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Title: Adjuvant chemotherapy for breast cancer in older women: An analysis of retrospective English Cancer Registration Data

Running Title: Adjuvant chemotherapy for breast cancer in older women

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Abstract.

Background: Adjuvant chemotherapy is recommended as a treatment for women with high recurrence risk early breast cancer. Older women are less likely to receive chemotherapy than younger women. This study has investigated the impact of chemotherapy on breast cancer specific survival in women aged 70+ using English Registry data.

Methods: Cancer registration data were obtained from two English regions from 2002 to 2012 (*n*=29,728). The impact of patient level characteristics on the probability of receiving adjuvant chemotherapy was explored using logistic regression. Survival modelling was undertaken to show the effect of chemotherapy and age/health status on breast cancer specific survival. Missing data was handled using multiple imputation.

Results: 11,735 surgically treated early breast cancer patients were identified. Use of adjuvant chemotherapy has increased over time. Younger age at diagnosis, increased nodal involvement, tumour size and grade, oestrogen receptor negative or HER2 positive disease were all associated with increased probability of receiving chemotherapy. Chemotherapy was associated with a significant reduction in the hazard of breast cancer specific mortality in women with high recurrence risk cancer, after adjusting for patient level characteristics (Hazard Ratio 0.74, 95% CI 0.67-0.81).

Discussion: Chemotherapy is associated with an improved breast cancer specific survival in older women with high recurrence risk early breast cancer. Lower rates of chemotherapy use in older women may, therefore, contribute to inferior cancer outcomes. Decisions on potential benefits for individual patients should be made on the basis of life expectancy, treatment tolerance and patient preference.

Keywords: Adjuvant chemotherapy, breast cancer, survival, older women, high risk

Introduction

Breast cancer is the most commonly diagnosed cancer in the UK. Incidence rates increase with age with over 30% of cases diagnosed in women over 70[1] [2] . This proportion will increase as population life expectancy improves.

Older cancer patients in the UK experience inferior access to cancer services and treatments compared with younger patients[3-5]. Audits of routinely collected cancer registry data(3) and cohort studies have shown lower rates of chemotherapy for older women compared with younger women with breast cancer in the UK and US and wide regional variation in these rates[3,6,7,8,9]. The difference in chemotherapy rates by age has been maintained over time. In 2006 16% of women over the age of 70 received chemotherapy compared with 38% aged 50-70[10]. Between 2014 and 2016 rates for women with ER – disease were 23% for those aged 70+ years compared with 61% for 50–69 years [3]. Furthermore, UK relative survival in older women with breast cancer is worse compared with many other developed nations including Belgium, Poland, Ireland and the Netherlands[11,12]. There is a clear need for research to elucidate how treatment decisions are made for older UK patients and how current practice is contributing to inferior outcomes.

Adjuvant chemotherapy is usually recommended for high recurrence risk early breast cancer patients. This usually includes patients with adverse tumour biology (oestrogen receptor (ER) negative, human epidermal growth factor receptor 2 (HER2) positive, high grade, high risk genomic array scores) and more advanced stage, according to complex algorithms. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG)[13] reported that surgery with adjuvant poly-chemotherapy was associated with a reduced risk of recurrence (12%) and death (13%) in patients aged 70+, compared with surgery without adjuvant chemotherapy. However, uncertainty in these estimates was large due to the small number of older breast cancer patients recruited in the trials and unplanned subgroup analyses are prone to bias.

There are several reasons why older women may not receive chemotherapy: They are more likely to have chronic co-morbidities and/or frailty, which can reduce their tolerance and resilience to treatment. For some, it may be judged that survival benefits from chemotherapy are small in comparison to potential side effects if life expectancy is compromised[14,15]. Older women are more likely to have ER positive disease which is[16, 17] associated with improved prognosis and treatable with adjuvant endocrine therapy.

The rates and severity of adverse effects from chemotherapy are higher in older women. In one analysis of women >70 receiving chemotherapy, the rate of febrile neutropenia was 19% and the treatment discontinuation rate was 23%. This was higher than observed in clinical trials where rates for age 65+ have been reported in the range 4% to 9% and rates for <60 at 2.5% [18]. Febrile neutropenia is a life-threatening toxicity in all patients, but particularly older patients where co-morbidities may further compromise outcomes. Adjuvant trastuzumab improves outcomes in HER2+ breast cancer[19] but is associated with cardiac toxicity. This risk, particularly when given alongside anthracycline-based chemotherapy, appears particularly pronounced in older women[20].Therefore, any decision to offer adjuvant chemotherapy to older women must consider not just the benefits in terms of disease recurrence, but immediate and long-term risks of toxicity.

Formulation of evidence-based chemotherapy guidelines for early breast cancer in older women requires evaluation of current routine practice and outcomes. This study consists of a retrospective analysis of routinely collected patient level data for breast cancer patients aged 70+ from two English cancer registry regions, diagnosed between 2002 and 2012. The analysis consists of two parts. Firstly, associations between patient level factors and the decision to offer adjuvant chemotherapy are analysed using descriptive and statistical methods. Trends in chemotherapy use over this period are also reported. Secondly, a

survival analysis describes how breast-cancer specific survival differs between patients treated with and without chemotherapy.

Methods

Cancer registration records were acquired for all new breast cancer diagnoses in women aged 70+ between 2002-12 within two English registration regions (West Midlands and Northern & Yorkshire), covering approximately 25% of the UK population. This cohort is broadly representative of the overall UK demography. Patients under the age of 70 at diagnosis were excluded from analysis, as were women who had no surgery (i.e. those who were treated with primary endocrine therapy. 49 patients (0.4% of those analysed) with a history of breast cancer prior to their index diagnosis were included. Variables in the dataset included age and date at diagnosis, screening or symptomatic presentation, tumour characteristics (size, nodal staging, grade, ER, HER2 and progesterone receptor (PR) status), and information on treatment episodes (date and type of treatment). Comorbidity was derived from linked Hospital Episode Statistics (HES) records as described elsewhere[21] and aggregated into a proxy for the Charlson Comorbidity Index (CCI). Income domain data from the Office for National Statistics (ONS) Indices of Multiple Deprivation were also analysed. English indices of deprivation (2010) were derived from linked postcodes. Dates and causes of death were linked from ONS death certification data. Deaths coded as other than “breast cancer” were treated as non-breast cancer deaths.

Analyses were restricted to women diagnosed with stage I-III disease, treated with surgery to the primary tumour within 6 months of diagnosis. Patients with missing stage were included given that surgery would unlikely be offered if metastases were detectable at diagnosis. Individuals were categorised as receiving “adjuvant chemotherapy” (“CT”) or “no chemotherapy” (“No CT”) according to whether they had a treatment episode including chemotherapy within 6 months of surgery, although in some cases the chemotherapy may

have been neoadjuvant. No subgroup analysis was performed regarding whether neoadjuvant or adjuvant chemotherapy was given on the basis that RCT evidence indicates that there is no survival difference between these two pathways[22]. Some analyses were restricted to patients at high risk of recurrence, based on criteria adopted from the AChEW study (at least one of the following; the primary tumour is ER-, is HER2+, is grade III, or there is nodal involvement in at least 4 regional lymph nodes) [6]. Each patient was also given a risk category score in the range 1-4, being the number of these risk indicators present for the patient.

To investigate temporal trends, the chemotherapy rate was plotted against diagnosis year for patients aged 70-79. Associations between patient and disease characteristics were assessed using logistic regressions. Survival models were estimated for breast cancer specific survival (BCSS). Patients were censored at the date of death from other causes. Patients alive on 17/01/17 had survival time censored at this date. Survival outcomes for patients treated with and without chemotherapy were compared using cumulative incidence plots. A more nuanced understanding of survival was obtained by plotting survival curves for patients with increasing levels of risk category score (as defined above).

Associations between patients, treatment characteristics and survival were investigated using multivariate proportional hazard regression, using Royston-Parmar restricted cubic spline parametric models [23]. The Royston-Parmar model is more flexible than the Cox Proportional Hazards model, relaxing the proportional hazards assumption for some variables by allowing the effect of that covariate to vary over time. It also specifies a flexible functional form for the underlying hazard, making it easier to extrapolate to predictions of future outcomes. (Additional details in supplementary materials, Figure S1). On the basis of exploratory analysis the effect of age at diagnosis was modelled as time varying and the others covariates were modelled as time invariant.

Some patients have incomplete data. It was known that some of the parameters which had high levels of missing data (for example, tumour grade, tumour size, nodal status) were more likely to be missing for patients who received PET and therefore had not had surgery. To mitigate against bias and the reduction in precision associated with deletion of incomplete cases, multiple imputation with chained equations (MICE) was used to produce 25 complete replications of the dataset. All logistic regression and survival models were applied to each of these datasets and the results were then combined to derive the final model [24]. Variables with over 50% missing data were excluded from the analysis. Supplementary material, Tables S1 and S2 give further details of the data pre-processing and multiple imputation processes.

Royston-Parmar models were estimated in Stata [25] using the package sptm2[23]. All other analyses were carried out using the statistical software package R (version 3.3.2)[26]. The user-contributed packages "mice" [27], "survival" [28]) and "ggplot2" [29] were used to implement the MICE algorithm, survival analyses and plots respectively.

RESULTS

Between 2002-12, 29,728 women were diagnosed with breast cancer and of these 11,735 were identified with stage I-III (or unknown) disease, treated with surgery within 6 months of diagnosis and included in this analysis (Figure 1). Patients receiving chemotherapy tended to be younger, with fewer comorbidities and had higher recurrence risk disease. Very few patients aged 80+ received chemotherapy, precluding meaningful analysis for this age group (*N*=122, <1%) (Figure 2); subsequent analyses were restricted to patients aged 70-79 at diagnosis. Table 1 shows patient characteristics for those aged 70 to 79, split by treatment.

There was evidence of increasing use of chemotherapy over time for the entire cohort and for those categorised as high risk (Figure 3). The logistic regression results are shown in

Table 2. Younger age at diagnosis (Odds ratio (OR) 0.76 per year >70, 95%CI 0.74-0.79), increased nodal involvement (OR 1-3 nodes 3.74, 3.12-4.48; 4+ nodes 7.21, 5.97-8.72), tumour size (OR 1.015 per mm, 1.011-1.019) and grade (OR Grade 2: 2.68, 1.74-4.13, Grade 3: 6.33, 4.11-9.75), or having HER2+ disease (OR 2.90, 2.48-3.41) were all associated with increased probability of receiving chemotherapy. Having ER+ disease (OR 0.31, 0.26-0,36) was associated with a lower probability of receiving chemotherapy.

Naive comparison of survival outcomes between the two treatment groups showed that BCSS and short term OS were worse for patients who received chemotherapy (Results not shown). However, this arises from the difference in risk profiles between the two treatment groups (Figures 4 and 5). Figure 4 shows the profile of high risk members of the treatment and non-treatment groups when they were also given a score based on the number of high risk indicators they had (one each for ER-, HER2+, grade 3, and 4 or more nodes involved). The majority of no-chemotherapy patients have only one risk indicator, whilst the majority of patients receiving chemotherapy have two or more. Patients receiving CT tended to have a higher risk score than those not treated. Figure 5 shows BCSS by risk group. When all patients with at least one high risk indicator were considered, chemotherapy was still associated with reduced BCSS. However, the two groups of patients (chemotherapy and no chemotherapy) may still have had markedly different characteristics which may have influenced their prognosis. When the analysis was repeated with only higher risk scoring patients (2+), the positive effect of chemotherapy becomes clear, even when allowing for the uncertainty caused by comparing fewer patients.

The more sophisticated analysis undertaken using the Royston-Parmar model, which takes account of the differing patient level characteristics between the chemotherapy and no chemotherapy treatment groups, shows that chemotherapy is associated with a significant

reduction in the hazard of breast cancer specific mortality (Hazard ratio 0.74, 95% CI 0,67-0.81, Table 3).

DISCUSSION

This study found that chemotherapy was associated with a reduction in breast cancer specific mortality for patients aged 70-79 treated surgically for breast cancer in two English regions, after adjustment for patient level characteristics. Current UK guidance states that chemotherapy should be considered for all women with disease characteristics indicating a high risk of recurrence[30].This is particularly relevant for patients with ER poor tumours, who cannot benefit from endocrine therapies. The results of this study suggest that this guidance remains appropriate for an older population.

These data suggest an increase in the use of chemotherapy in patients aged 70-79 since 2002. Furthermore, disease characteristics associated with a high risk of recurrence are positively associated with receipt of chemotherapy. However, many patients for whom CT would be indicated still did not receive it, in particular, patients aged 80+. This may be justifiable given that older patients are more likely to die of other causes than of breast cancer, so gains in survival may be small in absolute terms and the risk of adverse events will be higher. On the one hand, if the reduction in breast cancer mortality observed for those aged 70-79 years is maintained in older patients, then an otherwise healthy 80 year old would still be expected to benefit from chemotherapy. On the other hand, the risks of chemotherapy related morbidity and mortality will be higher and may outweigh any benefit.

Research into the impact of chemotherapy on survival outcomes for older patients is limited as clinical trials typically exclude this group. Our findings are largely consistent with the EBCTCG meta-analyses [31], which demonstrated clear evidence of a benefit for patients receiving chemotherapy aged 50 to 69 at diagnosis, especially those with ER-poor tumours. However insufficient women aged 70+ were included in to draw conclusions about the

benefits of chemotherapy in this population. A review of trials by Muss and colleagues [32] found similar reductions in breast cancer mortality for chemotherapy in younger and older patients with lymph-node positive cancer, but of 6487 patients only 159 (2%) were aged 70+. A retrospective analysis of the US Surveillance, Epidemiology, and End Results Program (SEER) database [33] of 41,390 women aged 65+ demonstrated a significant survival benefit for chemotherapy in patients with ER-poor tumours and positive lymph nodes, but not in other groups. This is consistent with the findings of the current study, although not directly comparable because the age range is lower (>65 rather than >70 years) and the present analysis has used a different approach to looking at recurrence risk markers.

A recent observational study [6] of the treatment decisions made by 24 UK NHS multidisciplinary teams (MDT) (*N*=803 patients) reported that the most commonly stated reasons for not offering chemotherapy were that "other treatments were more appropriate" (63%) and/or "perceived benefits too small" (54%), with co-morbidities (29%) and frailty (22%) also frequently cited, with considerable variation in decision making between practices. This suggests that some patients are probably under- or over-treated, highlighting the need for improved chemotherapy guidance in this age group.

The analysis in the current study includes women aged 70+ who received surgery for early breast cancer from a region containing roughly 25% of the UK population. It includes recipients of adjuvant and neo-adjuvant chemotherapy but excludes recipients of primary endocrine therapy and neo-adjuvant endocrine therapy. This inclusion of the majority of cases of operable breast cancer is a key strength of the study and mitigates against biases associated with exclusion criteria in many randomised controlled trials, typically excluding older women and those with comorbidities. However, observational datasets may suffer from bias in treatment estimates due to differences in patient characteristics not captured by the multivariate model. This includes treatment selection based on disease severity. The data show that patients with more advanced disease and more aggressive tumours are more

likely to receive chemotherapy. However, if any prognostic variables not in the dataset were used to determine treatment such as clinician and patient preference then this could bias the results, in either direction. Additional selection biases may arise from heterogeneity in health status of the cohort. The only data available on underlying health status other than age is comorbidity, scored using the HES-derived CCI and on cognitive function. These are likely to correlate with treatment choice and survival outcomes. However, this bias, if present, might be expected to impact on OS rather than BCSS. Further limitations include the lack of data on the chemotherapy regimens used, the dosage received or whether patients received a full course of chemotherapy. In addition, other outcomes, such as adverse events were not considered.

Treatment selection may reflect the preference of the patient and/or the clinician. Interest has increased in the role of shared decision making in health care, defined as: 'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences" [34]. The potential survival gains associated with CT have to be weighed against potential adverse events of treatment, which may reduce both life expectancy and quality of life. The relative importance attached to different outcomes will vary by patient; patients should be assisted to make informed decisions and supported in the deliberation of their options.

CONCLUSION

This study demonstrates that the use of chemotherapy in two English regions increased between 2002 and 2012 in patients aged 70-79. Although patients with high risk disease were more likely to receive chemotherapy, age remained a key determinant of treatment, once other factors were accounted for. The evidence suggests that adjuvant chemotherapy is associated with a reduction in the hazard of death from breast cancer, but it is not possible

to determine the effect treatment has on overall life expectancy without additional information on the underlying health status of the patient. Nevertheless, these data suggest that for older patients at high risk of recurrence, chemotherapy may improve survival. Decisions on potential benefit for individual patients should be made on the basis of predicted life expectancy, treatment tolerance and patient preference.

Supplementary information is available

on the Clinical Oncology website.

Acknowledgements

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Figure legends

Figure 1: Consort diagram of patients included in the analysis

Figure 2: Treatment received by age at diagnosis for patients with stage I,II,III or unknown stage.

Figure 3: Patients aged 70-79 treated surgically who received adjuvant chemotherapy, by year of diagnosis. Left: Total number of patients and number classified as high risk according to the ACHEW criteria by year. The mean proportion (across years) of patients who are high risk is 45% (s.d. 2%). Right: Proportion of patients. Shaded areas represent 95% confidence intervals.

Figure 4: Risk Category distribution by Treatment group. High risk patients were given a risk score according to how many of the risk indicators applied to them. This figure shows the distribution of the resulting risk scores for the high risk members of the two treatment groups.

Figure 5: Kaplan Meier Curves for Breast Cancer Specific Survival by Risk Score. Even when considering only high risk patients, a naive KM analysis shows that patients who received chemotherapy tended to have worse survival than those who did not. However, by limiting analysis to higher risk patients only (Risk score of 2 or more), the true benefit of chemotherapy is revealed. Shaded areas represent 95% confidence intervals.

Figure S1: Example of a restricted cubic spline function with 5 knots. The initial and final component functions are constrained to be linear with the remaining 4 being cubic. Further constraints are imposed to ensure that the composite function is smooth at the knots.

Figure S2: Time varying hazard ratio for age at diagnosis (per year over 70) as identified in the Royston-Parmar Model.

ADDITIONAL INFORMATION

Consent for Publication

Not applicable,

Availability of data and materials

The Cancer Registry data is confidential and therefore not available, Further details of methods are available on request from the authors.

Disclosure

The authors declare no conflict of interest.

Authorship

Conception and design : LW, SW, PR , KC and MR. Interpretation of data: JB, SW, PR , GH. Data analysis :SW, GH and PR. Interpretation of results and drafting of manuscript: LW, AR, SW, GH and JM. Reading, commenting on and approving the final manuscript: all authors

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Figure 1 : Consort Diagram of Patients included in the Analysis

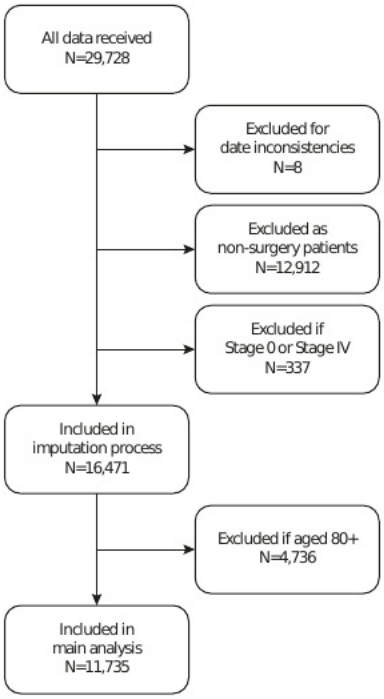
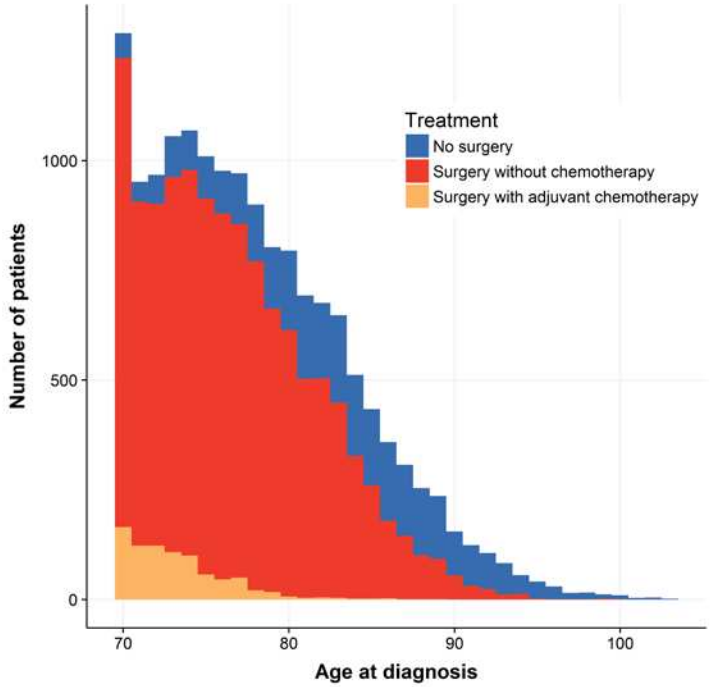


Figure 2: Treatment received by age at diagnosis for patients with stage I –III or unknown stage.



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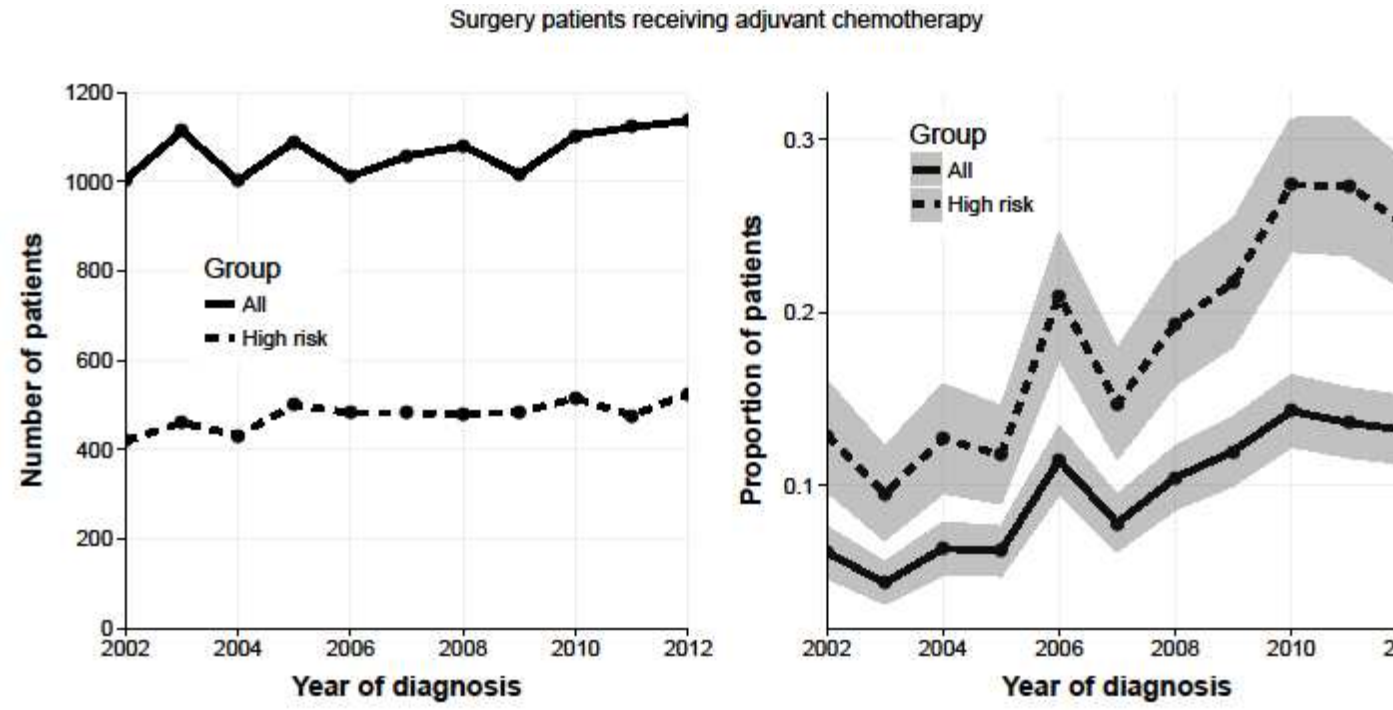

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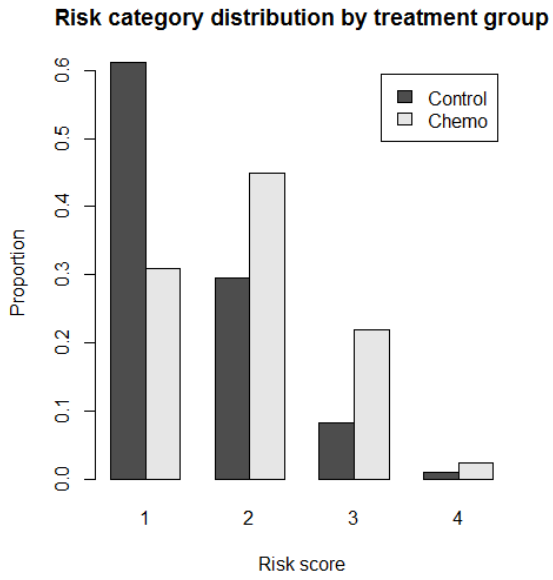

two treatment groups.

Figure 5: Kaplan Meier Curves for Breast Cancer Specific Survival by Risk Score. Even when considering only high risk patients, a naive KM analysis shows that patients who received chemotherapy tended to have worse survival than those who did not. However, by limiting analysis to higher risk patients only (Risk score of 2 or more), the true benefit of chemotherapy is revealed. Shaded areas represent 95% confidence intervals.

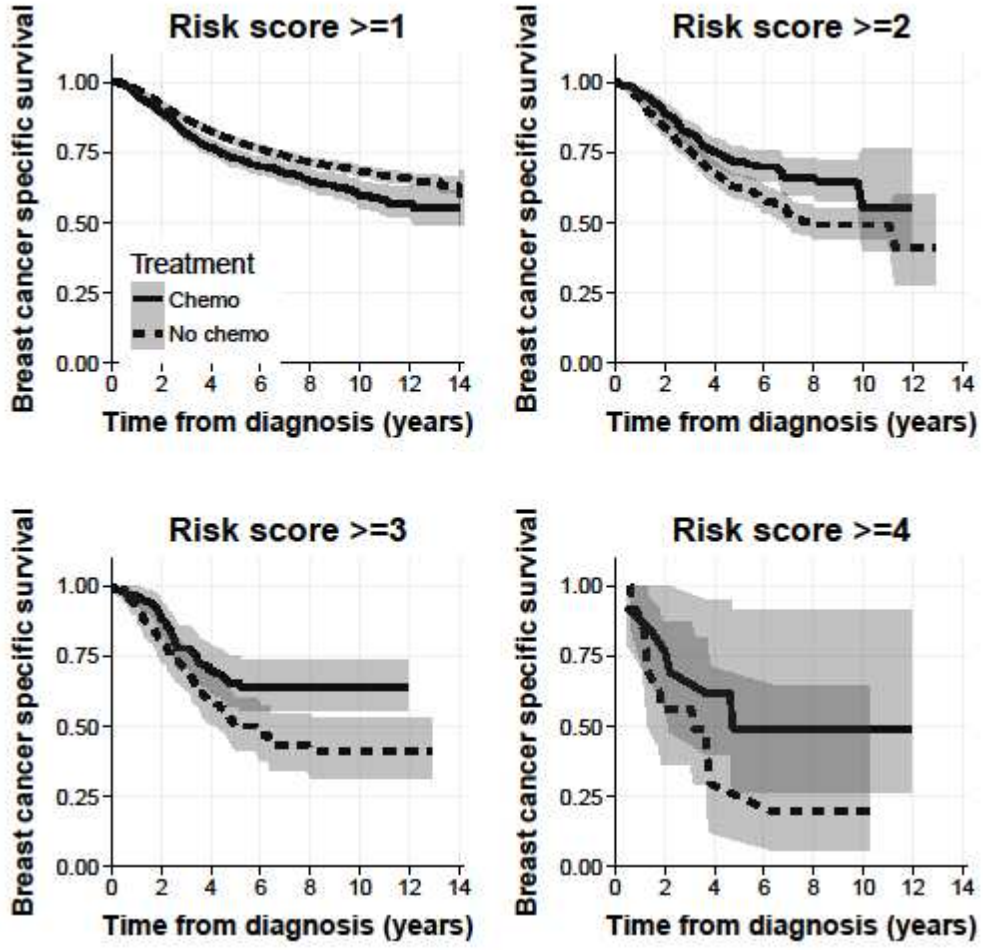

Table 1: Patient characteristics for patients with stage I –III or unknown stage, aged 70 to 79 years.
Columns show number (percent) of patients.

		Chemotherapy	No chemotherapy	Total
		1138 (100)	10597 (100)	11735 (100)
Age at Diagnosis	70 - 74	869 (76.4)	5556 (52.4)	6425 (54.8)
	75 - 79	269 (23.6)	5041 (47.6)	5310 (45.2)
Deprivation	1 (least deprived)	250 (22.0)	2013 (19.0)	2263 (19.3)
quintile	2	258 (22.7)	2318 (21.9)	2576 (22.0)
	3	205 (18.0)	2107 (19.9)	2312 (19.7)
	4	200 (17.6)	2062 (19.5)	2262 (19.3)
	5	225 (19.8)	2097 (19.8)	2322 (19.8)
Detection	Screened	149 (13.1)	1558 (14.7)	1707 (14.5)
	Symptomatic	989 (86.9)	9039 (85.3)	10028 (85.5)
ER*	N	602 (52.9)	1975 (18.6)	2577 (22.0)
	P	536 (47.1)	8622 (81.4)	9158 (78.0)
HER2	N	403 (35.4)	3709 (35.0)	4112 (35.0)
	P	238 (20.9)	436 (4.1)	674 (5.7)
	Missing / unknown	497 (43.7)	6452 (60.9)	6949 (59.2)
Tumour size (mm)	size < 10	19 (1.7)	941 (8.9)	960 (8.2)
	10≤size<20	198 (17.4)	3487 (32.9)	3685 (31.4)
	20≤size<50	658 (57.8)	4836 (45.6)	5494 (46.8)

	size ≥ 50	168 (14.8)	524 (4.9)	692 (5.9)
	Missing / unknown	95 (8.3)	809 (7.6)	904 (7.7)
Grade	1	24 (2.1)	1734 (16.4)	1758 (15.0)
	2	345 (30.3)	5527 (52.2)	5872 (50.0)
	3	750 (65.9)	2961 (27.9)	3711 (31.6)
	Missing / unknown	19 (1.7)	375 (3.5)	394 (3.4)
Nodes positive	0	259 (22.8)	4751 (44.8)	5010 (42.7)
	1 to 3	269 (23.6)	1562 (14.7)	1831 (15.6)
	4 or more	339 (29.8)	723 (6.8)	1062 (9.0)
	Node positive, number unknown	179 (15.7)	1055 (10.0)	1234 (10.5)
	Missing / unknown	92 (8.1)	2506 (23.6)	2598 (22.1)
Comorbidity Score	0	1042 (91.6)	9204 (86.9)	10246 (87.3)
(HES-derived CCI)	1	52 (4.6)	673 (6.4)	725 (6.2)
	2	33 (2.9)	302 (2.8)	335 (2.9)
	3	2 (0.2)	82 (0.8)	84 (0.7)
	4	1 (0.1)	23 (0.2)	24 (0.2)
	5	8 (0.7)	5 (0.0)	5 (0.0)
	6	0 (0)	4 (0.0)	4 (0.0)

* ER values were missing for some patients but it was assumed that hormone therapy was given if and only if ER was positive.

Table 2: Multivariable logistic regression of the odds of receiving adjuvant chemotherapy by individual characteristics (patients aged 70-79 only). Odds ratio > 1 indicates increased odds of receiving chemotherapy.

Variable		Odds ratio (CT vs no CT)	95% Confidence Interval	*P* value
Age at Diagnosis	per year over 70	0.763	(0.741, 0.787)	< 0.001
Deprivation quintile	1 (lowest)	ref	ref	ref
	2	0.845	(0.678, 1.053)	0.137
	3	0.731	(0.580, 0.923)	0.008
	4	0.694	(0.550, 0.877)	0.002
	5	0.656	(0.522, 0.825)	< 0.001
Detection Method	Symptomatic	ref	ref	ref
	Screening	1.177	(0.938, 1.477)	0.158
ER	Pos vs Neg	0.305	(0.261, 0.357)	< 0.001
HER2	Pos vs Neg	2.904	(2.476, 3.406)	< 0.001
Grade	1	ref	ref	ref
	2	2.680	(1.740, 4.128)	< 0.001
	3	6.334	(4.113, 9.754)	< 0.001
Nodes positive	0	ref	ref	ref
	1-3	3.739	(3.120, 4.483)	< 0.001
	4+	7.212	(5.966, 8.719)	<0.001

Tumour size	per mm increase in diameter	1.015	(1.011, 1.019)	<0.001

Table 3: Royston Parmar restricted cubic spline model of chemotherapy and other characteristics on the hazard of breast cancer mortality (patients aged 70-79 only).

Variable		Hazard Ratio (Breast cancer mortality)	95% Confidence Interval	*P* value
Chemotherapy	No	ref	ref	Ref
	Yes	0.737	(0.669 0.811)	<0.001
Diagnosis year	Per year after 2002	0.987	(0.973, 1.000)	0.819
Deprivation quintile	1 (lowest)	ref	ref	Ref
	2	0.979	(0.871, 1.101)	1.221
	3	1.136	(1.012, 1.276)	0.0306
	4	1.092	(0.970, 1.228)	0.145
	5	1.278	(1.141, 1.431)	<0.001
Detection Method	Symptomatic	ref	ref	Ref
	Screening	0.506	(0.438, 0.585)	<0.001
ER	Positive vs Negative	0.558	(0.514, 0.607)	<0.001
HER2	Positive vs Negative	1.037	(0.884, 1.217)	0.668
Grade	1	ref	ref	Ref
	2	1.787	(1.498, 2.131)	<0.001

	3	3.687	(3.118, 4.361)	<0.001
Nodes positive	0	ref	ref	Ref
	1-3	1.992	(1.817, 2.184)	<0.001
	4+	4.858	(4.427 : 5.330)	<0.001
Tumour size	per mm increase in diameter	1.015	(1.013, 1.017)	<0.001
Comorbidity	Per Charlson point	1.150	(1.086, 1.219)	<0.001