ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

ORIGINAL RESEARCH

Variation in chemotherapy prescribing rates and mortality in early breast cancer over two decades: a national data linkage study

E. Gray[1], J. D. Figueroa[1], O. Oikonomidou[1,2], I. MacPherson[3,4], G. Urquhart[5], D. A. Cameron[1,2] & P. S. Hall[1,2*]

[1]Institute of Genetics and Cancer, University of Edinburgh, Edinburgh; [2]Edinburgh Cancer Centre, NHS Lothian, Edinburgh; [3]Institute of Cancer Sciences, University of Glasgow, Glasgow; [4]The Beatson West of Scotland Cancer Centre, NHS Greater Glasgow and Clyde, Glasgow; [5]NHS Grampian, Aberdeen, UK

Available online xxx

Background: Regional variation in clinical practice may identify differences in care, reveal inequity in access, and explain inequality in outcomes. The study aim was to measure geographical variation in Scotland for adjuvant chemotherapy use and mortality in early-stage breast cancer.

Patients and methods: In this retrospective cohort study using population cancer registry-based data linkage, patients with surgically treated early breast cancer between 2001 and 2018 were identified from the Scottish Cancer Registry. Geographical regions considered were based on NHS Scotland organisational structure including 14 territorial Health Boards as well as three regional Cancer Networks. Regional variation in the proportion receiving chemotherapy, breast cancer mortality and all-cause mortality was investigated. Inter-regional comparisons of chemotherapy use were adjusted for differences in case mix using logistic regression. Comparison of breast cancer-specific mortality and all-cause mortality used regression with a parametric survival model. Time trends were assessed using moving average plots.

Results: Chemotherapy use ranged from 35% to 46% of patients across Health Boards without adjustment. Variation reduced between 2001 and 2018. Following adjustment for clinical case mix, variation between cancer networks was within 3 percentage points, but up to 10 percentage points from the national average in some Health Boards. Differences in breast cancer mortality and all-cause mortality between cancer networks were modest, with hazard ratios of between 0.933 (95% confidence interval 0.893-0.975) and 1.041 (1.002-1.082) compared with the national average. Survival improved over the time period studied.

Conclusion: With adequate case mix adjustment, variation in adjuvant chemotherapy use for early breast cancer in Scotland is small, with a trend towards greater convergence in practice and improved mortality outcomes in more recent cohorts. This suggests very limited regional inequity in access and convergence of clinical practice towards risk-stratified treatment recommendations. Outliers require assessment to understand the reasons for variance.

Key words: regional variation, breast cancer, chemotherapy, mortality

INTRODUCTION

Adjuvant chemotherapy for early-stage breast cancer has demonstrated efficacy in randomised studies, resulting in a mortality reduction of approximately one-third.[1] The implementation and evolution of adjuvant therapies, including chemotherapy, has likely contributed to sustained improvement in the survival of breast cancer patients over recent decades.[2] Balanced against survival gains are the side-effects of chemotherapy, which can be severe, and many cancers are of good prognosis even without chemotherapy. There is, therefore, a consensus in international guidelines that patients and clinicians should decide on chemotherapy depending on prognostic characteristics.[3-6]

High-quality care in early breast cancer includes appropriate use of adjuvant therapies through a patient-clinician shared decision-making process. Appropriate levels of treatment uptake among patients in whom it is recommended are considered as a marker of a well-functioning healthcare system. There is, however, no consensus on what the correct rate of chemotherapy use should be. Wide variation may indicate good or poor quality care in some areas. In Scotland, the National Cancer Quality Performance Indicators (QPIs) have recently set a benchmark of 85% chemotherapy use for patients that are estimated to have ≥5% overall survival benefit at 10 years from adjuvant

*Correspondence to: Dr Peter S. Hall, Edinburgh Cancer Research Centre, University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU, UK. Tel: +44-131-651-8510
E-mail: p.s.hall@ed.ac.uk (P. S. Hall).

chemotherapy treatment, but it is unknown to what extent historical treatment has met this level.[7]

Unwarranted variation in practice is a concern across health systems internationally,[8] where the causes may include inequitable access, uneven organisational performance or idiosyncratic clinical practice. Potential detriment to public health makes it essential to pursue accurate and timely identification of such differences in an attempt to drive health improvement.

Identification of unwarranted variation at population-level in breast cancer treatment has historically been difficult, due to the lack of systematic collection or availability of case mix factors such as deprivation, comorbidity and detailed cancer stage, including molecular markers. Recent developments in data infrastructure and linkage makes Scotland one of the first countries where this is now possible.[9]

In this study we investigated geographical variation in practice and outcomes over two decades using national population-level cancer registry data linked to routinely collected health system data with detailed case mix adjustment.

METHODS

Outline

This study assesses regional variation in clinical practice by reporting the proportions of patients using adjuvant chemotherapy. Regional variation may be defined as the difference between regions and the national average or pairwise differences between regions. Possible explanations of regional variation were also assessed. An estimate of the effect of regional variation in care provision (access and treatment decision making), rather than differences in patient population characteristics, was made by adjustment for individual patient characteristics using logistic regression.

Patient mortality across regions was assessed using a similar method. Survival, adjusted for case mix, was assessed using regression with parametric survival models to compare regions. If adjustment was successful, then any differences between regions would reflect the effects of differences in practice rather than differences in the patient populations.

Two geographical units of variation were considered. First, the 14 NHS Scotland Territorial Heath Boards (hereafter 'health boards') which are the organizations ultimately responsible for the delivery of patient care in NHS Scotland. Second, the three regional cancer networks that group together health boards in collaborative networks.

Patient data

Patient level data were extracted from the population-based Scottish Cancer Registry and linked to hospital inpatient and day case records (SMR01) and outpatient records (SMR00). All records in the registry with a diagnosis of primary invasive breast cancer (ICD-10 C50) diagnosed in the period between January 2001 and December 2018 were retrieved. Data selection and linkage was provided by Information Services Division. Deterministic linkage was achieved using the Community Health Index number unique individual identifiers, which includes a check digit. The linked datasets included all records linked to an included registry case from the period up to 5 years before the date of diagnosis. Follow-up data were available up to end September 2019. Deaths due to breast cancer were defined in accordance with the ICD-10 coding system for causes of death, recorded either as the primary cause of death or as one of three contributing causes of death. Data were restricted to the first occurrence of a primary breast cancer for each patient; subsequent primary breast cancers were excluded.

A health board and cancer network for each patient was assigned based on the recorded health board of residence. Patients do not necessarily receive all their healthcare services within their health board of residence. In Scotland, however, health boards are ultimately responsible for making provisions for all their residents, with a funding mechanism largely dependent on the size of the population in residence.[10] Chemotherapy use was recorded as a binary variable in registry data. Neoadjuvant and adjuvant chemotherapy use are both included. NHS Predict predicted benefit from adjuvant chemotherapy scores which were calculated using version 2.0, which takes into account human epidermal growth factor receptor 2 (HER2) and estrogen receptor (ER) status.[11] Unknown Ki67 status was assumed for all patients while HER2 status was assumed to be unknown when this was not available (including all patients diagnosed before 2009). In the PREDICT algorithm, chemotherapy was assumed to be classified as third generation, reflecting modern evidence-based regimens. No other prognostic variables were imputed.

Statistical methods

Unadjusted chemotherapy use probabilities for each health board are presented as descriptive statistics. Moving average of treatment use probabilities were used to display in line graphs the changes over time in the proportions using chemotherapy. A centred 2-year moving average was used.

Adjusted treatment probabilities were estimated for each health board, and separately for each network. Adjustment was made using logistic regression. Covariates included were age, year of diagnosis, prognosis (NHS Predict 10-year predicted survival as well as all component risk factors of NHS Predict as individual covariates, including interaction terms with ER status) and comorbidity weight (log total inpatient bed days and log total number of outpatient appointments in 5 years before diagnosis). Age and comorbidity are known to be inversely associated with use in this cohort, while poor prognosis is positively associated with chemotherapy use.[12,13]

A comparison of health boards to the national average was made using predictions of the regression model. The 99% confidence intervals (CIs) were calculated for adjusted therapy use probabilities and difference in treatment use probability from the national average for statistical inference.

A comparison of breast cancer-specific mortality and all-cause mortality outcomes across health boards and networks was made using regression with a parametric survival model.[12] Regression adjustment has previously been shown to be feasible in this setting.[13] The regression analysis made use of all covariates included in the treatment use-adjusted estimates with the additional use of socioeconomic status (SES) using the Scottish Index of Multiple Deprivation (SIMD) quintile. A Weibull distribution for survival times was selected from among candidate distributions (log-normal, log-logistic, exponential, Weibull and Gompertz) based on visual inspection and AIC statistics.

The sample was divided into time period cohorts, 2001-2006, 2007-2012, 2013-2018, because regional variation in practice and outcomes are likely to change over time. It is more meaningful to describe regional variation for specific periods of time short enough to allow a stable pattern of variation to be clear. Time periods must be long enough, however, to allow an adequate sample size for regional comparisons. There is a trade-off between these two competing needs and judgement is required in determining an appropriate time period over which to aggregate. We have selected 5-year periods as stated above over which to aggregate. Additionally, trends in survival over time were assessed via life tables and Kaplan—Meier cumulative failure plots of individual year cohorts (2002, 2007, 2012 and 2015). Chemotherapy use statistics are reported for each time period cohort as well as for the complete sample. Survival statistics are reported for the 2001-2006 and 2007-2012 cohorts only, because the 2013-2018 cohort has insufficient follow-up to allow a useful comparison.

To explore adherence to clinical guidelines, chemotherapy use was estimated by health boards for subgroups formed by Predict score thresholds using Predict version 2.0, i.e. <3% benefit score, 3%-5% benefit score and >5% benefit score.

All analysis was conducted with complete cases (no missing data for variables of interest) only. Previous analysis with these data found no informative patterns of missingness and little difference between complete case analysis and analysis using multiple imputation.[14] This suggests that a missing completely at random (MCAR) assumption and complete case analysis is reasonable.

Note that care should be taken when interpreting levels and changes over time in the smaller health boards—Orkney, Shetland and Western Isles—as the sample sizes in any given year, or even over the whole period, are too small for robust inference.

Project approval was granted by the Scottish Public Benefit and Privacy Panel which has delegated authority from the UK Health Research Authority Research Ethics service (PBPP ref: 1516-0251).

Table 1. Description of sample characteristics and number of patients in each region

Scottish Cancer Registry 2001-2018, linked to SMR00, SMR01					
Total number of subjects	48 978				
Total time at risk (years)	377 015				
Median follow-up (years)	6.98				
Number of breast cancer deaths	5906				
Number of other deaths	3907				
5-Year survival rate	88.8%				
Median age at diagnosis, years	59				
	N	(%)		*N*	(%)
Age, years <35	799	1.6	Health board		
35-49	9745	19.9	A&A	3634	7.42
50-64	21 978	44.9	Borders	1208	2.47
65-74	12 530	25.6	D&G	1771	3.62
≥75	3926	8	Fife	3422	6.99
Nodes 0	32 004	65.3	Forth Valley	2851	5.82
Nodes 1	7232	14.8	Grampian	4985	10.18
Nodes 2-4	5567	11.4	GGC	9544	19.49
Nodes 5-9	2077	4.2	Highland	3465	7.07
Nodes 10+	1795	3.7	Lanarkshire	5942	12.13
Grade I	7004	14.3	Lothian	7247	14.8
II	23 596	48.2	Orkney	225	0.46
III	18 378	37.5	Shetland	213	0.43
ER−	7688	15.7	Tayside	4192	8.56
ER+	41 290	84.3	Western Isles	278	0.57
Screen detected	18 791	38.4	Cancer Network		
Symptomatic	30 187	61.6	NoS	13 359	27.28
SIMD 1	8343	17	SCAN	13 648	27.87
SIMD 2	9539	19.5	WoSCAN	21 971	44.86
SIMD 3	10 325	21.1		Mean	s.d.
SIMD 4	10 356	21.1	Age, years	58.49	0.055
SIMD 5	10 414	21.3	Tumour size	22.13	0.074
PREDICT <3%	29 797	60.8	Inpatient days	2.37	0.052
3%-5%	10 064	20.5	PREDICT sc.	2.99	0.011
>5%	9117	18.6	Outpatient visits	6.15	0.041

A&A, Ayrshire and Arran; D&G: Dumfries and Galloway; ER, estrogen receptor; GGC, Greater Glasgow and Clyde; Nos, North of Scotland; SCAN, South East Cancer Network; SIMD, Scottish Index of Multiple Deprivation; WoSCAN, West of Scotland Cancer Network.

RESULTS

A total of 48 978 individuals were included following application of exclusion criteria (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100331).

Table 1 provides descriptive statistics of the data, including the number of patients in each of the geographic regions. Health boards range in size from Greater Glasgow and Clyde with 9544 patients to Shetland with only 213 patients. Orkney, Shetland and Western Isles health boards include such small numbers that any analysis of subgroups within these health boards or comparisons across boards is unlikely to be distinguishable from the play of chance. Analysis of subgroups, time trends and comparisons are feasible for other health boards and cancer networks.

Chemotherapy use

There was regional variation in adjuvant chemotherapy use between health boards and networks. The percentage of patients using chemotherapy in the different regions ranged from 35% to 46% (2001-2018 cohort). Looking at the 5-year time period cohorts separately (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2021.100331)

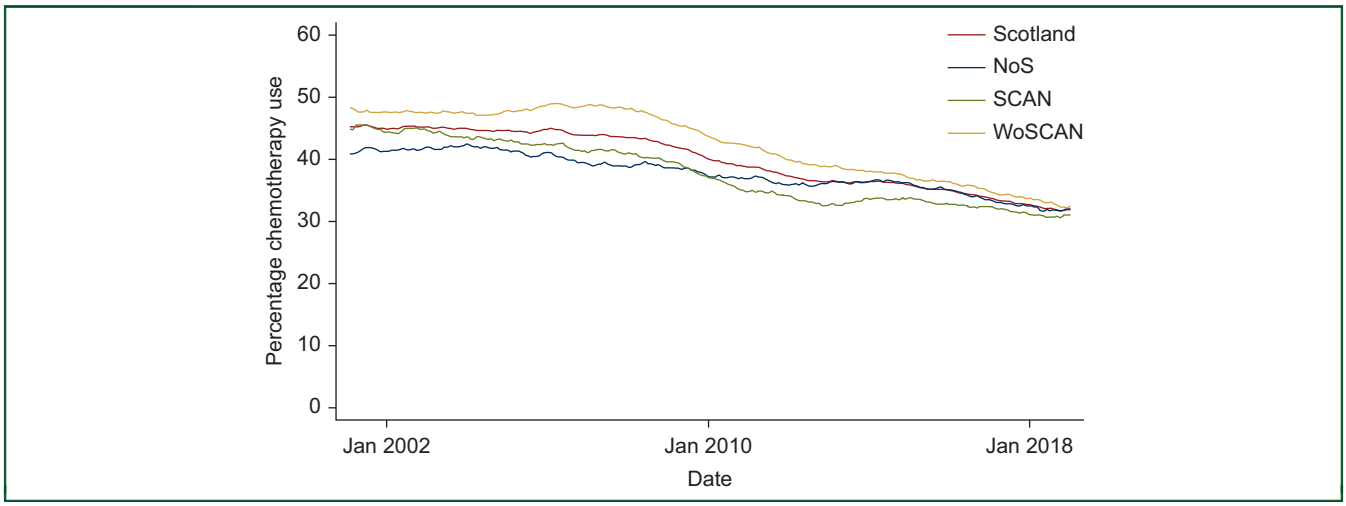

Figure 1. Moving average of percentage chemotherapy use by network, 2001-2018, 2-year window.
Nos, North of Scotland; SCAN, South East Cancer Network; WoSCAN, West of Scotland Cancer Network.

it is clear that chemotherapy use has reduced over time and the degree of regional variation was larger in the earlier 2001-2006 period. Figure 1 displays more clearly how practice in the three cancer networks has converged over time. The corresponding moving average figures for health boards within each network are available in the supplementary materials (Supplementary Figures S3-S5, available at https://doi.org/10.1016/j.esmoop.2021.100331). Adjustment for case mix further reduces observed differences in chemotherapy use.

Table 2 shows unadjusted and adjusted estimates of chemotherapy use for the full 2001-2018 time period cohort. Results for other time periods are available in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100331.

Post adjustment variation at the cancer network level is small, a range of ∼3 percentage points. Post adjustment variation between health boards has a larger range with three health boards having noticeable differences from the majority. Forth Valley and Fife health boards were ∼3-4 percentage points lower compared with the majority of boards. Tayside health board was ∼10% lower. Only the Tayside health board still appears to be a noticeable outlier in the most recent time period (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100331), while Forth Valley and Fife have converged to a greater degree.

Table 2. Logistic regression, unadjusted and adjusted estimates of chemotherapy use by health board, 2001-2018

Network/ health board	Unadjusted proportion chemotherapy	95% CI	Adjusted proportion chemotherapy	95% CI
Network				
NoS	0.40	(0.39-0.41)	0.39	(0.39-0.40)
SCAN	0.40	(0.40-0.41)	0.42	(0.41-0.42)
WoSCAN	0.44	(0.43-0.44)	0.43	(0.42-0.43)
Health Board				
A&A	0.45	(0.43-0.46)	0.46	(0.44-0.47)
Borders	0.41	(0.38-0.43)	0.43	(0.41-0.45)
D&G	0.37	(0.35-0.40)	0.43	(0.41-0.44)
Fife	0.40	(0.38-0.41)	0.39	(0.38-0.40)
Forth Valley	0.38	(0.36-0.39)	0.38	(0.37-0.40)
Grampian	0.44	(0.42-0.45)	0.43	(0.42-0.43)
GGC	0.44	(0.43-0.45)	0.43	(0.42-0.43)
Highland	0.39	(0.38-0.41)	0.43	(0.41-0.44)
Lanarkshire	0.46	(0.44-0.47)	0.44	(0.43-0.45)
Lothian	0.41	(0.39-0.42)	0.42	(0.42-0.43)
Orkney	0.44	(0.38-0.51)	0.45	(0.41-0.49)
Shetland	0.41	(0.35-0.48)	0.41	(0.37-0.46)
Tayside	0.35	(0.34-0.36)	0.32	(0.31-0.33)
Western Isles	0.36	(0.30-0.41)	0.41	(0.37-0.46)

Adjustment variables: age (5-year age bands), year of diagnosis, prognosis (NHS Predict 10-year predicted survival as well as component risk factors), comorbidities (log total inpatient bed days and log total number of outpatient appointments in 5 years before diagnosis).
A&A, Ayrshire and Arran; CI, confidence interval; D&G: Dumfries and Galloway; GGC, Greater Glasgow and Clyde; NoS, North of Scotland; SCAN, South East Cancer Network; WoSCAN, West of Scotland Cancer Network.

Treatment guidelines and chemotherapy use

Figure 2 displays the percentage of patients (2001-2018) using chemotherapy by PREDICT benefit subgroup across geographic units. Results for other time period cohorts are available in the Supplementary Figures S5-S7, available at https://doi.org/10.1016/j.esmoop.2021.100331. In the most recent period (patients diagnosed 2013-2018, Supplementary Figure S7, available at https://doi.org/10.1016/j.esmoop.2021.100331), chemotherapy use in the >5% PREDICT benefit score group was in the range of 70%-80%, compared with ∼60% in the 3%-5% groups, and 10%-20% in the <3% group. Regional variation in each PREDICT score group was roughly in the same range as for the total sample, i.e. only modest variation within these subgroups. Comparison of these charts indicates practice converging over time towards clinical guideline recommendations, stable or increasing use in the >5% group and decreasing use in the <3% group.

Outcomes

Regional variation in mortality was also small. Adjusted and unadjusted hazard ratios (HRs) for all-cause and breast

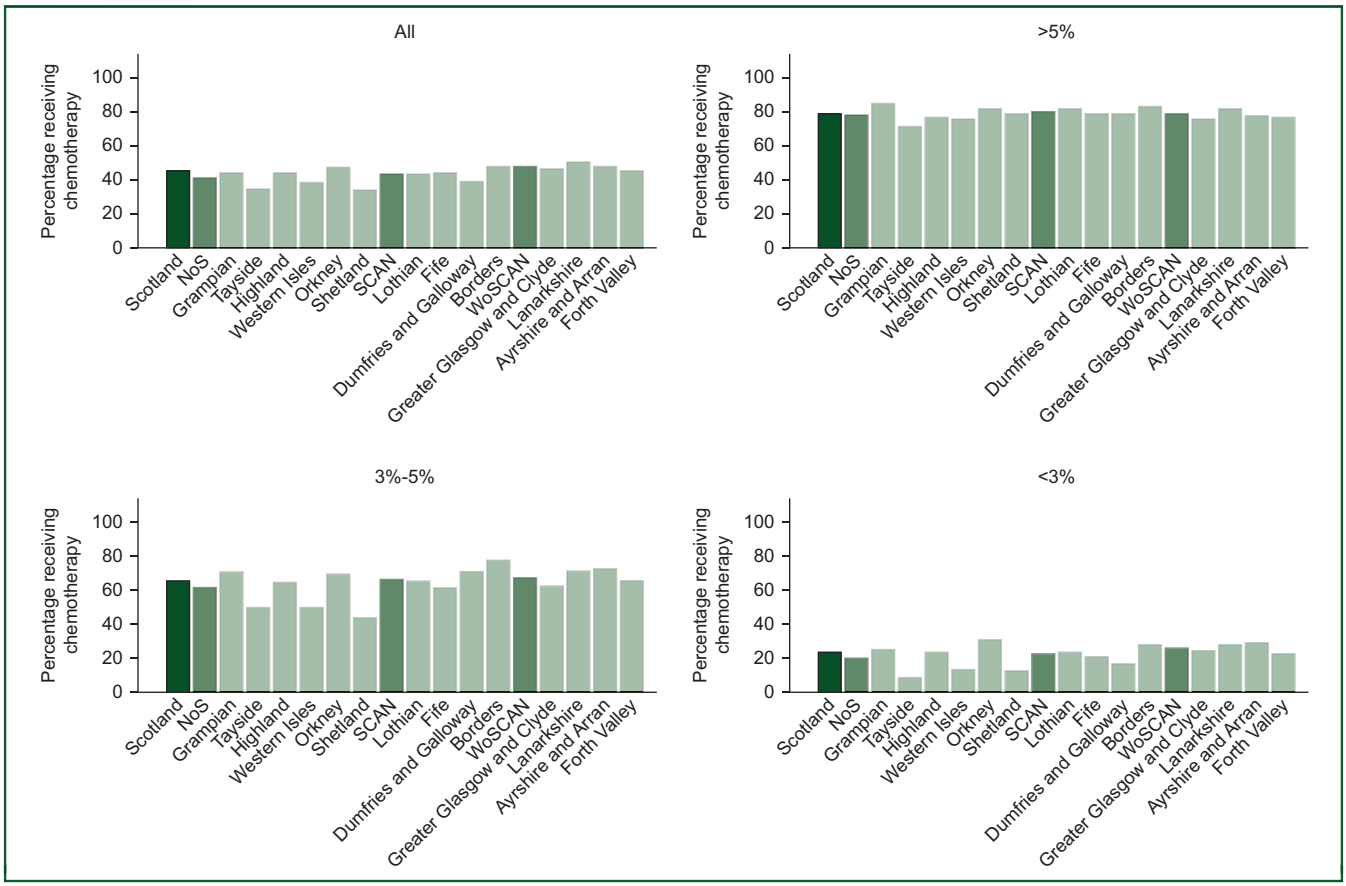

Figure 2. Percentage chemotherapy use in patients with PREDICT chemotherapy benefit score <5%, 3%-5% and <3% (full sample 2001-2018).
Nos, North of Scotland; SCAN, South East Cancer Network; WoSCAN, West of Scotland Cancer Network.

cancer mortality in comparison to a national average are reported in Table 3. Adjustment for case mix generally reduces the outcome differences as expected. A trend towards improved survival in more recent cohorts is clear; 5-year survival improved from 84.3% for the 2002 cohort to 90.8% for the 2012 cohort (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100331). Improvement was noticeable across all cancer networks with South East Cancer Network (SCAN) starting from a more favourable position in the earlier period (Supplementary Figures S8-S11, available at https://doi.org/10.1016/j.esmoop.2021.100331).

Differences at the cancer network level were small and there was only weak evidence of variation at the health board level. Compared with the national average, breast cancer mortality was lower in SCAN [0.933, 95% confidence interval (CI) 0.893-0.975]; all-cause mortality was also lower (0.976, 95% CI 0.944-1.009), but this difference did not achieve statistical significance. We find some evidence that patients in two health boards, Dumfries and Galloway and Tayside, experienced higher all-cause mortality than the national average, with adjusted HRs of 1.225 (95% CI 1.107-1.355) and 1.066 (95% CI 1.001-1.135), respectively. The results for the 2001-2006 and 2007-2012 cohorts are similar; however, evidence of a difference in mortality in Tayside is only found for the 2007-2012 cohort and not the 2001-2006 cohort (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100331).

DISCUSSION

In Scotland, the National Health Service (NHS) aims to offer equal access to all subject to clinical needs.[15] Patients' socioeconomic circumstances or location should not influence whether a desired treatment is available or not. Furthermore, care should be of equivalent quality and in line with best evidence-based practice. Whether or not this aim is achieved is an important question for health care planners, professionals and patients. Evaluation of available data on this topic is therefore vital.

A key strength of this study is that the registry and linked record data cover the whole population, have a relatively high level of completeness, and include extensive covariate data beyond many other observational datasets. Nevertheless, there are a number of weaknesses when using these data to assess regional variation. There is potential for bias in the comparison of different regions due to residual confounding, despite our best efforts to account for differences in case mix. Whether or not to include SES (as measured by SIMD) among the covariates was a difficult choice. This was omitted from the chemotherapy use analysis, because if there were regional variations that were

Table 3. All-cause mortality HR compared with national average, by health board and cancer network 2001-2018

Network/health board versus mean	All-cause mortality				Breast cancer mortality			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Network								
NoS	1.00	(0.96-1.03)	1.03	(0.99-1.07)	1.04	(1.00-1.08)	1.06	(1.01-1.11)
SCAN	0.94	(0.91-0.97)	0.98	(0.94-1.01)	0.91	(0.87-0.94)	0.93	(0.90-0.98)
WoSCAN	1.04	(1.02-1.06)	1.00	(0.98-1.02)	1.04	(1.01-1.07)	1.01	(0.98-1.04)
Health Board								
A&A	0.97	(0.91-1.04)	0.98	(0.91-1.06)	0.96	(0.88-1.05)	1.03	(0.93-1.13)
Borders	0.88	(0.77-1.00)	0.95	(0.83-1.08)	0.80	(0.68-0.94)	0.86	(0.71-1.02)
D&G	1.12	(1.02-1.23)	1.23	(1.11-1.36)	1.10	(0.98-1.23)	1.23	(1.07-1.40)
Fife	0.96	(0.90-1.03)	0.89	(0.83-0.96)	0.93	(0.85-1.02)	0.85	(0.77-0.94)
Forth Valley	1.02	(0.94-1.10)	1.07	(0.98-1.16)	0.99	(0.90-1.10)	1.05	(0.94-1.17)
Grampian	0.93	(0.88-0.99)	1.06	(0.99-1.12)	0.96	(0.90-1.04)	1.11	(1.02-1.20)
GGC	1.07	(1.03-1.11)	0.97	(0.93-1.02)	1.06	(1.01-1.11)	0.95	(0.89-1.01)
Highland	0.96	(0.89-1.03)	0.92	(0.84-1.02)	1.02	(0.94-1.11)	1.01	(0.89-1.14)
Lanarkshire	1.06	(1.00-1.12)	1.02	(0.96-1.08)	1.08	(1.02-1.15)	1.07	(0.99-1.15)
Lothian	0.90	(0.86-0.95)	0.97	(0.92-1.03)	0.87	(0.82-0.92)	0.93	(0.86-0.99)
Orkney	0.82	(0.59-1.14)	1.03	(0.72-1.47)	0.96	(0.67-1.38)	1.16	(0.75-1.78)
Shetland	1.04	(0.78-1.39)	1.30	(0.94-1.78)	1.09	(0.78-1.53)	1.20	(0.78-1.84)
Tayside	1.10	(1.04-1.17)	1.07	(1.00-1.14)	1.14	(1.06-1.23)	1.04	(0.96-1.13)
Western Isles	1.20	(0.94-1.53)	1.09	(0.83-1.44)	1.26	(0.96-1.67)	1.33	(0.95-1.87)

Adjustment variables: age (5-year age bands), year of diagnosis, prognosis (NHS Predict 10-year predicted survival as well as component risk factors), comorbidities (log total inpatient bed days and log total number of outpatient appointments in 5 years before diagnosis) and socioeconomic status (SIMD-decile).
A&A, Ayrshire and Arran; CI, confidence interval; D&G: Dumfries and Galloway; GGC, Greater Glasgow and Clyde; HR, hazard ratio; NoS, North of Scotland; SCAN, South East Cancer Network; SIMD, Scottish Index of Multiple Deprivation; WoSCAN, West of Scotland Cancer Network.

explained by differences in SES, this would still be considered unwarranted variation. Whereas for the analysis of survival outcomes we included SIMD among the covariates to account for the impact of the various factors linked to SES on health outcomes but unrelated to breast cancer care.

A specific limitation of the data is that we do not know the precise chemotherapy regimen used for each patient. Future research may address these limitations with more extensive medical record linkage. Neoadjuvant chemotherapy presents a challenge for this type of analysis, as this treatment may influence the recording and measurement of other covariates, for example tumour size obtained from pathology reports. Exclusion of neoadjuvant chemotherapy-treated women from the study may prevent bias from this measurement error, but would make time trends difficult to interpret and may introduce selection bias.

Adjuvant chemotherapy is recommended for patients with early-stage breast cancer when their potential to benefit outweighs the harms of treatment. Some treatment guidelines specify levels of predicted benefit from chemotherapy (for example, with risk estimates sourced from the NHS Predict decision tool[16]) that can be used as a threshold for making treatment recommendations; patients with a <3 percentage point improvement in survival over 10 years should not generally be recommended chemotherapy, those with a 3-5 percentage point benefit should discuss chemotherapy and if the benefit is >5 percentage points, then chemotherapy should be recommended.[17]

The pattern of regional variation in breast cancer chemotherapy use in Scotland is one of relatively small differences with a trend towards greater convergence over time. Chemotherapy use has declined somewhat across all health boards over time, with a smaller decline in health boards which began at the lowest levels. This reflects increased alignment with guidelines recommending against use when patients have $<3\%$ predicted survival benefit, along with a higher proportion of patients in this good prognosis group.

There are some important limitations to this analysis that arise from the nature of the data. No data were available for linkage that included the chemotherapy regimen or intensity. In the most recent years, chemotherapy use may have been influenced by multiparameter assays both in a trial setting[18] and clinical practice. Our linked data did not have information about assay use, but this is a minor issue as they were not adopted in Scotland until 2018.

Differences in mortality outcomes cannot be attributed directly to differences in chemotherapy use with this study design. Nevertheless, it is important to consider regional variation in outcomes alongside variations in clinical practice. The importance of investigating regional variations in practice is in proportion to regional variations in outcomes. Regional differences in mortality for this patient population were relatively small. This is reassuring in a system such as the NHS in which it is hoped equitable care would yield equitable outcomes. Some evidence is found for variation in mortality between Health Boards; although relatively small effects, these differences may be of some concern. These findings should encourage further investigation of whether the differences persist and their possible causes.

In terms of the appropriateness of care as defined by evidence-based guidelines, there are two notable results. Firstly, the proportion of patients with high ($>5\%$) predicted

benefit using chemotherapy is high, at ∼75% in recent years. This is lower than the target set as a QPI (85%) suggesting possible room for improvement or that the benchmark level has been set inappropriately high. Secondly, for those with low predicted benefit (<3%), the proportion using chemotherapy has decreased to around 15%-20% in recent years. In health boards with the lowest levels initial use, use in the <3% group increased slightly. The overall picture is one is which nearly all regions moved towards providing care with greater alignment to evidence-based guidelines. Given the encouraging time trends in survival, this suggests that overall population level of chemotherapy use has been safely reduced through risk-stratified treatment recommendations.

FUNDING

This work was supported by the Scottish Chief Scientist's Office (Ref: 16-26) and the Charon Fund (no grant number).

DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

All data used in the production of this manuscript are available through application to Public Health Scotland subject to approval by the Scottish Public Benefit and Privacy Panel.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. *Lancet*. 2012;379(9814):432-444.
2. Gondos A, Bray F, Brewster DH, et al. Recent trends in cancer survival across Europe between 2000 and 2004: a model-based period analysis from 12 cancer registries. *Eur J Cancer*. 2008;44(10):1463-1475.
3. (SIGN) SIGN. *SIGN 134: Treatment of Primary Breast Cancer;* 2013.
4. Denduluri N, Chavez-MacGregor M, Telli ML, et al. Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2018;36(23):2433-2443.
5. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30(8):1194-1220.
6. Burstein HJ, Curigliano G, Loibl S, et al. Estimating the benefits of therapy for early-stage breast cancer: The St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol*. 2019;30(10):1541-1557.
7. Information Services Division — NHS Scotland. *Breast Cancer Quality Performance Indicators, Patients Diagnosed between January 2015 and December 2017;* 2019.
8. Corallo AN, Croxford R, Goodman DC, Bryan EL, Srivastava D, Stukel TA. A systematic review of medical practice variation in OECD countries. *Health Policy*. 2014;114(1):5-14.
9. Research Data Scotland. Available at https://www.researchdata.scot/. Accessed December 20, 2020.
10. Information Services Division — NHS Scotland. Resource Allocation Formula. Available at https://www.isdscotland.org/Health-Topics/Finance/Resource-Allocation-Formula/. Accessed February 25, 2020.
11. Candido Dos Reis FJ, Wishart GC, Dicks EM, et al. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. *Breast Cancer Res*. 2017;19(1):58.
12. Jones A, Rice N, Bago d'Uva T, Balia S. *Applied Health Economics*. London, UK: Routledge; 2007.
13. Gray E, Marti J, Brewster DH, Wyatt JC, Piaget-Rossel R, Hall PS. Real-world evidence was feasible for estimating effectiveness of chemotherapy in breast cancer: a cohort study. *J Clin Epidemiol*. 2019;109:125-132.
14. Gray E, Marti J, Brewster DH, Wyatt JC, Hall PS. Independent validation of the PREDICT breast cancer prognosis prediction tool in 45,789 patients using Scottish Cancer Registry data. *Br J Cancer*. 2018;119(7):808-814.
15. NHS Scotland. *The Charter of Patient Rights and Responsibilities;* 2019.
16. Predict Breast Cancer. Available at https://breast.predict.nhs.uk/tool. Accessed December 20, 2020.
17. Down SK, Lucas O, Benson JR, Wishart GC. Effect of PREDICT on chemotherapy/trastuzumab recommendations in HER2-positive patients with early-stage breast cancer. *Oncol Lett*. 2014;8(6):2757-2761.
18. Stein RC, Dunn JA, Bartlett JMS, et al. OPTIMA prelim: a randomised feasibility study of personalised care in the treatment of women with early breast cancer. *Health Technol Assess*. 2016;20:xxiii-xxix. 1-201.