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Comparison of quadrant-specific breast cancer incidence trends in the United States and England between 1975-2013

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ABSTRACT

Background: UK breast cancer incidence rates suggest that upper outer quadrant (UOQ) cancers have risen disproportionately compared with other areas over time. We aimed to provide a comparison of the trend in quadrant-specific breast cancer incidence between the United States (US) and England, and determine whether a disproportionate UOQ increase is present.

Methods: Surveillance Epidemiology and End Result (SEER) cancer registry data were obtained on 630,007 female breast cancers from 1975-2013. English cancer registry data were obtained on 1,121,134 female breast cancers from 1979-2013. Temporal incidence changes were analysed using negative binomial regression. Interaction terms determined whether incidence changes were similar between sites.

Results: English breast cancer incidence in the UOQ rose significantly from 13% to 28% from 1979 to 2013 whereas no significant increase was observed among SEER data. The significant interaction between quadrant and year of diagnosis ($p<0.001$) in both SEER and English data indicates that breast cancer incidence in each quadrant changed at a different rate. Incidence in the UOQ rose disproportionately compared to the nipple (SEER IRR=0.81, $p<0.001$; England IRR=0.78, $p<0.001$) and axillary tail (SEER IRR=0.87, $p=0.018$; England IRR=0.69, $p<0.001$) in both SEER and England. In addition, incidence rose disproportionately in the UOQ compared to non-site specific tumours in England (Overlapping lesions IRR=0.81, $p=0.002$; NOS IRR=0.78, $p<0.001$). The proportion of non-site specific tumours was substantially higher in England than SEER throughout the study period (62% in England; 39% in SEER).

Conclusions: Breast cancer incidence in the UOQ increased disproportionately compared to non-site specific tumours in England but not in SEER, likely due to the decrease in non-site specific tumours observed in England over time. There may be real differences in incidence between the two countries, possibly due to differences in aetiology, but is much more likely to be an artefact of changing data collection methods and improvements in site coding in either country.

Keywords: Breast cancer, incidence trends, quadrant, upper outer quadrant, SEER, data collection

1. Introduction

The Upper Outer Quadrant (UOQ) is the most frequent tumour site of breast cancer [1-4], comprising 25% of all breast cancers in the UK [1] and 36% in a SEER-based study [5]. It is unclear why breast cancer is more frequently diagnosed in the UOQ than in any other quadrant although it is generally accepted that the greater proportion of epithelial tissue in this region is the main contributor [2, 3]. Previous research has shown that the reported incidence of breast cancer in the UOQ is not only greater, but according to data from the UK, is also rising disproportionately over time compared to other quadrants [6] ; suggesting that the higher incidence in this quadrant may be due to other causes, rather than just the greater amount of epithelial tissue.

The Surveillance Epidemiology and End Results (SEER) program collect and provide information on cancer registrations for a subset of the population in the United States of America (US). English cancer registries and the SEER program provide large population-based cohorts of breast cancer survivors. Previous studies [7, 8] have suggested that breast cancer incidence is higher in the SEER program than English registries due to differing rules for defining multiple primary breast cancers. SEER have developed their own rules for defining multiple primary cancers [9], whereas England closely follow the International Agency for Research on Cancer (IARC) rules [10], which tend to be more stringent. The introduction of breast screening in the US and the UK, together with advances in diagnostic testing, have led to improvements in the accuracy of data collection[11, 12]. Changes in accuracy of data over time and differing definitions have been shown to have an influence on cancer intelligence and must be taken into consideration throughout this study [7, 8, 11, 13-15].

The aim of this study was to provide a comparison of the trend in quadrant-specific breast cancer incidence between the US and England, and to investigate whether the apparent disproportionate increase in incidence of female breast cancer in the UOQ previously reported in the UK was also observed in the US. Findings are reported from the first study to investigate quadrant-specific breast cancer incidence data in the US.

2. Methods

2.1 Data Collection - SEER

Data was collected from the SEER 9 program of the National Cancer Institute (NCI) in the US. The SEER 9 program collects information on cancer incidence from 9 population-based registries in the US (Connecticut,

Hawaii, Iowa, New Mexico, Utah, San Francisco-Oakland, Seattle-Puget Sound, Michigan and Atlanta) [16]. The SEER 9 registries account for approximately 9.4% of the US population, have a standard case ascertainment of 98% and are considered to be the standard for quality control worldwide [9]. The number of malignant female breast cancers reported (1973-2013) were obtained through the SEER*stat statistical software [17] . Information on age at diagnosis (5-year bands) and quadrant of the breast were also obtained. Quadrant information was extracted using the following ICD-O-3 topography codes: C50.0 Nipple, C50.1 Central portion, C50.2 Upper Inner Quadrant (UIQ), C50.3 Lower Inner Quadrant (LIQ), C50.4 Upper Outer Quadrant (UOQ), C50.5 Lower Outer Quadrant (LOQ), C50.6 Axillary Tail, C50.8 Overlapping lesions and C50.9 Not otherwise specified (NOS). Data submitted to SEER in previous versions of ICD-O, were converted by SEER into ICD-O-3. Cancer site definitions were consistent over time due to no changes occurring between ICD-O-2 and ICD-O-3 regarding the definition of breast cancer [9].

2.2 Data Collection - England

The Office for National Statistics provided the number of malignant female breast cancers along with information on quadrant and age at diagnosis (5-year bands) from 1979 to 2013 for England. England collects information on cancer incidence on a national basis with the use of regional cancer registries. It was estimated that in 2006 ascertainment of cancer in England was 98-99% complete [13] and so comparable to SEER. Quadrant information was extracted using the following ICD-9 (for cancers diagnosed 1979-1994) and ICD-10 (for cancers diagnosed 1995-2013) codes: 174.0/C50.0 Nipple, 174.1/C50.1 Central portion, 174.2/C50.2 Upper Inner Quadrant (UIQ), 174.3/C50.3 Lower Inner Quadrant (LIQ), 174.4/C50.4 Upper Outer Quadrant (UOQ), 174.5/C50.5 Lower Outer Quadrant (LOQ), 174.6/C50.6 Axillary Tail, 174.8/C50.8 Overlapping lesions and 174.9/C50.9 Not otherwise specified (NOS). ICD-9 and ICD-10 for malignant breast cancer are comparable to ICDO-3 topography codes that are used by the SEER program.

2.3 Statistical Analysis

Seattle (Puget Sound) and Atlanta (Metropolitan) registries joined SEER 9 in 1974 and 1975, respectively, therefore to ensure all registries were included for the entire time frame 1973 and 1974 were excluded from all analyses using SEER data. Incidence rates for all malignant female breast cancers combined as well as for each quadrant were calculated by dividing the observed number of breast cancers by the mid-year general population

estimates for each age stratum (5-year bands) and year of diagnosis (SEER: 1975-2013; England: 1979-2013). Incidence rates presented graphically were age-standardised to the World (WHO 2000-2025) Standard Population [18]; this enabled a direct comparison between rates in SEER 9 and England.

Changes in breast cancer incidence over time by age group (<40, 40-44, 45-49….75-79, 80-84, 85+), quadrant and year of diagnosis were explored using negative binomial regression. Negative binomial regression was preferred to Poisson regression due to over-dispersion from non-zero counts yielding better model fit. A model was fitted to estimate the incidence rate ratios (IRR) adjusting for age group (<40 years taken as baseline), year of diagnosis and quadrant (UOQ baseline). Year of diagnosis was centered and multiplied by 10 to provide IRR by decade, to enable easier interpretation. Linearity of year of diagnosis was tested and higher powers were also considered (quadratic and cubic). Interactions were tested between age group and year, age group and quadrant and year and quadrant. IRRs for interactions can be interpreted as ratios of IRRs. Interactions were tested between $(year)^2$ and quadrant, and $(year)^3$ and quadrant, however these were not significant. Akaike's Information Criterion [19] values were also virtually identical for non-linear terms for year of diagnosis, so the simpler linear model without non-linear interactions was chosen to allow easier interpretation. IRR and the percentage change in incidence of breast cancer in each quadrant were calculated per decade, using the following calculation: the change in baseline incidence multiplied by the change in incidence within each quadrant. To provide an overall estimate of whether UOQ increases were different to all other quadrants combined, we refitted the negative binomial regression with a new definition of quadrant (UOQ, specific quadrant excluding UOQ and non-specific [overlapping and NOS]). All statistical analyses were carried out in Stata v.14.0 [20].

2.4 Sensitivity analysis – improvement in site-coding over time

To investigate how much of an effect the improvement in site-coding accuracy contributed to the change in incidence for specific sites, sensitivity analyses were conducted. The proportion of each specific site (excluding overlapping lesions and NOS) was calculated for the years 1975, 1996 and 2013 for the SEER registry and 1979, 1996 and 2013 for England. This proportion was then used to equally distribute the non-specific site codes (overlapping lesions and NOS) across specific sites (results can be found in Online Tables 3-4).

In cancer registries, it is unlikely that 100% of cancer registrations would have a specific site code; therefore further sensitivity analyses were conducted accounting for a proportion of non-site-specific tumours. The proportion of non-site-specific tumours for the most recent year (2013) was used as the standard level of missingness across all other years. The proportion of non-site-specific tumours over this standard level of missingness was then distributed equally among all other sites (results can be found in Online Tables 5-6).

3. Results

3.1. SEER

A third of all breast cancer recorded by the SEER 9 registries between 1975 and 2013 were located in the UOQ (n=114, 383). Tumours in overlapping sites and tumours NOS contributed 20.4% (n=128,515) and 18.2% (n=114,383) of breast cancers, respectively (Online Table 1). The number of breast cancers in the UOQ increased from 2,635 (27.2%) in 1975 to 7,313 (32.5%) in 2013, whereas the number of tumours NOS decreased from 3,476 (35.9%) to 3,044 (13.5%) in the same time period (Figure 1a, Online Table 1).

A quadratic trend in the overall incidence of female breast cancer with year of diagnosis was observed (Quadratic IRR=0.95, 95% confidence interval [CI]=0.93-098); after an initial increase in breast cancer over time, rates have stopped increasing (Figure 2, Table 1). The incidence rate in the UOQ was significantly higher compared to all other quadrants of the breast (IRR=0.02-0.61, $p<0.001$). However the change in incidence over time in the UOQ was not consistently different than all other quadrants. The significant interaction between quadrant and year of diagnosis ($p<0.001$) indicates that the incidence in the UOQ changed at a different rate than the nipple (IRR=0.81, $p<0.001$) and the axillary tail (IRR=0.87, p-value=0.018). However the incidence in the UOQ did not change at a significantly different rate than the central portion (IRR=0.96, p=0.428), LOQ (IRR=1.03, p=0.517), LIQ (IRR=1.10, p=0.064), UIQ (IRR=1.07, p=0.153, overlapping lesions (IRR=1.01, p=0.907) or tumours NOS (IRR=0.94, p=0.211). Interactions between ‘age and year’ and ‘age and quadrant’ ($p>0.05$) were not significant, therefore were not included in the model.

When the model was refit using an alternative definition of quadrant (UOQ, specific quadrants excluding UOQ, non-specific quadrants), the interaction between year and quadrant was not significant (p=0.181), suggesting the UOQ did not increase disproportionally compared to all other quadrants (Online Table 7).

Differences in the change in incidence over time for each of the quadrants can be seen in Figure 2. Breast cancer incidence significantly increased by 8%, 13% and 15% per decade for tumours in the LOQ, UIQ and LIQ, respectively (Table 2). In contrast, incidence significantly decreased by 9% and 15% per decade for tumours in the axillary tail and nipple, respectively. The percentage change in incidence per decade was not significant for tumours in the UOQ (p=0.253), central portion (p=0.994), overlapping lesions (p=0.184) and tumours NOS (p=0.532).

3.2 England

A fifth of all breast cancers recorded in England between 1979 and 2013 were located in the UOQ (n=228, 473) (Online Table 2). The majority of breast cancers did not have specific site coding, with 56% (n=62,450) coded as NOS and 5.6% (n=625,692) coded as overlapping lesions. The number of breast cancers in each quadrant increased from 1979 to 2013, the largest increase was observed in the UOQ from 2,668 (13.2%) to 12,542 (28.1%) (Figure 1b, Online Table 2).

A linear trend in the overall incidence of female breast cancer with year of diagnosis was observed (Linear IRR=1.33, CI=1.21-1.45) (Table 1, Figure 3). The incidence rate in the UOQ was significantly higher compared to all other quadrants of the breast (IRR=0.03-29, p<0.001) with the exception of tumour NOS (IRR=2.71, p<0.001). The significant interaction between quadrant and year of diagnosis (p<0.001) indicates that the incidence in the UOQ changed at a significantly different rate than the nipple (IRR=0.78, p<0.001), axillary tail (IRR=0.69, p<0.001), overlapping lesions (IRR=0.81, p=0.002) and tumour NOS (IRR=0.78, p<0.001). However breast cancer incidence did not change at a significantly different rate than the central portion (IRR=0.95, p=0.407), UIQ (IRR=0.99, p=0.936), LIQ (IRR=1.10, p=0.160) or LOQ (IRR=1.04, p=0.590). Interactions between ‘age and year’ and ‘age and quadrant’ (p>0.05) were not significant, therefore were not included in the model.

When the model was refit using an alternative definition of quadrant (UOQ, specific locations excluding UOQ, non-specific locations), the interaction between year and quadrant was significant (p<0.001) (Online Table 7). Breast cancer incidence in the UOQ changed at a different rate than tumours in non-specific sites (IRR=0.78, p<0.001).

The change in the incidence rate of breast cancer over time for each quadrant is illustrated in Figure 3. Breast cancer incidence significantly increased by 25%, 32%, 33%, 37% and 46% per decade for tumours in the central

portion, UIQ, UOQ, LOQ and LIQ, respectively (Table 2). The percentage change in incidence per decade was not significant for tumours in the nipple (p=0.445), axillary tail (p=0.061), overlapping lesions (p=0.140) and tumours NOS (p=0.498).

3.3 Sensitivity analysis - improvement in site-coding over time

For England, the proportion of tumours in each quadrant differed substantially when non-site-specific tumours where distributed (Online Table 4 & 6). Of particular note was the large increase in the proportion of tumours in the UOQ observed in England (13% in 1979 to 28% in 2013, Table 2) was weakened when non-site-specific tumours were distributed (26% to 28%, Online Table 6). In contrast, the proportion of tumours in each quadrant did not differ substantially when non-site-specific tumours where distributed among SEER data (Online Tables 3 & 5). For example, the increase in the proportion of tumours in the UIQ observed in the SEER registries (7% in 1975, 12% in 2013, Table 2) remained similar when the non-site-specific tumours were distributed (8% in 1975, 12% in 2013, Table 5).

4. Discussion

4.1 Main findings

To our knowledge this is the first study to show that data recorded suggests that the change in incidence of female malignant breast cancer over time within the US has taken place at a different rate in each quadrant of the breast. In the US the incidence in the UOQ apparently rose disproportionately compared to the nipple and axillary tail however did not increase at a significantly different rate than the central portion, LIQ, UIQ, LOQ, overlapping lesions or tumour NOS. Similarly in England the incidence in the UOQ apparently rose disproportionately compared to the nipple and axillary tail, however also increased more than the overlapping lesions and tumour NOS.

We confirm findings from a previous UK study [6] that the incidence in the UOQ is increasing annually as a linear trend in England, however no significant change in incidence was observed within SEER data. This previous study observed a disproportionate increase in incidence in the UOQ from 1979 to 2000 compared to all other sites combined (non-site specific tumours were excluded). We did not observe a disproportionate increase in UOQ compared to all site-specific quadrants combined in England (Online Table 7); however incidence in

the UOQ did rise disproportionately compared to the nipple, axillary tail and non-site specific tumours. Differences between the previous UK study and our findings drawn from English data may be due to a number of factors: firstly, as a result of an additional 13 years of diagnoses included in our analyses; secondly, the use of multivariable regression to adjust for the effects of age, year and individual quadrant interactions; thirdly, due to improvements in site coding, for example through the inclusion of a non-specific sites in our latest analysis.

The proportion of breast cancer recorded in the UOQ in SEER remained relatively stable from 1975 to 2013 (27-33% of all diagnoses), whereas in England, the proportion increased from 13% to 28% from 1979 to 2013. This may be due to the smaller decrease in the number of non-site-specific breast cancer; from 48% to 37% in the US from 1975 to 2013, compared to a decrease from 73% to 47% observed from 1979 to 2013 in England (Table 2). Detailed site coding has improved over time in England; however in 2013 there were still almost 50% of breast cancers with no detailed site information available compared to 37% in SEER. This disparity of detail of data collection makes direct comparison impossible. It is worth mentioning that some of the significant changes in incidence could be partly an artefact of being based upon changes from a lower initial rate, whereas those sites with non-significant changes based on higher rates will have a much stronger bearing on disease burden in the population.

The greater decrease in the number of non-site-specific tumours within England makes the comparison with the SEER registry difficult to interpret. However we accounted for this in the sensitivity analyses mentioned in section 3.3. Among English data any large increases in the proportion of site-specific tumours over time were weakened when the non-site-specific tumours were distributed, suggesting that any changes in incidence were due to improvements in site-coding. Among SEER data, similar proportions of site-specific tumours over time were observed when the non-site-specific tumours were distributed suggesting than other factors other an improvement in site-coding may have attributed to changes in incidence. It is interesting to note that in 2013 the proportion of tumours in the UOQ is similar in SEER and UK (33% vs 28%), the incidence in the UOQ in the UK has caught up to the higher rates in SEER at all times, perhaps due to improvements in data collection and site-coding. There may be real differences in incidence between the two countries, possibly due to differences in aetiology, or this could be due to a number of factors including an artefact of changing data collection methods in either country.

4.2 Data collection methods and issues

In the US breast cancer is diagnosed using physical examination, imaging studies and biopsies. The SEER registries code breast cancer site using these diagnostic reports; however if there are conflicting reports, site is coded according to the following priority: pathology report, operation report, physical examination and lastly mammogram [21].Data completion rates and data quality within the SEER registries are thought to be the gold standard worldwide; specifically defined data quality goals have been set and must be adhered to [22]. In England breast cancer is diagnosed using the same diagnostic tools as the US; however it is uncertain whether site is coded according to a priority order if there are inconsistencies as in the US [23]. Data completion rates in England are thought to be high for screen-detected breast cancers (30% of breast cancers) due to yearly audit reports since 1997, however data completion rates for symptomatic breast cancers (70% of breast cancers) are inferior, with audits commencing more recently [24]. In the UK pathology reports from surgery are a vital data source for cancer registries, thus individuals that have had surgery generally have a more complete cancer registration [24]. It has been observed that the US performs more open surgical biopsies than the UK, thus it is a possibility that this could explain the inferior data completion rates for breast cancer site in the UK [25].

Breast screening is implemented differently in the US and England, for example, age at invitation and interval between screening[25]. Breast screening was initiated in the early 1980s in the US and individuals are recommended to be screened at yearly intervals from the age of 40 onwards [26]. Breast screening was initiated between 1988 and 1991 in the UK with individuals aged 50-64 offered 3-yearly mammography; by 2004 the upper limit was increased to age 70 and two-view mammography was introduced [27, 28]. The introduction of screening has allowed the identification of smaller tumours [4] and with more regular screening in the US a higher proportion of smaller, non-symptomatic tumours being detected, thus allowing better site localisation [29]. Over 50% of breast cancers recorded in England were NOS, therefore the exact location of these tumours in the breast is unknown; highlighting that the apparent increase in incidence of tumours located in the UOQ is uninterpretable. Analyses of screen-detected and symptomatic data (collected separately in England) would provide further insight into the impact of different data collection methods on the incidence of breast cancer.

Several studies have highlighted the inadequacies of changing data collection methods and the bias this can create when analysing cancer registry data [7, 11, 13-15, 30-32]. Improved diagnostic tests have allowed the identification of multifocal disease in more than one quadrant of the breast that may have been previously missed. As more sources of ascertainment are used (introduction of histopathology and computerised systems), the apparent incidence of breast cancer will increase highlighting that along with epidemiological and treatment

factors, it is vital that the influence data collections methods have on cancer intelligence is acknowledged [11, 33].

Bray & Parkins' review of data quality within cancer registries explores the comparability of cancer data, stating that a standardised approach should be used internationally regarding the classification and coding of new cancers and how incidence is defined [7]. Higher rates of breast cancer from SEER data have been observed compared to other international registries due to different registration rules for multiple primary tumours [8, 34]. SEER count subsequent primary breast tumours as incident cases when diagnosed 5-years after the first primary or the second tumour is in the opposite breast [9]; whereas in England only one cancer is allowed per site (including bilateral as one site) unless the tumour is of a different histology [10]. We performed a sensitivity analyses to test how the different rules for recording multiple primary tumours would impact our analysis. Using SEER*stat software we applied the IARC rules for defining multiple primary tumours on the SEER data and reran all of the analyses. The results were almost identical when IARC rules were applied (see Online Tables 8-9 and Online Figure 1).

4.3 What this study adds

To our knowledge this is the first study to observe that the recorded disproportionate rise in breast cancer incidence in the UOQ, previously observed in the UK is not replicated by data from the US. As a result of these contradictory findings, this study highlights the difficulties of time-dependent analyses using cancer registry data and the importance of accurate and consistent data collection to avoid potentially damaging erroneous clinical conclusions being drawn. The study provides a large number of breast cancers (England= 1,121,134; US= 630,007) and high statistical power to allow for testing of interactions.

4.4 Limitations of this study

Potential limitations include the limited number of confounding variables and possible selection bias due inclusion of SEER data covering 9% of the population; however SEER covers a large and diverse population. This study may also exhibit bias between recorded site-specific and non-site-specific incidence, due to the number of cases not having site-specific information. However, we performed sensitivity analyses to account for the proportion of non-site-specific tumours.

5. Conclusion

To our knowledge this is the first study to show that the recorded disproportionate rise in breast cancer incidence in the UOQ previously observed in the UK is not replicated by data from the US. Breast cancer incidence in the UOQ increased disproportionately compared to non-site specific tumours in England but not in SEER, likely due to the decrease in non-site specific tumours observed in England over time. As a result of these contradictory findings, this study highlights the difficulties of time-dependent analyses using cancer registry data and the importance of accurate and consistent data collection to avoid potentially damaging erroneous clinical conclusions being drawn.

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Titles and Legends to Figures

Figure 1 Stacked bar chart showing the number of malignant breast cancers per year for each quadrant of the breast in A) SEER 9 registries (1975-2013) and B) England (1979-2013).

Figure 2 Trends in the annual incidence of female breast cancer in SEER 9 registries from 1975 to 2013 for each quadrant. Incidence rate has been standardized to the world standard population (WHO 2000-2025) [18]. (A P-value<0.5 corresponds to significant change in incidence over time [corresponds to Table 2])

Figure 3 Trends in the annual incidence of female breast cancer in England from 1979 to 2013 for each quadrant. Incidence rate has been standardized to the world standard population (WHO 2000-2025) [18]. (A P-value<0.5 corresponds to significant change in incidence over time [corresponds to Table 2])

Table 1 Multivariable negative binomial regression for breast cancer incidence with respect to: year of diagnosis, age at diagnosis and breast quadrant for SEER 9 registries and England.

	SEER		England	
Variable	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
Year of diagnosis (per decade†)				
Year	1.04 (0.97-1.12)	0.253	1.33 (1.21-1.45)	<0.001
Year^2	0.95 (0.93-0.98)	<0.001	-*	-
Age Group				
0-39 (reference)	1 (ref)		1 (ref)	
40-44	9.56 (8.43-10.85)	<0.001	9.56 (8.34-10.96)	<0.001
45-49	14.98 (13.21-16.99)	<0.001	14.91 (13.02-17.09)	<0.001
50-54	18.06 (15.92-20.48)	<0.001	18.92 (16.51-21.68)	<0.001
55-59	22.30 (19.67-25.29)	<0.001	20.70 (18.07-23.72)	<0.001
60-64	27.46 (24.21-31.14)	<0.001	24.29 (21.20-27.83)	<0.001
65-69	31.88 (28.11-36.16)	<0.001	24.90 (21.73-28.53)	<0.001
70-74	34.71 (30.60-39.37)	<0.001	25.23 (22.02-28.91)	<0.001
75-79	37.43 (32.99-42.47)	<0.001	26.94 (23.50-30.88)	<0.001
80-84	37.18 (32.76-42.21)	<0.001	27.20 (23.73-31.19)	<0.001
≥85	33.29 (29.31-37.81)	<0.001	18.17 (15.83-20.86)	<0.001
Quadrant of diagnosis				
UOQ (reference)	1 (ref)		1 (ref)	
Nipple	0.02 (0.02-0.03)	<0.001	0.05 (0.05-0.06)	<0.001
Central portion	0.15 (0.14-0.17)	<0.001	0.18 (0.16-0.21)	<0.001
UIQ	0.28 (0.24-0.31)	<0.001	0.28 (0.25-0.32)	<0.001
LIQ	0.14 (0.12-0.15)	<0.001	0.12 (0.11-0.14)	<0.001
LOQ	0.20 (0.18-0.22)	<0.001	0.18 (0.16-0.21)	<0.001
Axillary tail	0.03 (0.02-0.03)	<0.001	0.03 (0.02-0.03)	<0.001
Overlapping lesions	0.61 (0.55-0.69)	<0.001	0.29 (0.26-0.33)	<0.001
NOS	0.56 (0.50-0.63)	<0.001	2.71 (2.39-3.08)	<0.001
Interaction of Year and Quadrant of diagnosis (per decade)				
UOQ (reference)	1 (ref)		1 (ref)	
Nipple	0.81 (0.72-0.91)	<0.001	0.78 (0.69-0.89)	<0.001
Central portion	0.96 (0.86-1.07)	0.428	0.95 (0.83-1.08)	0.407
UIQ	1.07 (0.97-1.20)	0.153	0.99 (0.87-1.13)	0.936
LIQ	1.10 (0.99-1.23)	0.064	1.10 (0.96-1.25)	0.160
LOQ	1.03 (0.93-1.15)	0.517	1.04 (0.91-1.18)	0.590
Axillary tail	0.87 (0.78-0.98)	0.018	0.69 (0.60-0.79)	<0.001
Overlapping lesions	1.01 (0.91-1.12)	0.907	0.81 (0.71-0.92)	0.002
NOS	0.94 (0.84-1.04)	0.211	0.78 (0.68-0.89)	<0.001

† Year was centred and provided per decade to enable easier interpretation.
*model fit better without year^2, therefore year^2 not included in model
Definitions: UIQ= Upper Inner Quadrant, LIQ= Lower Inner Quadrant, UOQ= Upper Outer Quadrant, LOQ= Lower Outer Quadrant, NOS= not otherwise specified

Table 2 Average incidence rates per 100,000, Incidence Rate Ratio (IRR) (per decade) and percentage change in incidence over time (per decade) for SEER 9 registries and England (p-value corresponds to Figure 2 and 3)

	SEER				England			
Quadrant of Diagnosis	**IR per 100,000 1975-2013**	**IRR**	**%change**	**P-value**	**IR per 100,000 1979-2013**	**IRR**	**%change**	**P-value**
UOQ	33.5	1.04	4%	0.253	18.3	1.33	33%	<0.001
Nipple	0.8	0.85	-15%	<0.001	0.9	1.04	4%	0.445
Central Portion	5.4	1.00	0%	0.994	3.4	1.25	25%	<0.001
UIQ	9.6	1.13	13%	0.001	5.2	1.32	32%	<0.001
LIQ	4.9	1.15	15%	<0.001	2.5	1.46	46%	<0.001
LOQ	6.5	1.08	8%	0.037	3.5	1.37	37%	<0.001
Axillary Tail	0.8	0.91	-9%	0.033	0.4	0.91	-9%	0.061
Overlapping Lesions	20.4	1.05	5%	0.184	4.9	1.07	7%	0.140
NOS	17.6	0.98	-2%	0.532	46.3	1.03	3%	0.498

Definitions: IR- Incidence rate standardised to the WHO std population 2000-2025, IRR-Incidence Rate Ratio ,UIQ= Upper Inner Quadrant, LIQ= Lower Inner Quadrant, UOQ= Upper Outer Quadrant, LOQ= Lower Outer Quadrant, NOS= not otherwise specified