with women with low SES having a higher BC mortality [17, 38, 39]. Some data show women with low SES are more likely to be diagnosed with more aggressive BC subtypes, particularly ER- and TNBC subtypes [16-18]. However, evidence of whether survival rates for subtypes differ by SES has not been investigated previously. In multivariable analysis, deprivation was associated with statistically significantly higher BC mortality for luminal A and HER2 tumour subtypes but not TNBC and luminal B tumours, for which the association was attenuated and no longer statistically significant after adjusting for screening, treatment and the Charlson index for comorbidities.

Risk of breast cancer death for HER2+ tumours appeared particularly high, albeit with limited power and wide confidence intervals for the most deprived areas compared to the least deprived areas, and this finding will require confirmation in other datasets to determine if it holds. Cumulatively, our findings support socio-economic deprivation in survival may differ between subtypes.

Possible additional factors that could be contributing to survival differences by deprivation are alcohol intake, obesity and smoking. In Scotland, alcohol-related hospitalisation and mortality was up to 8 times higher across people from the most deprived areas. However, men and women in the most deprived areas of Scotland are less likely to drink hazardous or harmful alcohol levels than those in the least deprived areas (10% drinking at hazardous/harmful level vs 20%) [40]. Further, heavy drinking has been also consistently linked to weight gain [41]. In Scotland, obesity prevalence in women is around 30% and 20% in the most and least deprived areas respectively [42]. Smoking could also be a contributing factor given that prevalence was 30% compared to 9% in women in the most and least deprived areas of Scotland in 2018 [40]. The more marked differences by deprivation among women diagnosed with luminal A or HER2 enriched tumours than for luminal B and TNBC tumours may also be related to differences in prognosis between sub-types with deprivation having less effect among sub-types with poorer prognosis

This study has several strengths as to our knowledge is the first study in the UK to investigate BC incidence and survival by SIMD and molecular subtypes utilising high quality data from the Scottish cancer registry with linkage to mortality and comorbidity records. As for any observational study, the validity of our findings must be assessed in terms of potential confounding and bias. One of the main limitations is the possibility of unmeasured confounders. Although our analysis controlled for key potential confounders, there was no information about other risk factors, such as obesity alcohol consumption, smoking and physical activity. Another limitation is that survival rates can be affected by lead time and length biases [43] usually caused by the introduction of a national screening programme during the period of study. However, the national screening programme in Scotland was established in 1987 with full coverage by 1991, hence this type of bias is likely to have been minimal. Further, the validity of BC specific survival analysis depends on the accuracy of cause of death as recorded in the registry which assumes that the underlying cause of death has been accurately determined for each woman. Skyrud et al. [29] compared cause-specific and relative survival estimates and found cause-specific estimates to be as reliable as relative survival estimates, particularly for common cancers. Further, the use of relative survival would require lifetables for the BC molecular subtypes in order to calculate the expected survival which are currently not available. Another possible limitation is competing risks of death with women in most deprived areas being more likely to die from other causes than breast cancer. In order to minimise competing risks of death we restricted survival estimates to 5 years. Finally, the SIMD is an area-based measure of deprivation so it can misclassify individuals' SES [44]. Potential misclassification is a particular risk for rural areas where the index domains, particularly the 'access' domain fails to capture important singularities of the rural areas, such as, frequency and cost of public transport [45].

This analysis using high quality population- based data in Scotland shows differences in incidence and prognosis between an area-based measure of SES for different molecular subtypes of BC for the first time in the UK. More detailed data on risk factors by SES and tumour subtype would be helpful to prioritise the groups where inequities exist and where improvements in primary and secondary prevention of breast cancer would have the most impact.

Declarations

Funding

This project was funded by Wellcome Trust grant 207800/Z/17/Z.

Competing interests

S.M.B. holds shares in GlaxoSmithKline. Other authors declare no competing interests.

Author contributions

Conception and design of the study: I.M.E, J.D.F.and S.W. Material preparation, data collection and analysis: I.M.E and J.D.F. Interpretation of data: all authors. Drafting of the paper: I.M.E., J.D.F. and S.W. Revised work and provided important intellectual content: all authors. Final approval of the paper: all authors.

Ethics approval

Approval from the Public Benefit and Privacy Panel for Health and Social Care is a requirement for data access. Our project was approved by PBPP reference number 1718-0057.

References

1. Independent UK Panel on Breast Cancer Screening, *The benefits and harms of breast cancer screening: an independent review.* The Lancet, 2012. **380**(9855): p. 1778-1786.

2. Macmillan Cancer Support -NHS, *Deprivation and Survival from Breast Cancer in Scotland*. 2017.

3. Jang, B.-S. and J.H. Chang, *Socioeconomic status and survival outcomes in elderly cancer patients: A national health insurance service-elderly sample cohort study.* Cancer Medicine, 2019. **8**(7): p. 3604-3613.

4. Pruitt, S.L., et al., *Association of Area Socioeconomic Status and Breast, Cervical, and Colorectal Cancer Screening: A Systematic Review.* Cancer Epidemiology Biomarkers & Prevention, 2009. **18**(10): p. 2579.

5. Schrijvers, C.T., et al., *Deprivation and survival from breast cancer.* British journal of cancer, 1995. **72**(3): p. 738-743.

6. Woods, L.M., et al., *Impact of deprivation on breast cancer survival among women eligible for mammographic screening in the West Midlands (UK) and New South Wales (Australia): Women diagnosed 1997-2006.* Int J Cancer, 2016. **138**(10): p. 2396-403.

7. Mullooly, M., et al., *Divergent oestrogen receptor-specific breast cancer trends in Ireland (2004-2013): Amassing data from independent Western populations provide etiologic clues.* European Journal of Cancer, 2017. **86**: p. 326-333.

8. Engstrøm, M.J., et al., *Molecular subtypes, histopathological grade and survival in a historic cohort of breast cancer patients.* Breast Cancer Research and Treatment, 2013. **140**(3): p. 463-73.

9. Fallahpour, S., et al., *Breast cancer survival by molecular subtype: a population-based analysis of cancer registry data.* CMAJ open, 2017. **5**(3): p. E734-E739.

10. Howlader, N., et al., *Differences in Breast Cancer Survival by Molecular Subtypes in the United States.* Cancer Epidemiology, Biomarkers and Prevention, 2018. **27**(6): p. 619-626.

11. Anderson, W.F., H.A. Katki, and P.S. Rosenberg, *Incidence of breast cancer in the United States: current and future trends.* Journal of the National Cancer Institute, 2011. **103**(18): p. 1397-402.

12. Johansson, A.L.V., et al., *Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort.* Int J Cancer, 2019. **144**(6): p. 1251-1261.

13. Bastiaannet, E., et al., *Socioeconomic differences in survival among breast cancer patients in the Netherlands not explained by tumor size.* Breast Cancer Res Treat, 2011. **127**(3): p. 721-7.

14. Cross, C.K., J. Harris, and A. Recht, *Race, socioeconomic status, and breast carcinoma in the U.S: what have we learned from clinical studies.* Cancer, 2002. **95**(9): p. 1988-99.

15. Rutqvist, L.E. and A. Bern, *Socioeconomic gradients in clinical stage at presentation and survival among breast cancer patients in the Stockholm area 1977-1997.* Int J Cancer, 2006. **119**(6): p. 1433-9.

16. Bauer, K.R., et al., *Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry.* Cancer, 2007. **109**(9): p. 1721-8.

17. Thomson, C.S., et al., *Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival.* Journal of epidemiology and community health, 2001. **55**(5): p. 308-15.

18. Vona-Davis, L. and D.P. Rose, *The influence of socioeconomic disparities on breast cancer tumor biology and prognosis: a review.* Journal of Womens Health, 2009. **18**(6): p. 883-93.

19. Amirikia, K.C., et al., *Higher population-based incidence rates of triple-negative breast cancer among young African-American women : Implications for breast cancer screening recommendations.* Cancer, 2011. **117**(12): p. 2747-53.

20. Carey, L.A., et al., *Race, Breast Cancer Subtypes, and Survival in the Carolina Breast Cancer Study.* JAMA, 2006. **295**(21): p. 2492-2502.

21. Clarke, C.A., et al., *Age-Specific Incidence of Breast Cancer Subtypes: Understanding the Black–White Crossover.* JNCI: Journal of the National Cancer Institute, 2012. **104**(14): p. 1094-1101.

22. Gluz, O., et al., *Triple-negative breast cancer–current status and future directions.* Ann Oncol, 2009. **20**(12): p. 1913-27.

23. Mesa-Eguiagaray, I., et al., *Distinct temporal trends in breast cancer incidence from 1997 to 2016 by molecular subtypes: a population-based study of Scottish cancer registry data.* Br J Cancer, 2020. **123**(5): p. 852-859.

24. ISD- NHS Scotland. *National Cancer Registration Data Definitions Version 14.4*. 2017; Available from: https://www.isdscotland.org/Health-Topics/Cancer/Scottish-Cancer-Registry/Cancer-Metadata/_docs/Cancer-Registration-Definitions-v14-4.pdf.

25. Perou, C.M., et al., *Molecular portraits of human breast tumours.* Nature, 2000. **406**(6797): p. 747.

26. GDP Team-NHS National Services Scotland, *Deprivation Guidance for analysts*, Public Health & Intelligence, Editor. 2019: https://www.isdscotland.org/Products-and-Services/GPD-Support/Deprivation/_docs/PHI-Deprivation-Guidance-version-3-2.pdf.

27. Kendrick, S. and J. Clarke, *The Scottish Record Linkage System.* Health bulletin, 1993. **51**(2): p. 72-79.

28. Public Health Scotland. *Scottish Cancer Registry- cancer metadata*. Data and Intelligence 2020 [cited 2020.

29. Skyrud, K.D., F. Bray, and B. Møller, *A comparison of relative and cause-specific survival by cancer site, age and time since diagnosis.* International Journal of Cancer, 2014. **135**(1): p. 196-203.

30. National records of Scotland. *Mid-Year Population Estimates*. 2019 [cited 2019; Available from: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates.

31. National Records of Scotland, *Mid-2018 Population Estimates for Scotland: Methodology Guide*. 2019.

32. Clegg, L.X., et al., *Estimating average annual per cent change in trend analysis.* Stat Med, 2009. **28**(29): p. 3670-82.

33. Kaplan, E.L. and P. Meier, *Nonparametric estimation from incomplete observations.* Journal of the American statistical association, 1958. **53**(282): p. 457-481.

34. NHS Scotland, *Breast cancer clinical quality performance indicators*, Scottish cancer taskforce national cancer quality steering group, Editor. 2016.

35. Cox, D.R., *Regression Models and Life-Tables.* Journal of the Royal Statistical Society. Series B (Methodological), 1972. **34**(2): p. 187-220.

36. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.

37. Public Health Scotland. *Scottish breast screening pogramme statistics 2018/2019*. 2019; Available from: https://www.isdscotland.org/Health-Topics/Cancer/Publications/2017-04-25/2017-04-25-SBSP-Cancer-Report.pdf.

38. Harper, S., et al., *Trends in area-socioeconomic and race-ethnic disparities in breast cancer incidence, stage at diagnosis, screening, mortality, and survival among women ages 50 years and over (1987-2005).* Cancer Epidemiology and Prevention Biomarkers, 2009. **18**(1): p. 121-131.

39. Sprague, B.L., et al., *Socioeconomic status and survival after an invasive breast cancer diagnosis.* Cancer, 2011. **117**(7): p. 1542-51.

40. Cheong, C.K., et al., *The Scottish Health Survey 2018 edition; amended in February 2020: Volume 1, Main report.* 2020.

41. Traversy, G. and J.-P. Chaput, *Alcohol Consumption and Obesity: An Update.* Current obesity reports, 2015. **4**(1): p. 122-130.

42. Tod, E., et al., *Obesity in Scotland: a persistent inequality.* International journal for equity in health, 2017. **16**(1): p. 135-135.

43. Stockton, D. and J. McCann, *Cancer registries in monitoring, evaluating and planning breast cancer screening programmes.* Evaluation and Monitoring of Screening Programmes. Luxembourg: Office for Official Publications of the European Communities., 2001: p. 181-94.

44. Tunstall, R. and R. Lupton, *Is Targeting Deprived Areas an Effective Means to Reach Poor People? An Assessment of One Rationale for Area-Based Funding Programmes, CASE/70. London: London School*

of Economics and Political Science. 2003.

45. Robson, B., et al., *Deprivation in London: an alternative to IMD 2000.* Manchester: University of Manchester, 2001.

Tables

Table 1 Descriptive characteristics of women in Scotland diagnosed with invasive BC from 2000 to 2016 by extreme quintiles of the Scottish Index of Multiple Deprivation and known ER status.

	Most deprived quintile n=10946 (18%)				Least deprived quintile n=12909 (21%)			
	ER+		ER-		ER+		ER-	
	n	%	n	%	n	%	n	%
	8356	**[81]**	**1908**	**[19]**	**10394**	**[85]**	**1861**	**[15]**
Age								
<50 years	1523	[75]	517	[25]	2119	[81]	488	[19]
50-69 years	4219	[82]	920	[18]	5468	[86]	915	[14]
70 years or older	2614	[85]	471	[15]	2807	[86]	458	[14]
Scottish Region								
North	947	[81]	216	[19]	2658	[82]	602	[18]
South East	1423	[83]	288	[17]	3679	[88]	519	[12]
West	5986	[81]	1404	[19]	4057	[85]	740	[15]
Year of diagnosis								
2000-2003	1649	[79]	431	[21]	2121	[83]	423	[17]
2004-2007	1856	[81]	433	[19]	2235	[86]	368	[14]
2008-2011	2100	[82]	455	[18]	2590	[85]	470	[15]
2012-2016	2751	[82]	589	[18]	3448	[85]	600	[15]
Charlson Score Index								
0	7810	(93)	1769	(93)	10045	(97)	1814	(97)
1 or more	546	(7)	139	(7)	349	(3)	47	(3)
Tumour grade								
I	1103	(13)	25	(1)	1552	(15)	22	(1)
II	3576	(43)	244	(13)	5215	(50)	291	(16)
III	2331	(28)	1362	(71)	2797	(27)	1361	(72)
Unknown	1346	(16)	277	(15)	830	(8)	187	(10)
Tumour stage								
1	2850	(34)	439	(23)	4097	(40)	504	(27)
2	2966	(36)	789	(41)	3679	(35)	790	(42)

3	1151	(14)	335	(18)	1332	(13)	301	(16)
4	442	(5)	126	(7)	442	(4)	90	(5)
Unknown	947	(11)	219	(11)	844	(8)	176	(9)
Screen detected								
Yes	2346	(28)	279	(15)	3506	(34)	351	(19)
No	5831	(70)	1576	(83)	6781	(65)	1489	(80)
Unknown	179	(2)	53	(3)	107	(1)	21	(1)
PR status*								
Positive	3000	(69)	33	(4)	3269	(60)	53	(6)
Negative	569	(13)	780	(83)	643	(12)	717	(76)
Unknown	767	(18)	123	(13)	1543	(28)	169	(18)
HER2 status*								
Positive	487	(11)	250	(27)	599	(11)	292	(32)
Negative	3439	(79)	601	(64)	4405	(81)	572	(61)
Unknown	410	(10)	85	(9)	451	(8)	75	(8)
Surgery								
Yes	6846	(82)	1701	(89)	9237	(89)	1712	(92)
No	1462	(18)	196	(11)	1126	(11)	<200	(8)
Unknown	48	(0)	11	(0)	31	(0)	<10	(0)
Radiotherapy								
Yes	4736	(57)	1114	(58)	6780	(65)	1233	(66)
No	3163	(38)	6725	(36)	3292	(32)	564	(30)
Unknown	457	(5)	122	(6)	322	(3)	64	(4)
Chemotherapy								
Yes	2619	(31)	1286	(67)	3580	(34)	1330	(72)
No	5480	(66)	580	(31)	6660	(64)	510	(27)
Unknown	257	(3)	42	(2)	154	(2)	21	(1)
Hormone therapy								
Yes	7143	(86)	130	(7)	9050	(87)	134	(7)

No	600	(7)	1681	(88)	810	(8)	1663	(89)
Unknown	613	(7)	97	(5)	534	(5)	64	(4)
Vital status								
Alive	5421	(65)	1091	(57)	7888	(76)	1267	(68)
Dead	2935	(35)	817	(43)	2506	(24)	594	(32)
BC death^								
Yes	1872	(64)	661	(81)	1646	(66)	487	(82)
No	1063	(36)	156	(19)	860	(34)	107	(18)
Follow-up time in years								
Mean (SD)	6.6	(4.6)	5.9	(4.9)	7.4	(4.7)	6.7	(4.9)

N do not equal total due to missing ER status. ER status was missing in 6% of tumours diagnosed in most deprived areas and 5% of tumours in least deprived areas.

*PR and HER2 figures restricted to years 2009 to 2016.

^ BC death amongst those who died during follow-up.

 Follow-up time amongst those who died from BC.

Table 2 Five year breast cancer specific survival estimates (in %) with 95% confidence intervals by molecular subtype for women living in the most and least deprived areas of Scotland whose breast cancer was diagnosed 2000-2013

BREAST CANCER SPECIFIC SURVIVAL	Most deprived	Least deprived	Difference in proportions surviving (least minus most)
ER+			
deaths/cases	1664/6159	1513/7682	
5-year BCSS (95% CI)	80.5 (79.5, 81.5)	87.4 (86.7, 88.2)	6.9 (5.7, 8.1)
ER-			
deaths/cases	566/1432	420/1374	
5-year BCSS (95% CI)	65.1 (62.6, 67.6)	74.7 (72.3, 76.9)	9.6 (6.2, 13.0)
Luminal A			
deaths/cases	194/1134	177/1551	
5-year BCSS (95% CI)	85.0 (82.8, 87.0)	90.6 (89.1, 92.0)	5.6 (3.1, 8.1)
Luminal B			
deaths/cases	148/656	149/840	
5-year BCSS (95% CI)	81.1 (77.8, 83.9)	85.4 (82.8, 87.7)	4.3 (0.5, 8.1)
HER2 enriched			
deaths/cases	40/112	17/113	
5-year BCSS (95% CI)	64.5 (54.8, 72.7)	85.7 (77.8, 91.0)	21.2 (10.2, 32.2)
TNBC			
deaths/cases	79/252	65/243	
5-year BCSS (95% CI)	69.7 (63.5, 75.1)	74.8 (68.9, 79.8)	5.1 (-2.8, 13.0)

Figures

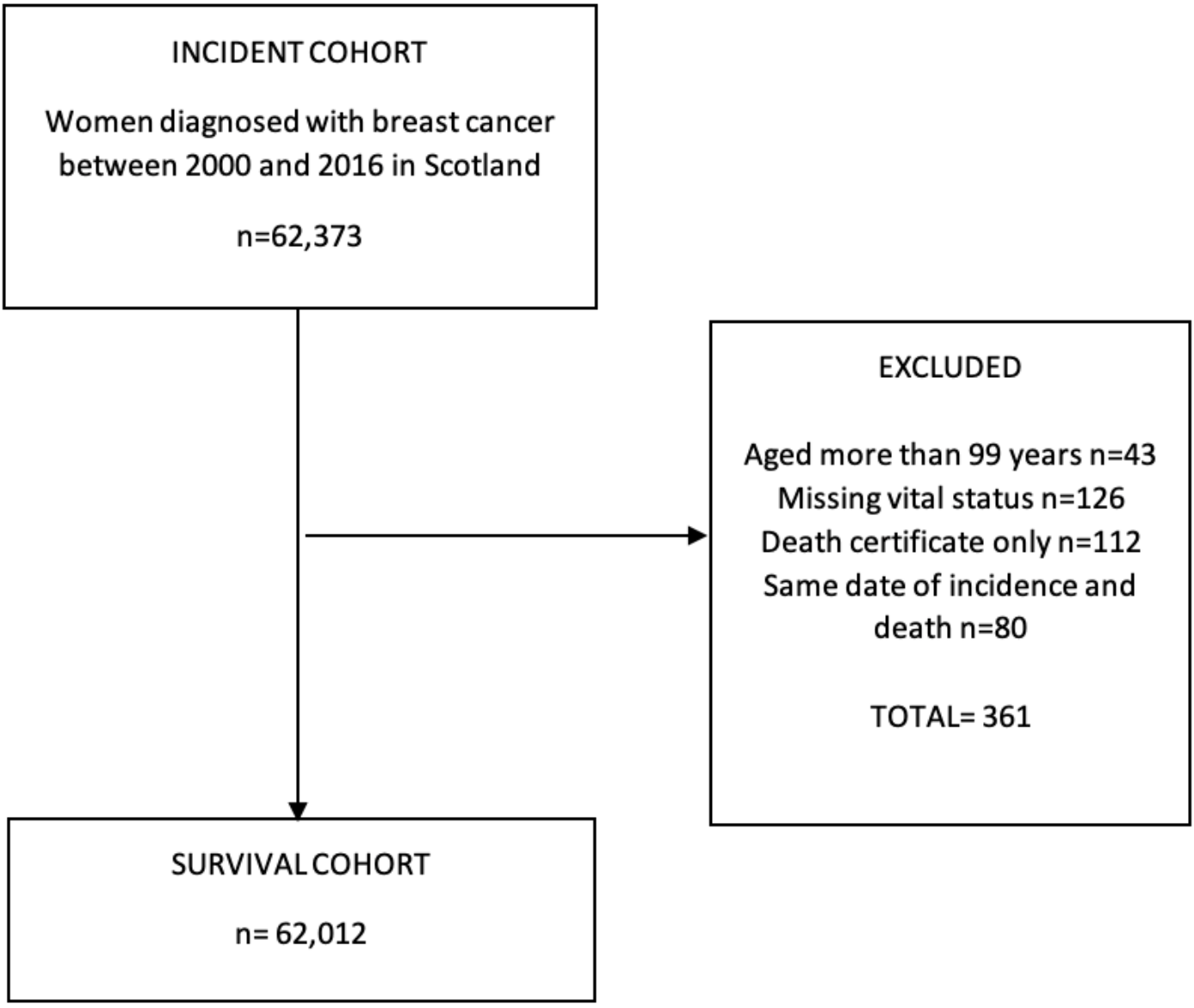

Figure 1

Flowchart describing incident and survival breast cancer cohorts based on number of women

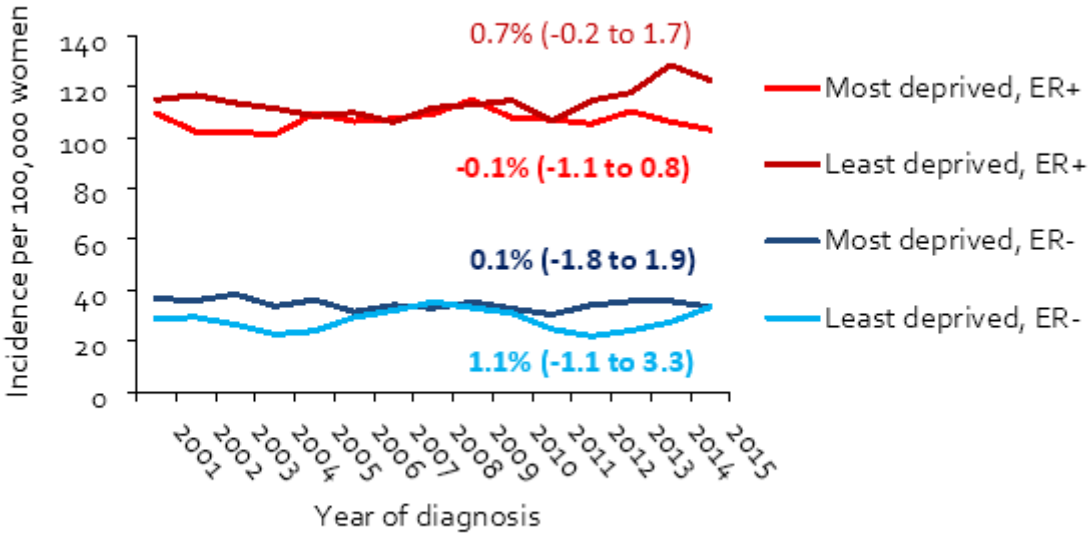

Figure 2

Breast cancer age-standardised incidence rates by ER status and calendar year in women living in the most and least deprived areas of Scotland for 2000-2016

Figure 2 footnote: estimates in graph are AAPC (95%CI) from 2000 to 2016.

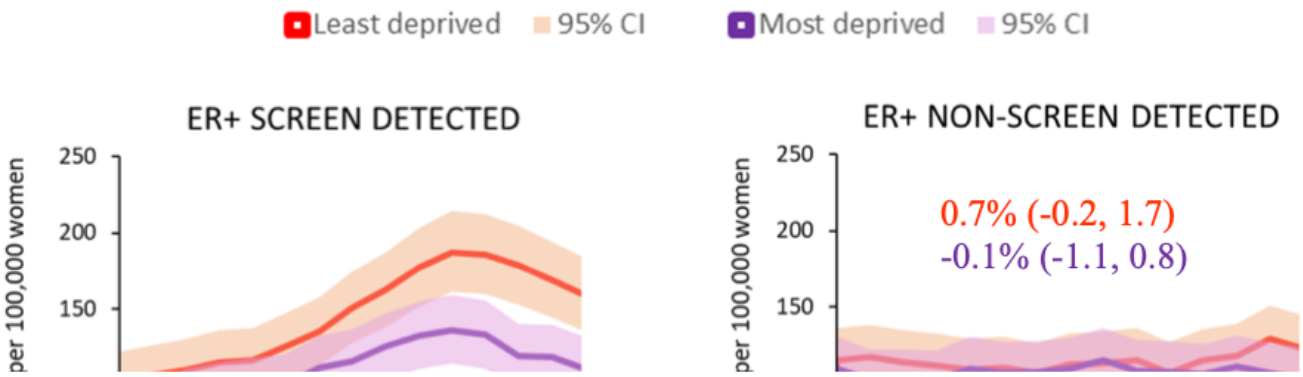

Figure 3

Breast cancer incidence rates in women living in most and least deprived areas of Scotland by ER status and method of detection by calendar year for 2000-2016

Figure 3 footnote: Estimates in graph are AAPC (95%CI) from 2000 to 2016.

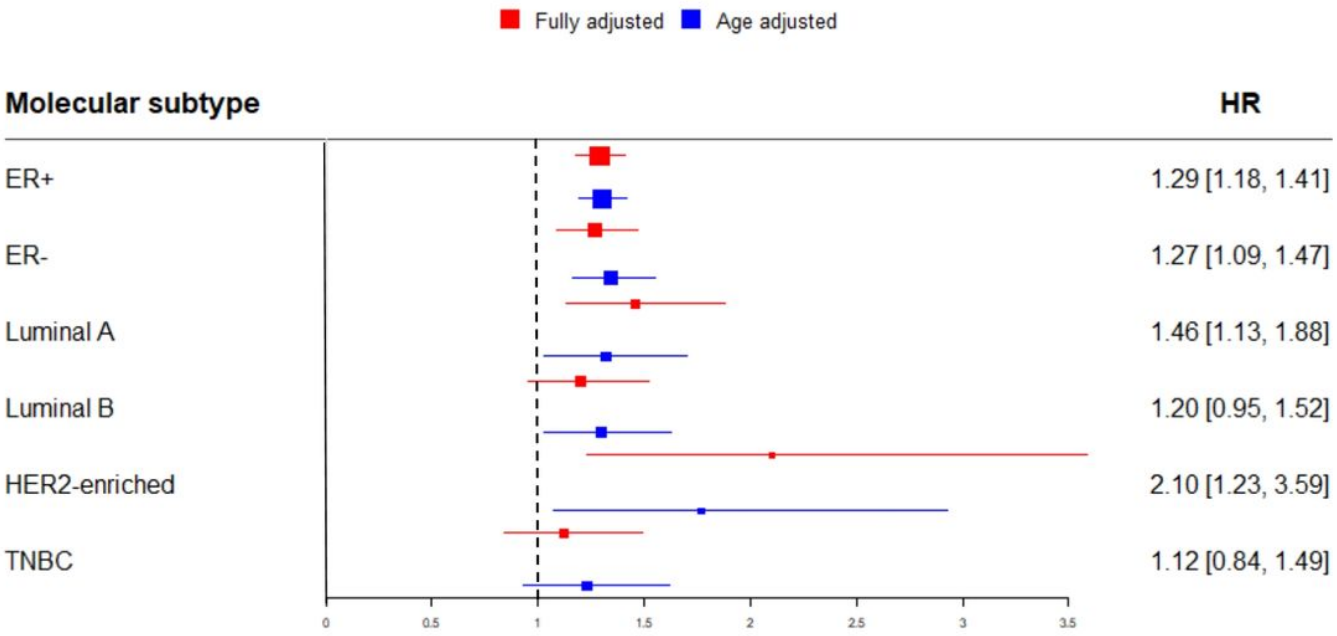

Figure 4

Adjusted hazard ratio (with 95% CI) for risk of BC death for women in the most compared to the least deprived quintiles by ER status and IHC defined molecular subtypes

Footnote: Fully adjusted model has age, incidence year, NHS region, tumour characteristics (TNM stage and method of detection, treatments (surgery, radiotherapy, chemotherapy and hormone therapy) and Charlson comorbidity index. Models carried out on complete cases separately by subtype with n=37667 (no deaths=5194) for ER+, n=7598 (no deaths=2073) for ER-, n=12762 (no deaths=604) for luminal A, n=6984 (no deaths=808) for luminal B, n=1029 (no deaths=159) for HER2 enriched and n=2,512 (no deaths=516) for TNBC.