Costs of early invasive breast cancer in England using national patient-level data

Running title: Costs of breast cancer

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This study was undertaken as part of the work by the National Audit of Breast Cancer in Older Patients (NABCOP). The Audit is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme, and funded by NHS England and the Welsh Government (www.hqip.org.uk/national-programmes). Neither the commissioner nor the funders had any involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The authors had full independence from the HQIP. The aim of the NABCOP is to evaluate the care of older women with breast cancer in England and Wales, and support NHS providers to improve the quality of hospital care for these women.

Precis: Costs of early invasive breast cancer varied by stage at diagnosis, age and geographic region in England.

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ABSTRACT

Objectives: This study aimed to use patient-level data to provide up-to-date estimates of early invasive breast cancer care costs by stage in England, and explore to what extent these costs vary across patient age and geographic region.

Methods: This study identified women aged 50 years and over diagnosed with early invasive breast cancer between 01 January 2014 and 31 December 2015 from linked cancer registration and routine hospital datasets generated from the usual care for all NHS trusts in England. Cost estimates were derived from hospital records in Hospital Episodes Statistics with additional chemotherapy and radiotherapy information from the national datasets. We fitted general linear regression models to analyse the cost data. The model that best fit the data was selected using the model selection criteria of Akaike information criterion (AIC).

Results: 55,662 women with early invasive breast cancer in England were included. The generalised linear model with log-gamma distribution fitted the data best. The costs of breast cancer care for one year following diagnosis were strongly dependent on stage at diagnosis controlling for other covariates. The estimated average per-patient hospital-related costs were £5,167 at stage I, £7,613 at stage II, and £13,330 at stage IIIA. Costs decreased with increasing age ($p<0.001$) and varied across region ($p<0.001$), deprivation level ($p<0.001$), referral source ($p<0.01$), presence of comorbidities ($p<0.001$), and tumour receptor (ER/PR/HER2) status ($p<0.001$).

Conclusions: In England, costs of breast cancer care increased with advancing stage of the disease at diagnosis. Breast cancer costs varied by age and geographic region.

HIGHLIGHTS

- UK estimates of the costs of breast cancer care by stage at diagnosis are out-of-date and may strongly bias the results of recent appraisals of the cost-effectiveness of breast cancer screening programmes.
- The linkage between different national datasets at individual patient level was not possible until recently. This study identified 55,662 women aged 50 years and over diagnosed with early invasive breast cancer in England. We used anonymised patient-level data from the English Cancer Registration services, linked to other national datasets to provide information on patient demographics, tumour characteristics, hospital admissions, and the use of chemotherapy and radiotherapy in both inpatient and outpatient settings.
- This study provides up-to-date estimates of breast cancer care costs by stage at diagnosis in England. Costs of early breast cancer care for one year following diagnosis increased with advancing stage of the disease. Breast cancer costs varied by age and geographic region in England.

INTRODUCTION

Breast cancer is the most commonly diagnosed female cancer in the United Kingdom (UK) [1]. As in other high-income countries, the number of women living with breast cancer in the UK is increasing due to rises in incidence rates [1], increases in the number of older women [2], improved survival [3] and as a result of earlier detection and treatment improvements. It has been clearly established that earlier diagnosis of breast cancer reduces mortality [4], but the costs of breast cancer care are not well understood [5].

Stage at diagnosis is an important factor shaping breast cancer treatment pathways. Treatment for more advanced breast cancer is more intensive and invasive [6], and tends to be associated with greater resource utilisation [7]. Costs of breast cancer care by stage at diagnosis are important in quantifying the gains from early detection. If early treatment lowers costs, this will help offset some costs of interventions that aim to achieve earlier diagnosis. Treatment costs by stage would also inform the cost-effectiveness of breast cancer screening programmes.

Existing UK data on the costs of breast cancer care by stage at diagnosis were published over 20 years ago and are out-of-date [8]. Recent National Institute for Health and Care Excellence (NICE) appraisals on the cost-effectiveness of breast cancer treatment have relied on modelled assumptions [9]. This may lead to biased estimates of the full cost as there are multi-modal treatments. The consequences of biased estimates are serious as, potentially, therapies may be incorrectly rejected or approved by NICE based on outdated costs. Up-to-date estimates of the costs of breast cancer care by stage are required.

In addition, recent evidence has revealed a differential approach to breast cancer management for older patients in the UK [10], which may explain the poorer survival of older women in the UK

compared to other European countries [11]. Moreover, little is known about the geographic variation in costs of breast cancer care across England. For example, significant variations in rates and types of immediate breast reconstruction procedures were observed among National Health Service (NHS) hospitals in England [12]. The differences in costs across patient age and region need to be determined.

In this study, we used patient-level data generated from the usual care for all NHS trusts in England to estimate the costs of primary breast cancer care incurred in the first year after diagnosis, by stage among women aged 50 years and over, diagnosed in England, and to explore to what extent breast cancer costs vary across different patient ages and regions.

METHODS

This study used data from the National Audit of Breast Cancer in Older Patients (NABCOP) project, a national clinical audit commissioned by the Healthcare Quality Improvement Partnership as part of its National Clinical Audit and Patient Outcomes Programme, using data generated from the usual care for all NHS trusts in England. The details of the national clinical audit were described elsewhere [13]. In brief, the audit uses anonymised patient-level data from the English and Welsh Cancer Registration services, linked to other national datasets to provide information on hospital admissions and the use of chemotherapy and radiotherapy. The Office for National Statistics (ONS) Death Register provides information on date and cause of death.

Population and data

The study population was restricted to women aged 50 years and over with newly diagnosed early invasive breast cancer (stages I, II and IIIA), as defined by ICD code C50 and stage at diagnosis, over the two years between 01 January 2014 and 31 December 2015 and who were treated within

the NHS in England. The data was available up to 31 December 2016 so that no patients were censored. This study was limited to early invasive disease because the primary treatment of early invasive disease conforms to a limited number of options and is typically delivered within one year. The treatment patterns for women with stage IIIb, IIIc, and IV disease are much more varied, being influenced by where the cancer has spread to. The duration of care can also be variable, with patients having a sequence of treatments depending upon how the tumour responds. The available data in this study did not capture second-line treatments and were insufficient to produce reliable cost estimates for patients with advanced disease.

The cancer registration dataset contained patient demographics including age at diagnosis, ethnicity, date of diagnosis, and geographic region (cancer alliance). The 19 cancer alliances were established by NHS England to deliver the national recommendations within the NHS Cancer Strategy and to drive local quality improvements [14]. The alliances are listed under Figure 1. Tumour characteristics included pathologic stage at diagnosis, tumour grade, oestrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2) status. ER, PR, and HER2 are breast cancer molecular markers that guide the selection of the most appropriate drug therapies and are individually recorded as positive, negative, or borderline.

Hospital admissions were identified from the Hospital Episode Statistics (HES) data. This contained date of admission, date of discharge, method of admission, method of discharge, date of spell (a continuous period of care in hospital) start, date of spell end, procedures undertaken (using the Office of Population Censuses and Surveys (OPCS) Classification of Surgical Operations version 4 codes) [15], and Healthcare Resource Group (HRG) [16]. The HES data were also used as the data source for regional deprivation measured as the Index of Multiple Deprivation (IMD) [17]

and comorbidity burden. Patient IMD scores were grouped into regional quintiles of deprivation, from most (=1) to least deprived (=5). Charlson Comorbidity Index was derived from the diagnosis fields within HES, which measures the presence of additional medical conditions co-occurring with breast cancer [18].

The use of chemotherapy and targeted therapy was identified from the Systematic Anti-Cancer Therapy (SACT) Dataset. The radiotherapy information was obtained from the National Radiotherapy Dataset (RTDS).

All these datasets were linked via a pseudonymised patient ID, generated from patients' NHS number, date of birth, sex and postcode by the National Cancer Registration and Analysis Service (NCRAS).

Resource use and measurement

The analysis was conducted from a payer/NHS perspective in line with the NICE recommendation [19]. We categorised resource use during the first year of breast cancer care into various aspects of the care pathway: 1) diagnosis (triple assessment in a single visit); 2) breast procedures (breast surgery (resection, reconstruction, and surgery for lymph node involvement), and hospital length of stay); 3) chemotherapy; 4) radiotherapy; 5) endocrine therapy; and 6) targeted therapy.

Patients with suspected breast cancer are recommended to undergo a triple diagnostic assessment in a single initial hospital visit, including clinical assessment, imaging (ultrasound and/or mammogram), and tissue biopsy [9,20]. We measured the use of these diagnostic interventions using dates of imaging and biopsy.

The types of breast resection surgeries include breast conserving surgery (BCS, removal of a part of the breast containing the cancer), mastectomy (removal of all breast), and mastectomy with

reconstruction. Also, we measured whether or not the patients had lymph node involvement and axillary surgeries based on HES data. Axillary surgeries covered the activities of sentinel node biopsy and axillary lymph node dissection [9]. A maximum length of stay is specified for each HRG code. Where the patient length of stay during a spell in hospital exceeded that point, we documented the excess hospital bed days recorded by the number of overnight admissions.

Whether patients received chemotherapy, radiotherapy, or targeted therapy were reported in SACT and RTDS datasets. ER+/PR+ patients aged over 50 years are recommended to receive postmenopausal endocrine therapy as per NICE guidelines [21,22]. However, information on endocrine therapy was not well captured in SACT. We assumed an aromatase inhibitor (anastrozole) was offered for these postmenopausal ER+/PR+ patients and the adherence to the aromatase inhibitor in the first year after diagnosis was 88.3% based on a meta-regression analyses of 17 studies [23].

Cost estimation

Healthcare Resource Groups (HRG) are groups of hospital admissions that have been judged to consume a similar level of resource [16]. We used unit costs from NHS reference costs [24] to assign costs using breast procedure-driven and diagnosis-driven core HRGs for the continuous inpatient spell. Some patient care episodes may have associated high-cost care elements that will generate unbundled HRGs as additions to the core HRG, such as chemotherapy, radiotherapy, and other high-cost drugs. Only records clearly related to breast cancer care were retained.

Excess hospital bed days are reimbursed at a daily cost based on the core spell HRG code, which distinguishes between elective (arranged in advance) and non-elective (not arranged in advance) admissions. As the unit costs of elective and non-elective excess bed days can be different in the

NHS reference costs [24], we applied the elective or non-elective excess hospital bed day adjustment to the estimated cost where the patient length of stay exceeded the maximum specified for a given HRG code using the information on admission method.

We used OPCS procedure codes from SACT and RTDS datasets to assign HRG codes to estimate the costs of chemotherapy and radiotherapy. We obtained the drug cost from the British National Formulary (BNF) [25] to estimate the endocrine therapy costs. In addition, we obtained the annual trastuzumab cost per patient including administration of treatment and cardiac monitoring from the NICE costing report to estimate the targeted therapy costs for HER2+ patients [22]. All costs were converted to 2016 values using the Hospital and Community Health Service Index [26].

Cost analysis

We first checked whether there was a large mass at zero or extreme values, and fitted generalised linear regression models to estimate the mean costs of primary breast cancer care up to one year after diagnosis for women in England. The model contained a number of explanatory variables to assess the relationship between cost and patient characteristics. Demographic variables included age at diagnosis, ethnicity, geographic regions, and IMD. Disease characteristics included disease stage, ER/PR/HER2 status, Charlson Comorbidity Index, and referral source (via screening or not). As the disease stage may have different effects on costs across regions in England, we added the interaction term of stage and region in the regression models. A modified RESET procedure was used to test the functional form [27].

Using a generalised linear model (GLM) enabled the cost estimates to handle common features of health care cost data, such as the substantial skewness with long right-hand tails [28], heteroskedastic errors and non-linear responses to covariates [29]. Typically, a log-link function with a Gamma

distribution fitted health care costs well [28]. However, there was no evidence that this was the dominant form of GLM in terms of model fit for cost data applications [30].

In this study, we compared the models checking distributions of linear-normal, log-normal, and log-gamma respectively. Modified Park Test was conducted to guide the choice of distribution reflecting the relationship between variance and mean. The preferred model was selected as the one with the minimum Akaike information criterion (AIC) values. We reported the average marginal effects of explanatory variables on the total costs for the models to obtain the additional costs related to different characteristics. We predicted costs of primary breast cancer care by subgroups to obtain the average costs among patients at different age groups or disease stages. We conducted the complete case analysis using only data from patients for whom all variables involved in the analysis were observed. All statistical analyses were undertaken in STATA, version 15.1.

RESULTS

The study included 55,662 women aged 50 years and over diagnosed with early invasive breast cancer in England between January 2014 and December 2015. The characteristics of the women by stage at diagnosis are presented in Table 1. The mean age was 67 years. The percentages of breast cancer patients diagnosed at stage I, stage II, and stage IIIA were 51%, 44%, and 6% respectively. 40% of breast cancer patients were screen-detected (found on mammography undertaken by the NHS National Breast Cancer Screening Programme), while the other 60% were referred from GP or other specialities, or detected due to an emergency presentation (<1%). 3% of patients in this study died within one year after diagnosis.

The resource use of breast cancer care is shown in Table 2. Determining whether a woman had triple diagnostic assessment was not straightforward because many imaging and biopsy dates were incomplete in the datasets [13]. Adopting a strict set of criteria for the analysis of English data suggested that among women diagnosed with early invasive breast cancer, and who were not referred from screening, 28% received triple assessment in a single visit. If the criteria were relaxed (assuming missing mammogram/biopsy dates were the same as the date of biopsy/mammogram respectively, incorporating the use of ultrasound where no mammogram was recorded, and allowing dates of biopsy and mammogram to differ by one day), the estimated proportion of women having a triple diagnostic assessment on the same day was 82%. The rates of mastectomy, mastectomy with reconstruction, and axillary lymph node dissection increased with more advanced cancer stage at diagnosis, while the rates of BCS and sentinel node biopsy decreased with advancing stage. The time spent in hospital was short for most breast cancer patients. Most women were typically admitted and discharged as day cases, and the excess hospital bed days per patient were 0.06 days showing increasing trend by advanced stage. In addition, the proportion of patients receiving chemotherapy or targeted therapy at stage IIIA was higher than stage I or II. The proportion receiving radiotherapy among patients having BCS was 88% compared to 41% for patients having mastectomy.

The crude costs of breast cancer care among 55,662 patients increased with more advanced disease, with very few (<3%) patients having zero costs and no extreme values (all values below £100,000). The subcategories of diagnosis and procedure costs, chemotherapy costs, radiotherapy costs, and targeted therapy costs all rose with higher stage (Appendix 1). There was some variation in the crude costs of primary breast cancer care across cancer alliances, with overall costs typically falling between £5,500 and £7,000 and the highest cost of £8,549 incurred in South East London

(Figure 1). The variation in total costs of breast cancer care across cancer alliances was driven by all component costs according to one-way analysis of variance (ANOVA) results.

The results of the compared regression models are shown in Table 3, using data from 22,325 patients for whom all variables involved in the analysis were observed. The modified RESET procedure supported the functional form of the model. Missing data in HES was negligible with the exception of Charlson Comorbidity Index (3%) while the level of incompleteness in Cancer Registry was larger with PR status (51%), HER2 status (17%), ER status (14%), and ethnicity (6%). The Modified Park Test indicated the choice of a gamma distribution and the GLM with log-gamma distribution reported the minimum AIC. The regression model showed that even controlling for other cancer characteristics the total cost of primary breast cancer care increased with advancing stage at diagnosis. Patients diagnosed at stage II incurred £1,912 (S.E. £72) more costs and patient at stage IIIA incurred £6,415 (S.E. £253) more costs compared to those diagnosed at stage I ($p<0.001$).

The regression model indicated that breast cancer costs decreased with increasing age ($p<0.001$), more comorbidities ($p<0.001$) and higher levels of deprivation ($p<0.001$). Patients with screen-detected cancers incurred lower costs than those diagnosed outside screening ($p<0.01$). There was strong evidence of lower costs in ER/PR+ patients and higher costs in HER2+ patients ($p<0.001$). There was also evidence that the costs of primary breast cancer care varied across regions in England ($p<0.001$). The average marginal effects are presented in Table 3 and Appendix 2.

We have reported the average predicted total costs of primary breast cancer care within one year after diagnosis using a GLM regression controlling for patient demographics and tumour characteristics. The costs of breast cancer care within one year after diagnosis was predicted to be

£6,774 (S.E. £32) for all stages, with £5,167 (S.E. £27) at stage I, £7,613 (S.E. £48) at stage II, and £13,330 (S.E. £213) at stage IIIA (Figure 2). The predicted costs of primary breast cancer care were £8,782 (S.E. £68) for patients aged 50-59 years, £7,062 (S.E. £50) for 60-69 years, £5,925 (S.E. £51) for 70-79 years, £3,459 (S.E. £42) for 80-89 years, and £1,266 (S.E. £39) for over 90 years respectively (Figure 3).

DISCUSSION

The principle aim of this study was to generate up-to-date estimates of initial early invasive breast cancer care costs by stage at diagnosis in England, controlling for patient demographics and tumour characteristics. Our results show that the costs of early breast cancer care for the first year after diagnosis increase with more advanced stage at diagnosis. The care costs of stage IIIA disease are more than double those of stage I disease. The finding is consistent with a global systematic review indicating increased breast cancer care costs with advanced stage, in which the treatment costs of breast cancer at stage II and stage III were reported to be 32% and 95% higher than stage I on average worldwide [5]. Previous studies of the treatment costs of breast cancer by stage at diagnosis were rather limited due to the poor availability of staging information and were predominantly from the US [5]. Before our analysis, there was only one very dated UK study estimating the costs of breast cancer care using patient-level data, reporting that the four-year costs of breast cancer were £6,039 at stage I, £6,749 at stage II, and £6,614 at stage III (converted to 2016 values) [8]. Our study has therefore provided important updated evidence on primary treatment costs for breast cancer by stage in England. This is important for future comparative assessment of the cost-effectiveness of breast cancer screening and therapy interventions.

Compared to younger breast cancer patients, older patients were shown to incur lower costs. This is consistent with the studies that found older patients received fewer treatments in the UK. The

different patterns of resource utilisation might be a reason why the survival of older breast cancer patients in the UK and Ireland has been reported to be lower compared to other European countries [11]. Nonetheless, differences in the patterns of care among younger and older patients may arise for various reasons, including unmeasured differences in the disease, differences in the prevalence and severity of comorbidities and frailty that may contraindicate breast cancer treatments (e.g. surgery, chemotherapy or radiotherapy), differences in patient preferences and cultural attitudes, and less-involvement of older patients in the decision making process [13].

This study shows that patients with higher comorbidities incurred lower costs of breast cancer care for the first year after diagnosis. This is probably because patients with major comorbid conditions were more frail and had poorer ability to tolerate intensive breast cancer therapies. For example, significant comorbidity precludes surgery[9] and platinum-based chemotherapy is often considered to be suitable only for fit patients with no significant comorbidities[31].

HER2 status is a major cost driver of breast cancer care in the first year after diagnosis in addition to the stage at diagnosis. Breast cancer patients with positive HER2 are eligible for targeted therapy with trastuzumab [21,32]. The trastuzumab cost per patient including administration of treatment and cardiac monitoring is £15,080 based on NICE costing report [22], which makes HER2 status a leading driver of the costs of breast cancer care in the first year after diagnosis among patients with early invasive breast cancer.

We further observed that the costs of breast cancer care varied across regions in England, after taking the differences in stage distributions across regions into consideration. This is of concern because it suggests different utilisation of breast cancer care across England. In the UK, hospitals receive payment based on the procedure types according to the NHS National Tariff Payment

System [33]. The tariffs are defined nationally and aligned to promote efficient and high-quality care but the actual cost of performing certain procedures can exceed the income that hospitals receive [12]. The potential for a financial loss may impact on the provision of different treatment options in hospitals and therefore be reflected by the total costs of breast cancer care across cancer alliances in England. An examination of costs could highlight areas for review locally and there would probably be a benefit in having benchmark costs for particular patient groups for regional audit. In addition to financial considerations, future research could also examine whether the regional variation in costs of breast cancer care is related to service provision and/or capacity barriers.

The advantages of our study population are: (i) it includes all patients with a registered diagnosis of early invasive breast cancer in England, diagnosed and treated in an NHS trust, (ii) individual patient-based information is available on a large number of variables such as socio-demographic factors, comorbidities, and referral source; (iii) information on tumour characteristics and treatment received is included; (iv) linkage between multiple national databases allows more comprehensive analysis.

Our study is subject to some limitations. We only included breast cancer patients aged 50 years and over, and limited the follow-up period to one year following diagnosis. However, some treatments for early invasive breast cancer are likely to fall outside the one-year period, such as endocrine therapy and HER2 therapy. Also, we excluded patients with metastatic breast cancer and did not consider the costs of recurrence. This will underestimate the overall cost of care throughout the entire patient pathway. Costs of care in the context of higher stage disease are likely to be disproportionately underestimated given the higher risk of recurrence. Also some costs are not captured in this study relating to managing side effects, GP visits, etc. Although stage and receptor status are included in the analysis, some other tumour characteristics are not considered

such as the influence of multicentricity and the presence of ductal carcinoma in situ (DCIS) with the invasive cancer. Moreover, using the standard errors of the average predicted costs by stage in an economic evaluation requires careful consideration. Patient and tumour characteristics were assumed to be fixed within each stage subgroup when costs were predicted. As the distribution of characteristics in each subgroup also has some uncertainty, the true uncertainty of the average costs by stage might be underestimated. In addition this study used data that were available up to 31 December 2016. Some newly approved drugs after 2016 were not captured in this analysis.

We have identified the key methodological differences in cost analysis in the previously published global systematic review comparing treatment costs of breast cancer by stage across countries [5]. As no single regression model is dominant in costing analyses, we explored different regression models to deal with the skewness issue. In this study, we compared regression models with different distributions (linear-normal, log-normal, and log-gamma). Based on the model selection criteria, we evidenced that the GLM with a log-gamma distribution fit the data best.

Moreover, there are many missing data in the imaging and biopsy dates due to the incomplete reporting of data. We adopted the relaxed criteria as described and assumed 82% of patients had a triple diagnostic assessment on the same day. To enable a better understanding of triple diagnostic assessment for breast cancer patients, data completion on imaging and biopsy dates needs to be improved. In this study, we conducted complete case analysis using only data from 22,537 patients for whom all variables involved in the analysis were observed. Missing data in HES was negligible with the exception of Charlson Comorbidity Index (3%) while the level of incompleteness in Cancer Registry was larger with PR status (51%), HER2 status (17%), ER status (14%), and ethnicity (6%). In further research, one could use multiple imputation for missing data [34].

In conclusion, this study provides up-to-date estimates of initial breast cancer care costs by stage at diagnosis in England. Costs of early invasive (stage I, II and IIIA) breast cancer care up to one year after diagnosis increased with advancing stage of the disease at diagnosis. Breast cancer costs varied by age and geographic region in England.

ETHICS APPROVAL

The study is exempt from UK National Research Ethics Committee approval as it involved secondary analysis of an existing dataset of anonymised data. The NABCOP has approval for processing health care information under Section 251 (reference number: 16/CAG/0079) for all NHS patients aged 50 years and over diagnosed with breast cancer in England and Wales. Also this analysis has received ethics approval from the London School of Hygiene & Tropical Medicine Ethics Committee (reference number 16184).

ROLE OF THE FUNDING SOURCE

This study was undertaken as part of the work by the National Audit of Breast Cancer in Older Patients (NABCOP). The Audit is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme, and funded by NHS England and the Welsh Government (www.hqip.org.uk/national-programmes). Neither the commissioner nor the funders had any involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The authors had full independence from the HQIP. The aim of the NABCOP is to evaluate the care of older women with breast cancer in England and Wales, and support NHS providers to improve the quality of hospital care for these women.

TABLES

Table 1 Cohort characteristics by stage at diagnosis

Variables		All (n=55,662)	Stage I (n=28,232)	Stage II (n=24,358)	Stage IIIA (n=3,072)
Age (years)	Mean (sd)	67 (11)	66 (10)	69 (12)	66 (11)
	50-59 years	15,766 (28%)	8,227 (29%)	6,492 (27%)	1,047 (34%)
	60-69 years	18,698 (34%)	10,930 (39%)	6,897 (28%)	871 (28%)
	70-79 years	12,441 (22%)	5,977 (21%)	5,760 (24%)	704 (23%)
	80-89 years	7,294 (13%)	2,665 (9%)	4,229 (17%)	400 (13%)
	90+ years	1,463 (3%)	433 (2%)	980 (4%)	50 (2%)
Ethnicity	White	49,175 (88%)	24,877 (88%)	21,559 (89%)	2,739 (89%)
	Asian	1,364 (2%)	633 (2%)	633 (3%)	98 (3%)
	Black	766 (1%)	304 (1%)	398 (2%)	64 (2%)
	Other	862 (2%)	444 (2%)	367 (2%)	51 (2%)
	Unknown	3,495 (6%)	1,974 (7%)	1,401 (6%)	120 (4%)
Charlson Comorbidity Index	0	46,078 (83%)	23,760 (84%)	19,698 (81%)	2,620 (85%)

	1	5,084 (9%)	2,477 (9%)	2,342 (10%)	265 (9%)
	2	1,764 (3%)	772 (3%)	889 (4%)	103 (3%)
	3+	914 (2%)	392 (1%)	492 (2%)	30 (1%)
	Unknown	1,822 (3%)	831 (3%)	937 (4%)	54 (2%)
Index of Multiple Deprivation	1 (most deprived)	7,608 (14%)	3,674 (13%)	3,468 (14%)	466 (15%)
	2	9,830 (18%)	4,871 (17%)	4,410 (18%)	549 (18%)
	3	11,585 (21%)	5,945 (21%)	5,011 (21%)	629 (20%)
	4	13,023 (23%)	6,725 (24%)	5,600 (23%)	698 (23%)
	5 (least deprived)	13,616 (24%)	7,017 (25%)	5,869 (24%)	730 (24%)
Tumour grade	Low	9,463 (17%)	7,163 (25%)	2,170 (9%)	130 (4%)
	Intermediate	30,152 (54%)	15,285 (54%)	13,300 (55%)	1,567 (51%)
	High	14,885 (27%)	5,170 (18%)	8,393 (54%)	1,322 (43%)
	Unknown	1,162 (2%)	614 (2%)	495 (2%)	53 (2%)
ER status	Positive	41,872 (75%)	22,109 (78%)	17,601 (72%)	2,162 (70%)
	Negative	6,196 (11%)	2,379 (8%)	3,316 (14%)	501 (16%)
	Borderline	22 (<1%)	9 (<1%)	12 (<1%)	1 (<1%)

	Not performed/unknown	7,572 (14%)	3,735 (13%)	3,429 (14%)	408 (13%)
PR status	Positive	19,078 (34%)	10,114 (36%)	7,949 (33%)	1,015 (33%)
	Negative	8,386 (15%)	3,515 (12%)	4,238 (17%)	633 (21%)
	Borderline	58 (<1%)	29 (<1%)	27 (<1%)	2 (<1%)
	Not performed/unknown	28,140 (51%)	14,574 (52%)	12,144 (50%)	1,422 (46%)
HER2 status	Positive	5,494 (10%)	2,144 (8%)	2,900 (12%)	450 (15%)
	Negative	38,589 (69%)	20,320 (72%)	16,234 (67%)	2,035 (66%)
	Borderline	2,296 (4%)	1,165 (4%)	988 (4%)	143 (5%)
	Not performed/unknown	9,283 (17%)	4,603 (16%)	4,236 (17%)	444 (14%)
Referral source	Screen-detected	22,193 (40%)	15,512 (55%)	6,072 (25%)	609 (20%)
	Not screen-detected	33,469 (60%)	12,720 (45%)	18,286 (75%)	2,463 (80%)
Death within one year	Dead	1,506 (3%)	446 (2%)	942 (4%)	118 (4%)
	Alive	54,156 (97%)	27,786 (98%)	23,416 (96%)	2,954 (96^)

Sd: standard deviation

Table 2 Resource use – n (%) unless otherwise stated

Resource use	All (n=55,662)	Stage I (n=28,232)	Stage II (n=24,358)	Stage IIIA (n=3,072)
1. Diagnosis				
Breast ultrasound[#]	16,548 (30%)	7,394 (26%)	8,157 (33%)	997 (32%)
Mammography[#]	21,518 (39%)	10,012 (35%)	10,154 (42%)	1,352 (44%)
Biopsy[#]	43,523 (78%)	23,505 (83%)	17,998 (74%)	2,020 (66%)
2. Breast procedures				
Breast conserving surgery (BCS)	35,718 (64%)	21,962 (78%)	12,753 (52%)	1,003 (33%)
Mastectomy	12,585 (23%)	3,342 (12%)	7,411 (30%)	1,832 (60%)
Mastectomy and reconstruction	2,627 (5%)	1,131 (4%)	1,294 (5%)	202 (7%)
Axillary lymph node dissection	10,044 (18%)	835 (3%)	6,783 (28%)	2,426 (79%)
Sentinel node biopsy	42,091 (76%)	24,462 (87%)	16,469 (68%)	1,160 (38%)
Excess hospital bed days – mean (sd)	0.06 (1.24)	0.03 (0.77)	0.09 (1.55)	0.15 (1.81)
3. Chemotherapy				
Chemotherapy received	9,498 (17%)	2,404 (9%)	5,731 (24%)	1,363 (44%)
4. Radiotherapy				

Radiotherapy received	37,336 (67%)	19,895 (70%)	14,888 (61%)	2,553 (83%)
1) Radiotherapy received among patients having BCS	31,290 (88%)	19,181 (87%)	11,196 (88%)	913 (91%)
2) Radiotherapy received among patients having mastectomy	5,098 (41%)	348 (10%)	3,170 (43%)	1,580 (86%)
5. Endocrine therapy				
Endocrine therapy received[†]	37,157 (67%)	19,581 (69%)	15,639 (64%)	1,936 (63%)
6. Targeted therapy				
Targeted therapy received	3,606 (6%)	1,250 (4%)	2,002 (8%)	354 (12%)

[#]Data on imaging and biopsy dates were incomplete in the datasets. Adopting a strict set of criteria, 28% received triple assessment in a single visit. If we assumed missing mammogram/biopsy dates were the same as the date of biopsy/mammogram respectively, incorporated the use of ultrasound where mammogram was not reported, and allowed dates of biopsy and mammogram to differ by one day, the estimated proportion of women having a triple diagnostic assessment on the same day was 82%.

[†]We assumed 88.3% ER+/PR+ breast cancer patients received endocrine therapy based on a meta-regression analyses of 17 studies [23].

Table 3 Results for first-year total costs of breast cancer care comparing alternative models – average marginal effects (standard error)

Variables	Linear-Normal	Log-Normal	Log-Gamma
Stage II	1883 (81)***	1758 (70)***	1912 (72)***
Stage IIIA	5859 (160)***	4468 (130)***	6415 (253)***
Age 60-69 years	-985 (92)***	-761 (79)***	-1071 (100)***
Age 70-79 years	-2484 (104)***	-2275 (88)***	-2338 (102)***
Age 80-89 years	-5055 (135)***	-5110 (113)***	-4792 (97)***
Age 90+ years	-6795 (275)***	-6918 (238)***	-6986 (95)***
Region	***	***	***
Region × Stage	***	***	***
AIC	447,464	446,456	430,636
N		22,325	

The reference group is patients aged 50-59 years diagnosed at stage I from North East and Cumbria. We controlled for ethnicity, Charlson Comorbidity Index, Index of Multiple Deprivation, ER/PR/HER2 status, and referral source (presented in Appendix 2).

We conducted the complete case analysis and the sample size was 22,325 patients for whom all variables involved in the analysis were observed. Missing data in HES was negligible with the exception of Charlson Comorbidity Index (3%) while the level of incompleteness in Cancer Registry was larger with PR status (51%), HER2 status (17%), ER status (14%), and ethnicity (6%).

***p<0.001

FIGURES

Figure 1 Crude costs of first-year primary breast cancer care by region

Regions are numbered from 1 to 19 for (1) North East and Cumbria (6.2% of breast cancer patients diagnosed in this region), (2) Lancashire and South Cumbria (2.8%), (3) Greater Manchester (4.9%), (4) West Yorkshire (4.3%), (5) Humber, Coast and Vale (2.8%), (6) South Yorkshire, Bassetlaw, North Derby (3.2%), (7) Cheshire and Merseyside (5.1%), (8) West Midlands (10.7%), (9) East Midlands (7.2%), (10) East of England (11.7%), (11) Peninsula (3.9%), (12) Somerset, Wiltshire, Avon & Gloucestershire (5.4%), (13) Wessex (5.8%), (14) Thames Valley (4%), (15) Surrey and Sussex (6.3%), (16) Kent and Medway (3.7%), (17) West London (5.4%), (18) South East London (2.2%), and (19) North Central and East London (4.5%). The vertical lines at the top are 95% confidence intervals around the total costs.

Figure 2 Predicted population average costs of first-year primary breast cancer care by stage at diagnosis

We predicted the first-year costs of breast cancer treatment by stage at diagnosis controlling for age group, ethnicity, Charlson Comorbidity Index, Index of Multiple Deprivation, tumour receptor (ER/PR/HER2) status, referral source, and regions. The predicted costs were £5,167 (S.E. £27) at stage I, £7,613 (S.E. £48) at stage II, and £13,330 (S.E. £213) at stage IIIA for the population average. The vertical lines at the top are 95% confidence intervals around the total costs.

F-test showed p-value <0.001.

Figure 3 Predicted costs of first-year primary breast cancer care by age groups

The predicted costs of primary breast cancer care were £8,782 (S.E. £68) for patients aged 50-59 years, £7,062 (S.E. £50) for 60-69 years, £5,925 (S.E. £51) for 70-79 years, £3,459 (S.E. £42) for 80-89 years, and £1,266 (S.E. £39) for over 90 years respectively.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359-386.
2. Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ.* 2014;348:g366.
3. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet.* 2015;385(9972):977-1010.
4. SEER Program. *Division of Cancer Prevention and Control, Surveillance Program, Cancer Statistics Branch.* Bethesda: Md: National Cancer Institute; 1973–2002.
5. Sun L, Legood R, Dos-Santos-Silva I, Gaiha SM, Sadique Z. Global treatment costs of breast cancer by stage: A systematic review. *PLoS One.* 2018;13(11):e0207993.
6. Bomb M, Hiom S, Kumar H, et al. *Saving lives, averting costs.* Cancer Research UK;2014.
7. Lo-Fo-Wong DNN, Sitnikova K, Sprangers MAG, De Haes HCJM. Predictors of health care use of women with breast cancer: A systematic review. *Breast Journal.* 2015;21(5):508-513.
8. Wolstenholme JL, Smith SJ, Whynes DK. The costs of treating breast cancer in the United Kingdom: implications for screening. *Int J Technol Assess Health Care.* 1998;14(2):277-289.
9. National Institue for Health and Care Excellence (NICE). *Clinical Guideline (CG80): Early and locally advanced breast cancer: diagnosis and treatment.* London: NICE;2009.
10. West Midlands Cancer Intelligence Unit. *The Second All Breast Cancer Report. Focussing on Inequalities: Variation in breast cancer outcomes with age and deprivation.* National Cancer Intelligence Network;2011.
11. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. *Lancet Oncol.* 2014;15(1):23-34.
12. Mennie JC, Mohanna PN, O'Donoghue JM, Rainsbury R, Cromwell DA. National trends in immediate and delayed post-mastectomy reconstruction procedures in England: A seven-year population-based cohort study. *Eur J Surg Oncol.* 2017;43(1):52-61.
13. National Audit of Breast Cancer in Older Patients. *2018 Annual Report.* 2018.
14. NHS England. Cancer Alliances – improving care locally. https://www.england.nhs.uk/cancer/improve/cancer-alliances-improving-care-locally/.
15. Health and Social Care Information Centre. OPCS-4 Classification. https://data.gov.uk/dataset/5c4c884a-f91f-44be-91b6-32ea0b1a7e11/nhs-classifications-opcs-4. Accessed 25th February, 2019.
16. Health and Social Care Information Centre. Introduction to Healthcare Resource Groups. http://content.digital.nhs.uk/hrg. Accessed 01 July, 2017.

17. Department for Communities and Local Government. English indices of deprivation. 2015; https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015. Accessed 12 July, 2017.
18. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol.* 2011;173(6):676-682.
19. National Institue for Health and Care Excellence (NICE). *Social value judgements: principles for the development of NICE guidance.* 2008.
20. National Institue for Health and Care Excellence (NICE). *Clinical Guideline (CG1): Guideline on improving outcomes in breast cancer.* London: NICE;2002.
21. National Institute for Health and Care Excellence (NICE). *Early and locally advanced breast cancer: diagnosis and treatment.* Cardiff, Wales, UK: National Institute for Health and Clinical Excellence;2009.
22. National Institute for Health and Clinical Excellence. *National costing report: Early and locally advanced breast cancer/Advanced breast cancer.* London, UK: National Institute for Health and Clinical Excellence;2009.
23. Huiart L, Ferdynus C, Giorgi R. A meta-regression analysis of the available data on adherence to adjuvant hormonal therapy in breast cancer: summarizing the data for clinicians. *Breast Cancer Res Treat.* 2013;138(1):325-328.
24. Department of Health. *NHS reference costs 2015 to 2016.* 2016.
25. British National Formulary. *British National Formulary.* London: BMJ Group and Pharmaceutical Press (Royal Pharmaceutical Society of Great Britain); 2018.
26. Curtis L. *Unit Costs of Health and Social Care 2011.* Canterbury, Kent: Personal Social Services Research Unit (PSSRU);2011.
27. Ramsey JB. Tests for Specification Errors in Classical Linear Least-Squares Regression Analysis. 1969;31(2):350-371.
28. Deb P, Norton EC. Modeling Health Care Expenditures and Use. *Annual Review of Public Health.* 2018;39(1):489-505.
29. Jones AM. *Models for health care.* Oxford: Oxford University Press; 2011.
30. Deb P, Norton EC, Manning WG. *Health Econometrics using Stata.* College Station: Stata Press; 2017.
31. National Institue for Health and Care Excellence (NICE). *NICE guideline [NG101]: Early and locally advanced breast cancer: diagnosis and treatment.* London: NICE;2018.
32. National Institute for Health and Care Excellence (NICE). *Advanced breast cancer: diagnosis and treatment.* Cardiff, Wales, UK: National Institute for Health and Clinical Excellence;2009.
33. Department of Health. *Policy paper confirmation of payment by results (PbR) arrangements for 2011-12.* London: Department of Health;2011.
34. Oostenbrink JB, Al MJ. The analysis of incomplete cost data due to dropout. *Health Econ.* 2005;14(8):763-776.