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Title page

Predictors of early death in female breast cancer patients in the UK: a cohort study.

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Abstract

Objectives: To identify factors predicting early death in women with breast cancer. **Design:** Cohort study. **Setting:** 29 trusts across six cancer networks in the North Thames area. **Participants:** 15,037 women with primary breast cancer diagnosed between January 1996 and December 2005. **Methods:** Logistic regression analyses to determine predictors of early death and factors associated with lack of surgical treatment. **Main exposures:** Age at diagnosis, mode of presentation, ethnicity, disease severity, comorbidities, treatment and period of diagnosis in relation to the Cancer Plan. **Main outcome measures:** Death from any cause within one year of diagnosis, and receipt of surgical treatment. **Results:** By 31st December 2006 4,765 women had died, 980 in the year after diagnosis. Older age and disease severity independently predicted early death. Women over 80 were more likely to die early than women under 50 (OR 8.05, 95% CI 5.96 to 10.88). Presence of distant metastases on diagnosis increased the odds of early death more than eight-fold (OR 8.41, 95% CI 6.49 to 10.89). Two or more recorded comorbidities were associated with a nearly four-fold increase. There was a significant decrease in odds associated with surgery (OR 0.29, 95% CI 0.24 to 0.35). Independently of disease severity and comorbidities, women over 70 were less likely than those under 50 to be treated surgically and this was even more pronounced in those aged over 80 (OR 0.09, 95% CI 0.07 to 0.10). Other factors independently associated with a reduced likelihood of surgery included a non-screening presentation, non-white ethnicity and additional comorbidities. **Conclusions:** These findings may partially explain the survival discrepancies between the UK and other European countries in female breast cancer patients. The study identifies a group of women with a particularly poor prognosis for whom interventions aiming at early detection may be targeted.

ARTICLE FOCUS

- Several studies have shown that the UK has lower survival for breast cancer than some other European countries with a similar expenditure on health care.
- Differences have been shown to occur mainly in older patients and in the first year after diagnosis.
- Several reasons/explanations have been proposed.

KEY MESSAGES

- This study shows that breast cancer patients dying in the first year after diagnosis are more likely to be older, have more advanced disease and existing comorbidities.
- Surgical treatment and (to a lesser extent) radiotherapy and tamoxifen usage were associated with a reduced risk of early death.
- The likelihood of receiving surgery was inversely related to age, independently of comorbidity and disease severity.
- These findings suggest that early detection, management of comorbidities and optimization of treatment of older patients are important target areas to improve outcomes.

STRENGTHS AND LIMITATIONS

- This is a large cohort of women diagnosed with breast cancer and the results may be generalisable to women treated for breast cancer in the UK during the same time period.
- Many variables that may be related to both risk factors and outcomes have not been assessed in this study. However, their correlation with death within a year would have to be very strong to explain the strong associations seen in our data.

Introduction

Despite the decline in breast cancer mortality rates seen in the UK since the late 1980s, survival rates are still substantially lower than in many other European countries.[1;2] It has been difficult to pinpoint the reasons for these differences. Beral and Peto [3] have suggested that they may be due to bias relating to artefacts in cancer registration rather than to genuine differences in diagnosis and management of breast cancer. However, a recent study by Møller et al [4] has shown that such effects are unlikely to make a significant contribution to observed differences in survival. The effects of incomplete ascertainment and registration from death certificates only on survival comparisons based on cancer registry data have been investigated in detail by Robinson et al.[5]

One important observation in some studies remains unexplained, namely that of poorer survival in UK patients soon after their diagnosis. Sant et al [6] demonstrated a higher risk of death in women with breast cancer in the UK in the first six months after diagnosis than in other European countries. This was particularly pronounced for the youngest (under 29 years) and oldest (over 80 years) age groups. Six months from diagnosis, survival patterns in the UK became more similar to those in the other European countries. Further analysis of the survival differential has revealed that disparities between the UK and northern European countries (Sweden and Norway) occur mainly for older women in the first year after diagnosis.[7] Eighty-one percent of the excess UK deaths occur within two years of diagnosis.

The aim of this study was to investigate factors associated with early mortality (within one year following diagnosis) in a sample of UK women diagnosed with breast cancer during 1996-2005. Since surgical intervention with a curative intent is strongly related to reduced mortality, a secondary aim of the study was to identify the patient characteristics most often associated with the failure to use this treatment option.

Subjects and methods

We conducted a cohort study using data from the North Thames Prospective Audit of Breast Cancer, set up in 1996 by Health Authorities in the North Thames area to monitor the implementation of the Calman-Hine recommendations in 29 trusts in six participating cancer networks: North London, North East London, West London, South West London, Mount Vernon and Mid-Anglia. Providers submitted detailed demographic, diagnostic and treatment data for all new primary cases of malignant female breast cancer diagnosed between January 1996 and December 2005. The number of participating trusts varied from year to year, with a maximum of 26 trusts submitting partial or complete datasets in 2000 and a minimum of seven trusts submitting data in 2005.

Women were followed from their date of entry into the audit to death or censoring at 31st December 2006, an average of 5.6 years. Date of death was confirmed through linking patients to the NHS Central Register using the NHS Strategic Tracing Service (NSTS) or matching with records in the Thames Cancer Registry (TCR). For those who were neither traced nor matched, date of death was taken from the breast audit database, if it was recorded. Women who were either traced or matched but who had no date of death in any of the three databases were assumed to be alive at 31st December 2006. Women who could not be traced in the NHS Central Register or matched to the TCR database and who had no date of death recorded in the audit database were excluded from analyses, as we could not be sure of their vital status. The study also excluded women with *in situ* breast cancer without any invasive component at diagnosis. After these exclusions, a total of 15,037 women were available for analysis.

Data on different treatment modes (surgery, radiotherapy, chemotherapy and tamoxifen) were taken from the Audit database, augmented by information from the TCR database where possible. Cases were matched to Hospital Episode Statistics (HES) data using name, NHS number, date of birth, and date of diagnosis within 90 days of that recorded in the audit database in order to obtain further information on receipt of surgery. Women with a C50 diagnosis (breast cancer) and a B or T8 code in the HES surgery field were regarded as having had surgery. Only 98 cases were re-coded on this basis, illustrating the completeness of the audit database in this respect.

Cause of death was available from the TCR database for 85% of the women who died during the study period. A categorical variable accounting for calendar period of diagnosis was included to adjust for diagnosis and treatment in relation to the implementation of the Cancer Plan. As per the methodology of Rachet et al [8], the following periods were considered: before 27/09/2000 (when the plan was published); 28/09/2000-31/12/2003 (initialization period); after 01/01/2004 (implementation). Patient age was categorized as: <50 years, 50 to 59 years, 60 to 69 years, 70 to 79 years and 80 years and over. Pathological tumour size was assigned to one of five groups: <10mm, 10 to 19mm, 20 to 39mm, 40 to 49mm and 50mm and over. Information on existing comorbidities was obtained from the matched HES dataset. This information was then summarised using the Charlson Comorbidity Index (0, 1 or 2+).[9]

Clinical, demographic, pathological and treatment-related factors were compared between women who died from any cause within one year of their diagnosis and those who survived beyond this year. Univariate analyses were performed using chi^2 tests and unadjusted (bivariate) logistic regression models. A multivariate logistic regression model investigated the independent contribution of all covariates. This model included surgery but not collinear covariates, i.e. variables that were only known for patients who had surgery, namely tumour size and node status.

The regression models assessed the effects of age, ethnicity, mode of presentation (screening, symptoms or incidental), distant metastases at diagnosis, comorbidities, period of diagnosis and treatments (surgery, radiotherapy, tamoxifen and chemotherapy) on early death from any cause. The results are presented as odds ratios (ORs), both unadjusted (univariate) and fully adjusted (multivariate), with 95% confidence intervals (CIs).

Additional logistic regression models were used to determine which factors were associated with use of surgery. All analyses were conducted using STATA 10.

Results

The study population consisted of 15,037 women of whom 4,456 (30%) were over 70 years old at the time of their diagnosis. The majority of women (78%) presented symptomatically, and 82% of those with known ethnicity were recorded as white. Over a mean follow up of 5.6 years there were 4,765 deaths. Table 1 shows the underlying cause of death in these women. 980 women (6.5% of the total) died within a year of their diagnosis, and of these 464 women were known to have died from breast cancer. Amongst those for whom the cause of death was known, there was no significant difference in the proportions dying from different causes between those who died within or after the first year since diagnosis (chi^2 = 10.6; 9 df; p = 0.30). However, significantly more of the women who died early had an unrecorded cause of death (26% versus 12%).

Table 2 describes the characteristics of women who survived one year beyond diagnosis and those who did not, and Table 3 shows the results of the logistic regression analyses. In univariate analyses (chi^2 values in Table 2 and unadjusted odds ratios in Table 3), older age (>60 years), white ethnicity, distant metastases at diagnosis, positive nodes and larger tumours (>20mm) were all significantly linked with death within one year of diagnosis (p<0.001 for all chi^2 tests). Comorbidities on diagnosis were also associated with an increased likelihood of early death (Charlson Index ≥ 2: OR 5.55, 95% CI 4.56 to 6.76). Women presenting because of symptoms (OR 7.91, 95% CI 5.21 to 12.01) or whose cancer was discovered incidentally (OR 11.98, 95% CI 7.37 to 19.48) were significantly more likely to die early, compared to those whose cancer was identified through screening.

Surgical treatment was associated with highly significantly reduced odds of early death from any cause (OR 0.12, 95% CI 0.11 to 0.14), as was treatment with chemotherapy (OR 0.60, 95% CI 0.51 to 0.71) and radiotherapy (OR 0.27, 95% CI 0.23 to 0.32). There was no significant association between tamoxifen usage and early death (OR 0.94, 95% CI 0.79 to 1.12). The time period in which women were diagnosed (before, during or after implementation of the Cancer Plan) was not significantly associated with death within a year of diagnosis in univariate models (chi^2 = 3.54; p = 0.17).

The results of the multivariate logistic regression analysis to assess the factors independently associated with early death are shown as the adjusted odds ratios in Table 3. This model excluded tumour size and nodal status, which are only known in women who received surgical treatment. There was a clear and independent association between increasing age and the risk of early death, with an eight-fold increase in the odds of early death in women aged 80 or more compared to those aged < 50 at diagnosis (OR: 8.05, 95% CI 5.96 to 10.88). In this adjusted analysis, white ethnicity was not independently associated with early death. The significant associations noted in the univariate analyses were upheld (though generally attenuated) in the multivariate model, except for chemotherapy. Women receiving chemotherapy were more likely than those not treated with chemotherapy to die within a year of their diagnosis (OR 1.49, 95% CI 1.19 to 1.86). Surgery was associated with a reduced risk of early death (OR 0.29, 95% CI 0.24 to 0.35), as was radiotherapy (OR 0.61, 95% CI 0.51 to 0.74) and also tamoxifen (OR 0.64, 95% CI 0.51 to 0.80). Women who were most recently diagnosed with breast cancer (post-2003) were less likely to die early (OR 0.71, 95% CI 0.52 to 0.98). Women with missing data for ethnicity, presentation or metastases were at increased risk of early death compared to the reference categories.

Overall, 13.3% of women did not have surgery as part of their treatment (Table 2), and this proportion was significantly greater in women who died within a year of diagnosis (50% vs. 11%). The characteristics of women who did or did not receive surgical treatment are shown in Table 4. Those receiving surgery were significantly younger, and were more likely to present via screening, to be free of metastases at diagnosis and to have fewer comorbidities. For those of known ethnicity, there was no difference in the proportions receiving surgery between white and non-white women. However, the proportion of cases with unknown ethnicity was significantly greater in those not receiving surgery (38.7% versus 23.8%).

In multivariate analysis (Table 5), mode of presentation, older age (particularly > 80 years), distant metastases on presentation and comorbidities were independent predictors of no surgical treatment (70-79 years old versus < 50 years old: OR 0.27, 95% CI 0.23 to 0.33; > 80 years old versus < 50 years old: OR 0.09, 95% CI 0.07 to 0.10; symptomatic presentation versus screening: OR 0.34, 95% CI 0.26 to 0.45; incidental presentation versus screening: OR 0.28, 95% CI 0.20 to 0.40; distant metastases on diagnosis: OR 0.16, 95% CI 0.12 to 0.20; severe comorbidities: OR 0.50, 95% CI 0.41 to 0.62). White ethnicity was independently linked with an increased likelihood of surgical treatment compared to non-white ethnicity (OR 1.39, 95% CI 1.16 to 1.65).

Discussion

This study in more than 15,000 women diagnosed with breast cancer in the North Thames area found that age and disease severity at diagnosis were independent predictors of early death from any cause. In the women analysed here, distant metastases on diagnosis were a strong predictor of early death, increasing the odds of dying within a year of diagnosis more than eight-fold (OR 8.41, 95% CI 6.49 to 10.89). This effect was independent of age, comorbidities and treatment. Surgery was strongly associated with a reduced risk of early death, and older patients were less likely to receive surgery.

Radiotherapy and tamoxifen treatments were independently associated with reduced likelihood of early death, while chemotherapy was associated with increased odds of dying within a year of diagnosis (OR 1.49, 95% 1.19 to 1.86). This relationship with chemotherapy is likely to be a reflection of selection bias, whereby only the most severe cases are given this form of treatment. A similar bias, but in the opposite direction, may apply to surgery – i.e. with very ill patients selectively not being operated upon. However, the association between surgery and death within one year remained apparent in a model correcting for age and co-morbidity. These findings are consistent with those in a recent study by Brewster et al[10] that found age, deprivation, emergency admission, tumour stage and grade and absence of treatment were independent factors associated with death within 30 days of diagnosis.

Poorer prognosis of older women with breast cancer has been attributed variously to treatment received,[11-18] more severe disease on presentation[14;19-22] and to the presence of comorbidities.[11] Stage was identified as the most important factor explaining breast cancer survival discrepancies between European countries for women diagnosed between 1990 and 1992,[20] particularly in older age groups.

Patient comorbidity has been shown to be a potentially important confounder in studies of treatment received,[16;23] but our analyses suggest that older women are less likely to receive surgery even after adjusting for comorbidities. A recent report from the National Cancer Intelligence Network based on data from 2007 confirms a high proportion of older women in the UK do not receive surgical treatment: 61% of women aged over 80 did not have surgery.[24] This group is likely to have a particularly poor prognosis. Nearly 40% of women who died early in our study were aged over 80 years and 66% (252/383) of them had not had surgery.

Age was strongly inversely associated with the likelihood of receiving surgery. This reflects the well described pattern in other studies that older women are less likely to receive treatment than younger women.[11;25] Women over 80 years old attending breast units in Manchester in 2002, for example, were less likely to have surgery than women aged 65 to 79 years even after adjusting for poorer general health, including comorbidities.[12]

Great improvements in cancer services have been made during the past decade. To investigate whether the implementation of the Cancer Plan has had any observable effect on survival, this research included a categorical variable controlling for calendar period of diagnosis in the multivariate analyses. This method was similar to that employed by Rachet et al [8] in their assessment of the NHS Cancer Plan for England. In our study, women diagnosed after 2003 had reduced odds of early death compared to women diagnosed before the Cancer Plan was published (OR 0.71, 95% CI 0.52 to 0.98). This is suggestive of a survival benefit resulting from changes to cancer services after 2000.

While women of white ethnicity were at greater odds of early death in univariate analyses, this association was no longer significant when the model was adjusted for the other covariates. The white women were in general older than the non-white women, and this may explain these findings. However, in the adjusted analysis, white women were more likely to be treated surgically than those belonging to non-white ethnic groups.

Our results may be generalisable to women treated for breast cancer in the UK during the same time period. Five-year relative survival of this sample (based on life tables for London during the period 1996-2001) was 84.1%. This compares well with recent estimates from the Office for National Statistics,[26] which reports a value of 82% for women diagnosed between 2000 and 2006.

We suspect a complex relationship between the exposures studied here, some of which may be on the same causal pathway for early death. For example, high age and comorbidity may be rational and adequate reasons for not offering surgery. While a number of patient and treatment characteristics were strongly and independently linked with early death, these associations must be interpreted with caution and with a consideration for unmeasured confounding factors. For instance, the selection of a patient's treatment will depend on a number of factors, including some not measured here such as their own preferences or established practices within the organisation in which they are treated.[27] Furthermore, their presentation to health services depends, among other factors, on access to treatment and knowledge of cancer symptoms. Many of these variables may be linked to both risk factors and outcomes and they have not been assessed in this study. However, for any underlying confounder to explain the strong statistical associations seen in our data, they would need to have a very strong correlation with death within a year of diagnosis.

Another potential limitation of this study is missing information. Women with missing data on ethnicity, presentation and distant metastases were more likely to die within a year of their diagnosis and were less likely to receive surgical treatment. They may represent women who were seriously ill at diagnosis and who were not scheduled for surgery. An analysis of the characteristics of patients with several missing data elements suggests that these women tend to be older, have more severe disease (as determined by a proxy of tumour size) and are more likely to die early. A failure to record important details relating to their diagnosis and treatment may be a reflection of the care they receive. With respect to this study, if women with missing information have worse disease and are generally older, then the estimates of association between these variables and early death will be biased towards underestimates of the true effects.

Retrospective analyses rely on records in which some information may be inaccurate. In this study a particular effort was made to ensure that the surgical status of women was recorded correctly as this was considered an important marker of the quality of treatment and was expected to be strongly associated with outcome. Time and resource constraints precluded this additional effort being extended to other variables to verify database entries. However, an earlier study looking at trends in the treatment of breast cancer,[28] concluded that the audit database was a reasonably reliable source of such data.

The effects of deprivation on disease severity and ultimately on mortality were not explored in this study. Such analyses rely on potential patient identifiers such as postcode data that were not available to us. Deprivation has been linked to poorer patient outcomes for UK breast cancer patients in several studies [10;29-31] and stated aims of the Cancer Plan and the Cancer Reform Strategy [32-34] are to tackle the inequalities in cancer survival between different socioeconomic groups in England.

Conclusions

Our findings offer more detailed insights into the determinants of death in the first year after a diagnosis of breast cancer, a period shown to be important in international comparisons. As expected, early death is linked to older age and to the presence of comorbidities. Comorbidities can be addressed in the long run through general health policy, but two other determinants of early death identified by this study are potential avenues for intervention.

Firstly, the findings relating to disease severity lend empirical support to the notion that late diagnosis is a major determinant of early death. This supports the rationale for projects that focus on increasing awareness of breast symptoms and the importance of screening. Secondly, surgery is independently associated with a large reduction in the risk of early death, and older women were – independently of disease severity and comorbidity - much less likely to receive surgery. Assuming surgery is an indicator of attempts at curative treatment, there may be benefits of increased treatment activity for older women.

Table 1: Cause of death in women with breast cancer, by length of survival

Cause of death	Survival <1 year from diagnosis	Survival >1 year from diagnosis	Total
	Number (%)	Number (%)	Number (%)
Breast cancer	464 (63.9)	2,015 (60.5)	2,479 (61.1)
Lung cancer	4 (0.6)	38 (1.1)	42 (1.0)
Colorectal cancer	3 (0.4)	32 (1.0)	35 (0.9)
Other/Unspecified cancer	39 (5.4)	232 (7.0)	271 (6.7)
Ischaemic Heart Disease	34 (4.7)	137 (4.1)	171 (4.2)
Stroke	14 (1.9)	79 (2.4)	93 (2.3)
Other Cardiovascular Disease	43 (5.9)	204 (6.1)	247 (6.1)
Senility	16 (2.2)	92 (2.8)	108 (2.7)
Pneumonia	38 (5.2)	205 (6.2)	243 (6.0)
All other causes	71 (9.8)	294 (8.8)	365 (9.0)
Total with known cause of death	726 (100.0)	3328 (100.0)	4054 (100.0)
Cause of death not known	254 (25.9)	457 (12.1)	711 (14.9)
Total cases	980	3,785	4,765

Table 2: Characteristics of participants who did or did not survive first year after diagnosis

Patient characteristics	Survival <1 year from diagnosis Number (%)	Survival >1 year from diagnosis Number (%)	P-value*
Age at diagnosis (years)			
<50	88 (9.0)	3,712 (26.4)	
50-59	91 (9.3)	3,648 (26.0)	
60-69	148 (15.1)	2,894 (20.6)	
70-79	270 (27.6)	2,373 (16.9)	
>80	383 (39.1)	1,430 (10.2)	< 0.001
Ethnicity			
Non-white	75 (7.7)	1,983 (14.1)	
White	488 (49.8)	8,610 (61.3)	
Not known	417 (42.6)	3,464 (24.6)	< 0.001
Presentation			
Screening	23 (2.3)	2,274 (16.2)	
Symptoms	763 (77.9)	9,531 (67.8)	
Incidental	64 (6.5)	528 (3.8)	
Not known	130 (13.3)	1,724 (12.3)	< 0.001
Distant metastases at diagnosis			
No	312 (31.8)	7,977 (56.7)	
Yes	156 (15.9)	271 (1.9)	
Not known	512 (52.2)	5,809 (41.3)	< 0.001
Tumour size (mm)			
<10	12 (1.2)	1,220 (8.7)	
10-19	73 (7.4)	4,016 (28.6)	
20-39	83 (8.5)	3,103 (22.1)	
40-49	86 (8.8)	1,953 (13.9)	
≥50	99 (10.1)	799 (5.7)	
Not known	627 (64.0)	2,966 (21.1)	< 0.001
Node status			
Negative	95 (9.7)	5,492 (39.1)	
Positive	167 (17.0)	4,213 (30.0)	
Not known	718 (73.3)	4,352 (31.0)	< 0.001
Surgery			
No	489 (49.9)	1,513 (10.8)	
Yes	491 (50.1)	12,544 (89.2)	< 0.001
Radiotherapy			
No	454 (46.3)	3,395 (24.2)	
Yes	256 (26.1)	7,079 (50.4)	
Not known	270 (27.6)	3,583 (25.5)	< 0.001
Chemotherapy			
No	520 (53.1)	6,482 (46.1)	
Yes	203 (20.7)	4,200 (29.9)	
Not known	257 (26.2)	3,375 (24.0)	< 0.001

Tamoxifen			
No	172 (17.6)	2,321 (16.5)	
Yes	601 (61.3)	8,630 (61.4)	
Not known	207 (21.1)	3,106 (22.1)	0.49
Charlson index (comorbidities)			
0 (minor)	203 (20.7)	6,755 (48.1)	
1 (moderate)	48 (4.9)	359 (2.6)	
≥ 2 (severe)	231 (23.6)	1,384 (9.8)	
Not known	498 (50.8)	5,559 (39.5)	< 0.001
Cancer plan (diagnosis date)			
pre 2000	624 (63.7)	9,057 (64.4)	
2000 to 2003	292 (29.8)	3,897 (27.7)	
post 2003	64 (6.5)	1,103 (7.8)	0.79
Total cases	980	14,057	

* P-value for comparison of proportions, excluding 'not known' category where present. For age, tumour size, Charlson index and cancer plan test is for trend; for all other factors test is for heterogeneity.

Table 3: Crude and adjusted odds ratios and 95% confidence intervals for early death from any cause

Factor		Number of cases	Early deaths Number (%)	Odds Ratios			
				Unadjusted		Adjusted	
				Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval
Age at diagnosis (years)	< 50	3,800	88 (2.3)	1.00	-	1.00	-
	50 - 59	3,739	91 (2.4)	1.05	0.78 - 1.42	1.41	1.03 - 1.93
	60 - 69	3,042	148 (4.9)	2.16	1.65 - 2.82	2.61	1.94 - 3.50
	70 - 79	2,643	270 (10.2)	4.80	3.75 - 6.14	4.62	3.45 - 6.18
	80 +	1,813	383 (21.1)	11.30	8.89 - 14.36	8.05	5.96 - 10.88
Ethnicity	Non-white	2,058	75 (3.6)	1.00	-	1.00	-
	White	9,098	488 (5.4)	1.50	1.17 - 1.92	1.25	0.96 - 1.63
	Not known	3,881	417 (10.7)	3.18	2.47 - 4.09	2.24	1.70 - 2.94
Presentation	Screening	2,297	23 (1.0)	1.00	-	1.00	-
	Symptoms	10,294	763 (7.4)	7.91	5.21 - 12.01	3.31	2.13 - 5.14
	Incidental	592	64 (10.8)	11.98	7.37 - 19.48	3.92	2.30 - 6.66
	Not known	1,854	130 (7.0)	7.46	4.76 - 11.67	2.77	1.72 - 4.48
Distant metastases at diagnosis	No	8,289	312 (3.8)	1.00	-	1.00	-
	Yes	427	156 (36.5)	14.72	11.73 - 18.47	8.41	6.49 - 10.89
	Not known	6,321	512 (8.1)	2.25	1.95 - 2.60	1.35	1.13 - 1.60
Tumour size (mm)	< 10	1.232	12 (1.0)	1.00	-	-	-
	10-19	4,089	73 (1.8)	1.85	1.00 - 3.41	-	-
	20 - 39	3,186	83 (2.6)	2.72	1.48 - 5.00	-	-
	40 - 49	2,039	86 (4.2)	4.48	2.44 - 8.22	-	-
	50 +	898	99 (11.0)	12.60	6.87 - 23.08	-	-
	Not known	3,593	627 (17.4)	21.49	12.09 - 38.20	-	-
Node status	Negative	5,587	95 (1.7)	1.00	-	-	-

	Positive	4,380	167 (3.8)	2.29	1.78 - 2.96	-	-
	Not known	5,070	718 (14.2)	9.54	7.67 - 11.86	-	-
Surgery	No	2,002	489 (24.4)	1.00	-	1.00	-
	Yes	13,035	491 (3.8)	0.12	0.11 - 0.14	0.29	0.24 - 0.35
Radiotherapy	No	3,849	454 (11.8)	1.00	-	1.00	-
	Yes	7,335	256 (3.5)	0.27	0.23 - 0.32	0.61	0.51 - 0.74
	Not known	3,853	270 (7.0)	0.56	0.48 - 0.66	0.65	0.48 - 0.87
Chemotherapy	No	7,002	520 (7.4)	1.00	-	1.00	-
	Yes	4,403	203 (4.6)	0.60	0.51 - 0.71	1.49	1.19 - 1.86
	Not known	3,632	257 (7.1)	0.95	0.81 - 1.11	1.20	0.89 - 1.62
Tamoxifen	No	2,493	172 (6.9)	1.00	-	1.00	-
	Yes	9,231	601 (6.5)	0.94	0.79 - 1.12	0.64	0.51 - 0.80
	Not known	3,313	207 (6.2)	0.90	0.73 - 1.11	0.93	0.70 - 1.24
Charlson Index (comorbidities)	0 (minor)	6,958	203 (2.9)	1.00	-	1.00	-
	1 (moderate)	407	48 (11.8)	4.45	3.19 - 6.20	2.54	1.77 - 3.65
	2+ (severe)	1,615	231 (14.3)	5.55	4.56 - 6.76	3.55	2.85 - 4.42
	Not known	6,057	498 (8.2)	2.98	2.52 - 3.52	1.10	0.90 - 1.34
Cancer Plan (diagnosis date)	pre 2000	9,681	624 (6.4)	1.00	-	1.00	-
	2000 - 2003	4,189	292 (7.0)	1.09	0.94 - 1.26	0.90	0.75 - 1.07
	post 2003	1,167	64 (5.5)	0.84	0.65 - 1.10	0.71	0.52 - 0.98

Table 4: Characteristics of women who did or did not have surgery

Patient characteristics	Surgery: No Number (%)	Surgery: Yes Number (%)	P-value*
Age at diagnosis (years)			
<50	213 (10.6)	3,587 (27.5)	
50-59	182 (9.1)	3,557 (27.3)	
60-69	219 (10.9)	2,823 (21.7)	
70-79	526 (26.3)	2,117 (16.2)	
>80	862 (43.1)	951 (7.3)	< 0.001
Ethnicity			
Non-white	238 (11.9)	1,820 (14.0)	
White	989 (49.4)	8,109 (62.2)	
Not known	775 (38.7)	3,106 (23.8)	0.36[a]
Presentation			
Screening	61 (3.0)	2,236 (17.2)	
Symptoms	1,527 (76.3)	8,767 (67.3)	
Incidental	117 (5.8)	475 (3.6)	
Not known	297 (14.8)	1,557 (11.9)	< 0.001
Distant metastases at diagnosis			
No	680 (34.0)	7,609 (58.4)	
Yes	151 (7.5)	276 (2.1)	
Not known	1,171 (58.5)	5,150 (39.5)	< 0.001
Radiotherapy			
No	1,014 (50.6)	2,835 (21.7)	
Yes	339 (16.9)	6,996 (53.7)	
Not known	649 (32.4)	3,204 (24.6)	< 0.001
Chemotherapy			
No	1,107 (55.3)	5,895 (45.2)	
Yes	311 (15.5)	4,092 (31.3)	
Not known	584 (29.2)	3,048 (23.4)	< 0.001
Tamoxifen			
No	260 (13.0)	2,233 (17.1)	
Yes	1,315 (65.7)	7,916 (60.7)	
Not known	427 (21.3)	2,886 (22.1)	< 0.001
Charlson index (comorbidities)			
0	309 (15.4)	6,649 (51.0)	
1	47 (2.3)	360 (2.8)	
≥ 2	181 (9.0)	1,434 (11.0)	
Not known	1,465 (73.2)	4,592 (35.2)	< 0.001
Cancer plan (diagnosis date)			
pre 2000	1336 (66.7)	8345 (64.0)	
2000 to 2003	522 (26.1)	3667 (28.1)	
post 2003	144 (7.2)	1023 (7.8)	0.025
Total cases	2,002	13,035	

* P-value for comparison of proportions, excluding 'not known' category where present. For age, Charlson index and cancer plan test is for trend; for all other factors test is for heterogeneity.

[a] P-value when 'not known' category is included: < 0.001

Table 5: Crude and adjusted odds ratios and 95% confidence intervals for surgical treatment

Factor		Number of cases	Surgical cases Number (%)	Odds Ratios Unadjusted Odds Ratio	Unadjusted Confidence Interval	Adjusted Odds Ratio	Adjusted Confidence Interval
Age at diagnosis (years)	< 50	3,800	3,587 (94.4)	1.00	-	1.00	-
	50 - 59	3,739	3,557 (95.1)	1.16	0.95 - 1.42	0.99	0.80 - 1.22
	60 - 69	3,042	2,823 (92.8)	0.77	0.63 - 0.93	0.73	0.59 - 0.89
	70 - 79	2,643	2,117 (80.1)	0.24	0.20 - 0.28	0.27	0.23 - 0.33
	80 +	1,813	951 (52.5)	0.07	0.06 - 0.08	0.09	0.07 - 0.10
Ethnicity	Non-white	2,058	1,820 (88.4)	1.00	-	1.00	-
	White	9,098	8,109 (89.1)	1.07	0.92 - 1.25	1.39	1.16 - 1.65
	Not known	3,881	3,106 (80.0)	0.52	0.45 - 0.61	0.93	0.77 - 1.11
Presentation	Screening	2,297	2,236 (97.3)	1.00	-	1.00	-
	Symptoms	10,294	8,767 (85.2)	0.16	0.12 - 0.20	0.34	0.26 - 0.45
	Incidental	592	475 (80.2)	0.11	0.08 - 0.15	0.28	0.20 - 0.40
	Not known	1,854	1,557 (84.0)	0.14	0.11 - 0.19	0.39	0.29 - 0.53
Distant metastases at diagnosis	No	8,289	7,609 (91.8)	1.00	-	1.00	-
	Yes	427	276 (64.6)	0.16	0.13 - 0.20	0.16	0.12 - 0.20
	Not known	6,321	5150 (81.5)	0.39	0.36 - 0.43	0.36	0.31 - 0.40
Charlson Index (comorbidities)	0 (minor)	6,958	6,649 (95.6)	1.00	-	1.00	-
	1 (moderate)	407	360 (88.5)	0.36	0.26 - 0.49	0.70	0.49 - 0.99
	2+ (severe)	1,615	1,434 (88.8)	0.37	0.30 - 0.45	0.50	0.41 - 0.62
	Not known	6,057	4,592 (75.8)	0.15	0.13 - 0.17	0.20	0.17 - 0.23
Cancer Plan (diagnosis date)	pre 2000	9,681	8,345 (86.2)	1.00	-	1.00	-
	2000 - 2003	4,189	3,667 (87.5)	1.12	1.01 - 1.25	1.11	0.97 - 1.27
	post 2003	1,167	1,023 (87.7)	1.14	0.95 - 1.37	0.75	0.60 - 0.94

Contributorship Statement

DR, LH and CS designed the study. DR, DT and CS collated and analysed the data. CS wrote the first draft and DR, HM and LH finalised the manuscript. All authors contributed to the interpretation of the data, and reviewed and revised the manuscript, and have read and approved the final draft. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data sharing

No additional data available.

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Title page

Predictors of early death in female breast cancer patients in the UK: a cohort study.

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Abstract

Objectives: To identify factors predicting early death in women with breast cancer. **Design:** Cohort study. **Setting:** 29 trusts across seven cancer networks in the North Thames area. **Participants:** 15,037 women with primary breast cancer diagnosed between January 1996 and December 2005. **Methods:** Logistic regression analyses to determine predictors of early death and factors associated with lack of surgical treatment. **Main exposures:** Age at diagnosis, mode of presentation, ethnicity, disease severity, comorbidities, treatment and period of diagnosis in relation to the Cancer Plan. **Main outcome measures:** Death from any cause within one year of diagnosis, and receipt of surgical treatment. **Results:** By 31st December 2006 4,765 women had died, 980 in the year after diagnosis. Older age and disease severity independently predicted early death. Women over 80 were more likely to die early than women under 50 (OR 8.05, 95% CI 5.96 to 10.88). Presence of distant metastases on diagnosis increased the odds of early death more than eight-fold (OR 8.41, 95% CI 6.49 to 10.89). Two or more recorded comorbidities were associated with a nearly four-fold increase. There was a significant decrease in odds associated with surgery (OR 0.29, 95% CI 0.24 to 0.35). Independently of disease severity and comorbidities, women over 70 were less likely than those under 50 to be treated surgically and this was even more pronounced in those aged over 80 (OR 0.09, 95% CI 0.07 to 0.10). Other factors independently associated with a reduced likelihood of surgery included a non-screening presentation, non-white ethnicity and additional comorbidities. **Conclusions:** These findings may partially explain the survival discrepancies between the UK and other European countries in female breast cancer patients. The study identifies a group of women with a particularly poor prognosis for whom interventions aiming at early detection may be targeted.

ARTICLE FOCUS

- Several studies have shown that the UK has lower survival for breast cancer than some other European countries with a similar expenditure on health care.
- Differences have been shown to occur mainly in older patients and in the first year after diagnosis.
- Several reasons/explanations have been proposed.

KEY MESSAGES

- This study shows that breast cancer patients dying in the first year after diagnosis are more likely to be older, have more advanced disease and existing comorbidities.
- Surgical treatment and (to a lesser extent) radiotherapy and tamoxifen usage were associated with a reduced risk of early death.
- The likelihood of receiving surgery was inversely related to age, independently of comorbidity and disease severity.
- These findings suggest that early detection, management of comorbidities and optimization of treatment of older patients are important target areas to improve outcomes.

STRENGTHS AND LIMITATIONS

- This is a large cohort of women diagnosed with breast cancer and the results may be generalisable to women treated for breast cancer in the UK during the same time period.
- Many variables that may be related to both risk factors and outcomes have not been assessed in this study. However, their correlation with death within a year would have to be very strong to explain the strong associations seen in our data.

Introduction

Despite the decline in breast cancer mortality rates seen in the UK since the late 1980s, survival rates are still substantially lower than in many other European countries.[1;2] It has been difficult to pinpoint the reasons for these differences. One important observation in some studies remains unexplained, namely that of poorer survival in UK patients soon after their diagnosis. Sant et al[3] demonstrated a higher risk of death in women with breast cancer in the UK in the first six months after diagnosis than in other European countries. This was particularly pronounced for the youngest (under 29 years) and oldest (over 80 years) age groups. Six months from diagnosis, survival patterns in the UK became more similar to those in the other European countries. Further analysis of the survival differential has revealed that disparities between the UK and northern European countries (Sweden and Norway) occur mainly for older women in the first year after diagnosis.[4] Eighty-one percent of the excess UK deaths occur within two years of diagnosis.

Beral and Peto [5] have suggested that observed differences in survival may be due to bias relating to artefacts in cancer registration rather than to genuine differences in diagnosis and management of breast cancer. However, a recent study by Møller et al [6] has shown that such effects are unlikely to make a significant contribution to observed differences in survival. The effects of incomplete ascertainment and registration from death certificates only on survival comparisons based on cancer registry data have been investigated in detail by Robinson et al.[7]

The aim of this study was to investigate factors associated with early mortality (within one year following diagnosis) in a sample of UK women diagnosed with breast cancer during 1996-2005. Since surgical intervention with a curative intent is strongly related to reduced mortality, a secondary aim of the study was to identify the patient characteristics most often associated with the failure to use this treatment option.

Subjects and methods

We conducted a cohort study using data from the North Thames Prospective Audit of Breast Cancer, set up in 1996 by Health Authorities in the North Thames area to monitor the implementation of the Calman-Hine recommendations in 29 trusts in seven participating cancer networks: North London, North East London, West London, South West London (Royal Marsden Hospital, Brompton Road), Mount Vernon, Mid-Anglia and South Essex. The audit used a common dataset and a standard proforma across the providers to collect detailed demographic, diagnostic and treatment data for all new primary cases of malignant female breast cancer diagnosed between January 1996 and December 2005. Trained data collectors used either Thames Cancer Registry (TCR) Access-based software or the British Association of Surgical Oncology (BASO) software for breast audit to record information. The number of participating trusts varied from year to year, with a maximum of 26 trusts submitting partial or complete datasets in 2000 and a minimum of seven trusts submitting data in 2005.

Women were followed from their date of entry into the audit to death or censoring at 31st December 2006, an average of 5.6 years. Date of death was confirmed through linking patients to the NHS Central Register using the NHS Strategic Tracing Service (NSTS) or matching with records in the Thames Cancer Registry (TCR). For those who were neither traced nor matched, date of death was taken from the breast audit database, if it was recorded. Women who were either traced or matched but who had no date of death in any of the three databases were assumed to be alive at 31st December 2006. Women who could not be traced in the NHS Central Register or matched to the TCR database and who had no date of death recorded in the audit database were excluded from analyses, as we could not be sure of their vital status. The study also excluded women with *in situ* breast cancer without any invasive component at diagnosis. After these exclusions, a total of 15,037 women were available for analysis.

Data on different treatment modes (surgery, radiotherapy, chemotherapy and tamoxifen) were taken from the Audit database, augmented by information from the TCR database where possible. Cases were matched to Hospital Episode Statistics (HES) data using name, NHS number, date of birth, and date of diagnosis within 90 days of that recorded in the audit database in order to obtain further information on receipt of surgery. Women with a C50 diagnosis (breast cancer) and a B or T8 code in the HES surgery field were regarded as having had surgery. Only 98 cases were re-coded on this basis, illustrating the completeness of the audit database in this respect.

Cause of death was available from the TCR database for 85% of the women who died during the study period. A categorical variable accounting for calendar period of diagnosis was included to adjust for diagnosis and treatment in relation to the implementation of the Cancer Plan. As per the methodology of Rachet et al [8], the following periods were considered: before 27/09/2000 (when the plan was published); 28/09/2000-31/12/2003 (initialization period); after 01/01/2004 (implementation). Patient age was categorized as: <50 years, 50 to 59 years, 60 to 69 years, 70 to 79 years and 80 years and over. Pathological tumour size was assigned to one of five groups: <10mm, 10 to 19mm, 20 to 39mm, 40 to 49mm and 50mm and over. Information on additional diagnoses was obtained from the matched HES dataset and was used to determine the Charlson Comorbidity Index for matched patients. This is a weighted index based on the number and severity of 17 potential serious comorbid conditions that affect mortality.[9] The index was categorised into the groups 0,1 and 2+.

Clinical, demographic, pathological and treatment-related factors were compared between women who died from any cause within one year of their diagnosis and those who survived beyond this year. All cause mortality, rather than death from breast cancer, was used partly because specific cause of death was not known in 15% of the women, but also because the international study[4] which highlighted the adverse survival in English women in the first year post diagnosis was also based on all cause mortality. An analysis restricted to breast cancer-specific mortality produced broadly similar results.

Univariate analyses were performed using chi^2 tests and unadjusted (bivariate) logistic regression models. A multivariate logistic regression model investigated the independent contribution of all covariates. This model included surgery but not collinear covariates, i.e. variables that were only known for patients who had surgery, namely tumour size and node status.

The regression models assessed the effects of age, ethnicity, mode of presentation (screening, symptoms or incidental), distant metastases at diagnosis, comorbidities, period of diagnosis and treatments (surgery, radiotherapy, tamoxifen and chemotherapy) on early death from any cause. The results are presented as odds ratios (ORs), both unadjusted (univariate) and fully adjusted (multivariate), with 95% confidence intervals (CIs).

Additional logistic regression models were used to determine which factors were associated with use of surgery. All analyses were conducted using STATA 10.

Results

The study population consisted of 15,037 women of whom 4,456 (30%) were over 70 years old at the time of their diagnosis. The majority of women (78%) presented symptomatically, and 82% of those with known ethnicity were recorded as white. Over a mean follow up of 5.6 years there were 4,765 deaths. Table 1 shows the underlying cause of death in these women. 980 women (6.5% of the total cohort and 20.6% of all deaths) died within a year of their diagnosis, and of these 464 women were known to have died from breast cancer. Amongst those for whom the cause of death was known, there was no significant difference in the proportions dying from different causes between those who died within or after the first year since diagnosis (chi^2 = 10.6; 9 df; p = 0.30). However, significantly more of the women who died early had an unrecorded cause of death (26% versus 12%).

Table 2 describes the characteristics of women who survived one year beyond diagnosis and those who did not, and Table 3 shows the results of the logistic regression analyses. In univariate analyses (chi^2 values in Table 2 and unadjusted odds ratios in Table 3), older age (>60 years), white ethnicity, distant metastases at diagnosis, positive nodes and larger tumours (>20mm) were all significantly linked with death within one year of diagnosis (p<0.001 for all chi^2 tests). Comorbidities on diagnosis were also associated with an increased likelihood of early death (Charlson Index ≥ 2: OR 5.55, 95% CI 4.56 to 6.76). Women presenting because of symptoms (OR 7.91, 95% CI 5.21 to 12.01) or whose cancer was discovered incidentally (OR 11.98, 95% CI 7.37 to 19.48) were significantly more likely to die early, compared to those whose cancer was identified through screening. ‘Incidental’ cancers comprised mainly interval cancers and non-symptomatic referrals from any source other than the patient's GP.

Surgical treatment was associated with highly significantly reduced odds of early death from any cause (OR 0.12, 95% CI 0.11 to 0.14), as was treatment with chemotherapy (OR 0.60, 95% CI 0.51 to 0.71) and radiotherapy (OR 0.27, 95% CI 0.23 to 0.32). There was no significant association between tamoxifen usage and early death (OR 0.94, 95% CI 0.79 to 1.12). The time period in which women were diagnosed (before, during or after implementation of the Cancer Plan) was not significantly associated with death within a year of diagnosis in univariate models ($chi^2 = 3.54$; p = 0.17).

The results of the multivariate logistic regression analysis to assess the factors independently associated with early death are shown as the adjusted odds ratios in Table 3. This model excluded tumour size and nodal status, which are only known in women who received surgical treatment. There was a clear and independent association between increasing age and the risk of early death, with an eight-fold increase in the odds of early death in women aged 80 or more compared to those aged < 50 at diagnosis (OR: 8.05, 95% CI 5.96 to 10.88). In this adjusted analysis, white ethnicity was not independently associated with early death. The significant associations noted in the univariate analyses were upheld (though generally attenuated) in the multivariate model, except for chemotherapy. Women receiving chemotherapy were more likely than those not treated with chemotherapy to die within a year of their diagnosis (OR 1.49, 95% CI 1.19 to 1.86). Surgery was associated with a reduced risk of early death (OR 0.29, 95% CI 0.24 to 0.35), as was radiotherapy (OR 0.61, 95% CI 0.51 to 0.74) and also tamoxifen (OR 0.64, 95% CI 0.51 to 0.80). Women who were most recently diagnosed with breast cancer (post-2003) were less likely to die early (OR 0.71, 95% CI 0.52 to 0.98). Women with missing data for ethnicity, presentation or metastases were at increased risk of early death compared to the reference categories.

Overall, 13.3% of women did not have surgery as part of their treatment (Table 2), and this proportion was significantly greater in women who died within a year of diagnosis (50% vs. 11%). The characteristics of women who did or did not receive surgical treatment are shown in Table 4. Those receiving surgery were significantly younger, and were more likely to present via screening, to be free of metastases at diagnosis and to have fewer comorbidities. For those of known ethnicity, there was no difference in the proportions receiving surgery between white and non-white women. However, the proportion of cases with unknown ethnicity was significantly greater in those not receiving surgery (38.7% versus 23.8%).

In multivariate analysis (Table 5), mode of presentation, older age (particularly > 80 years), distant metastases on presentation and comorbidities were independent predictors of no surgical treatment (70-79 years old versus < 50 years old: OR 0.27, 95% CI 0.23 to 0.33; > 80 years old versus < 50 years old: OR 0.09, 95% CI 0.07 to 0.10; symptomatic presentation versus screening: OR 0.34, 95%

CI 0.26 to 0.45; incidental presentation versus screening: OR 0.28, 95% CI 0.20 to 0.40; distant metastases on diagnosis: OR 0.16, 95% CI 0.12 to 0.20; severe comorbidities: OR 0.50, 95% CI 0.41 to 0.62). White ethnicity was independently linked with an increased likelihood of surgical treatment compared to non-white ethnicity (OR 1.39, 95% CI 1.16 to 1.65).

Discussion

Poorer prognosis of older women with breast cancer has been attributed variously to treatment received,[10-17] more severe disease on presentation[13;18-21] and to the presence of comorbidities.[10] Stage was identified as the most important factor explaining breast cancer survival discrepancies between European countries for women diagnosed between 1990 and 1992,[19] particularly in older age groups.

This study in more than 15,000 women diagnosed with breast cancer in the North Thames area found that age and disease severity at diagnosis were independent predictors of early death from any cause. In the women analysed here, distant metastases on diagnosis were a strong predictor of early death, increasing the odds of dying within a year of diagnosis more than eight-fold (OR 8.41, 95% CI 6.49 to 10.89). This effect was independent of age and treatment. It was also independent of patient comorbidities, although this should be interpreted with some caution as comorbidity data were available only for the 60% of participants who could be successfully linked to the HES dataset. Surgery was strongly associated with a reduced risk of early death, and older patients were less likely to receive surgery.

Great improvements in cancer services have been made during the past decade. To investigate whether the implementation of the Cancer Plan has had any observable effect on survival, this research included a categorical variable controlling for calendar period of diagnosis in the multivariate analyses. This method was similar to that employed by Rachet et al [8] in their assessment of the NHS Cancer Plan for England. In our study, women diagnosed after 2003 had reduced odds of early death compared to women diagnosed before the Cancer Plan was published (OR 0.71, 95% CI 0.52 to 0.98). This is suggestive of a survival benefit resulting from changes to cancer services after 2000.

While women of white ethnicity were at greater odds of early death in univariate analyses, this association was no longer significant when the model was adjusted for the other covariates. The white women were in general older than the non-white women, and this may explain these findings. However, in the adjusted analysis, white women were more likely to be treated surgically than those belonging to non-white ethnic groups. These results should perhaps be treated with caution, given the large proportion (26%) of cases for which ethnicity was not known.

Radiotherapy and tamoxifen treatments were independently associated with reduced likelihood of early death, while chemotherapy was associated with increased odds of dying within a year of diagnosis (OR 1.49, 95% 1.19 to 1.86). This relationship with chemotherapy is likely to be a reflection of selection bias, whereby only the most severe cases are given this form of treatment. A similar bias, but in the opposite direction, may apply to surgery – i.e. with very ill patients selectively not being operated upon. However, the association between surgery and death within one year remained apparent in a model correcting for age and co-morbidity. These findings are consistent with those in a recent study by Brewster et al[22] that found age, deprivation, emergency admission, tumour stage and grade and absence of treatment were independent factors associated with death within 30 days of diagnosis.

A recent report from the National Cancer Intelligence Network based on data from 2007 confirms a high proportion of older women in the UK do not receive surgical treatment: 61% of women aged over 80 did not have surgery.[23] This group is likely to have a particularly poor prognosis. Nearly 40% of women who died early in our study were aged over 80 years and 66% (252/383) of them had not had surgery.

In our study, age was strongly inversely associated with the likelihood of receiving surgery. This reflects the well described pattern in other studies that older women are less likely to receive treatment than younger women.[10;24] Women over 80 years old attending breast units in Manchester in 2002, for example, were less likely to have surgery than women aged 65 to 79 years even after adjusting for poorer general health, including comorbidities.[11]

Patient comorbidity has been shown to be a potentially important confounder in studies of treatment received,[15;25] but our analyses suggest that older women are less likely to receive surgery even after adjusting for comorbidities. Comorbidity data were missing for approximately 40% of participants. Patients with missing comorbidity data were less likely to receive surgery although there was no association between these missing data and early death after adjustment for other factors.

One potential limitation of this study is missing information. Women with missing data on ethnicity, presentation and distant metastases were more likely to die within a year of their diagnosis and were less likely to receive surgical treatment. They may represent women who were seriously ill at diagnosis and who were not scheduled for surgery. An analysis of the characteristics of patients with several missing data elements suggests that these women tend to be older, have more severe disease (as determined by a proxy of tumour size) and are more likely to die early. Additionally, a failure to record important details relating to their diagnosis and treatment may be an indication that such patients are receiving worse care. With respect to this study, if women with missing information have worse disease and are generally older, then the estimates of association between these variables and early death will be biased towards underestimates of the true effects.

Retrospective analyses rely on records in which some information may be inaccurate. In this study a particular effort was made to ensure that the surgical status of women was recorded correctly as this was considered an important marker of the quality of treatment and was expected to be strongly associated with outcome. Time and resource constraints precluded this additional effort being extended to other variables to verify database entries. However, an earlier study looking at trends in the treatment of breast cancer,[26] concluded that the audit database was a reasonably reliable source of such data.

The effects of deprivation on disease severity and ultimately on mortality were not explored in this study. Such analyses rely on potential patient identifiers such as postcode data that were not available to us. Deprivation has been linked to poorer patient outcomes for UK breast cancer patients in several studies [22;27-29] and stated aims of the Cancer Plan and the Cancer Reform Strategy [30-32] are to tackle the inequalities in cancer survival between different socioeconomic groups in England.

We suspect a complex relationship between the exposures studied here, some of which may be on the same causal pathway for early death. For example, high age and comorbidity may be rational and adequate reasons for not offering surgery. While a number of patient and treatment characteristics were strongly and independently linked with early death, these associations must be interpreted with caution and with a consideration for unmeasured confounding factors. For instance, the selection of a patient's treatment will depend on a number of factors, including some not measured here such as their own preferences or established practices within the organisation in which they are treated.[33] Furthermore, their presentation to health services depends, among other factors, on access to treatment and knowledge of cancer symptoms. Many of these variables may be linked to both risk factors and outcomes and they have not been assessed in this study. However, for any underlying confounder to explain the strong statistical associations seen in our data, they would need to have a very strong correlation with death within a year of diagnosis.

Five-year relative survival in our sample (based on life tables for London during the period 1996-2001) was 84.1%. This is similar to recent estimates from the Office for National Statistics,[34] which reports a value of 82% for women diagnosed between 2000 and 2006. Thus our cohort sample is likely to be reasonably representative of the UK population of women diagnosed with breast cancer during this period. Table 6 compares the audit data to the total registrations for female breast cancer in the North Thames region at TCR. Mean ages at diagnosis were similar throughout the study period. Likewise, the proportion of patients dying within one year of diagnosis were broadly similar, though slightly lower in the audit database (6.5% vs 7.7% overall.) The proportion of total cases represented in the audit varied between 61% in 1997 and 13% in 2004, with an overall figure of 37%. (The decrease in the number of registered cases in 2005 is an artefact due to changes in the TCR catchment area.) In general, there was a higher representation in the earlier years, which may have implications for the applicability of the results to more recent times.

Conclusions

Our findings offer detailed insights into the determinants of death in the first year after a diagnosis of breast cancer, a period shown to be important in international comparisons. As expected, early death is linked to older age and to the presence of comorbidities. Comorbidities can be addressed in the long run through general health policy, but two other determinants of early death identified by this study are potential avenues for intervention.

Firstly, the findings relating to disease severity lend empirical support to the notion that late diagnosis is a major determinant of early death. This supports the rationale for projects that focus on increasing awareness of breast symptoms and the importance of screening. Secondly, surgery is independently associated with a large reduction in the risk of early death, and older women were – independently of disease severity and comorbidity - much less likely to receive surgery. Assuming surgery is an indicator of attempts at curative treatment, there may be benefits of increased treatment activity for older women.

Table 1: Cause of death in women with breast cancer, by length of survival

Cause of death	Survival		Total
	<1 year from diagnosis	>1 year from diagnosis	
	Number (%)	Number (%)	Number (%)
Breast cancer	464 (63.9)	2,015 (60.5)	2,479 (61.1)
Lung cancer	4 (0.6)	38 (1.1)	42 (1.0)
Colorectal cancer	3 (0.4)	32 (1.0)	35 (0.9)
Other/Unspecified cancer	39 (5.4)	232 (7.0)	271 (6.7)
Ischaemic Heart Disease	34 (4.7)	137 (4.1)	171 (4.2)
Stroke	14 (1.9)	79 (2.4)	93 (2.3)
Other Cardiovascular Disease	43 (5.9)	204 (6.1)	247 (6.1)
Senility	16 (2.2)	92 (2.8)	108 (2.7)
Pneumonia	38 (5.2)	205 (6.2)	243 (6.0)
All other causes	71 (9.8)	294 (8.8)	365 (9.0)
Total with known cause of death	726 (100.0)	3328 (100.0)	4054 (100.0)
Cause of death not known	254 (25.9)	457 (12.1)	711 (14.9)
Total cases	980	3,785	4,765

Table 2: Characteristics of participants who did or did not survive first year after diagnosis

Patient characteristics		**Survival** <1 year from diagnosis Number (%)	>1 year from diagnosis Number (%)	**P-value***
Age at diagnosis (years)				
	<50	88 (9.0)	3,712 (26.4)	
	50-59	91 (9.3)	3,648 (26.0)	
	60-69	148 (15.1)	2,894 (20.6)	
	70-79	270 (27.6)	2,373 (16.9)	
	>80	383 (39.1)	1,430 (10.2)	< 0.001
Ethnicity				
	Non-white	75 (7.7)	1,983 (14.1)	
	White	488 (49.8)	8,610 (61.3)	
	Not known	417 (42.6)	3,464 (24.6)	< 0.001
Distant metastases at diagnosis				
	No	312 (31.8)	7,977 (56.7)	
	Yes	156 (15.9)	271 (1.9)	
	Not known	512 (52.2)	5,809 (41.3)	< 0.001
Tumour size (mm)				
	<10	12 (1.2)	1,220 (8.7)	
	10-19	73 (7.4)	4,016 (28.6)	
	20-39	83 (8.5)	3,103 (22.1)	
	40-49	86 (8.8)	1,953 (13.9)	
	≥50	99 (10.1)	799 (5.7)	
	Not known	627 (64.0)	2,966 (21.1)	< 0.001
Node status				
	Negative	95 (9.7)	5,492 (39.1)	
	Positive	167 (17.0)	4,213 (30.0)	
	Not known	718 (73.3)	4,352 (31.0)	< 0.001
Charlson index (comorbidities)				
	0 (minor)	203 (20.7)	6,755 (48.1)	
	1 (moderate)	48 (4.9)	359 (2.6)	
	≥ 2 (severe)	231 (23.6)	1,384 (9.8)	
	Not known	498 (50.8)	5,559 (39.5)	< 0.001
Diagnosis date (In relation to Cancer Plan)	pre 2000	624 (63.7)	9,057 (64.4)	
	2000 to 2003	292 (29.8)	3,897 (27.7)	
	post 2003	64 (6.5)	1,103 (7.8)	0.79
Presentation				
	Screening	23 (2.3)	2,274 (16.2)	
	Symptoms	763 (77.9)	9,531 (67.8)	
	Incidental	64 (6.5)	528 (3.8)	
	Not known	130 (13.3)	1,724 (12.3)	< 0.001
Surgery				
	No	489 (49.9)	1,513 (10.8)	
	Yes	491 (50.1)	12,544 (89.2)	< 0.001

Radiotherapy			
No	454 (46.3)	3,395 (24.2)	
Yes	256 (26.1)	7,079 (50.4)	
Not known	270 (27.6)	3,583 (25.5)	< 0.001
Chemotherapy			
No	520 (53.1)	6,482 (46.1)	
Yes	203 (20.7)	4,200 (29.9)	
Not known	257 (26.2)	3,375 (24.0)	< 0.001
Tamoxifen			
No	172 (17.6)	2,321 (16.5)	
Yes	601 (61.3)	8,630 (61.4)	
Not known	207 (21.1)	3,106 (22.1)	0.49
Total cases	980	14,057	

* P-value for comparison of proportions, excluding 'not known' category where present. For age, tumour size, Charlson index and cancer plan test is for trend; for all other factors test is for heterogeneity.

Table 3: Crude and adjusted odds ratios and 95% confidence intervals for early death from any cause

Factor		Number of cases	Early deaths Number (%)	Odds Ratios			
				Unadjusted		Adjusted *	
				Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval
Age at diagnosis (years)	< 50	3,800	88 (2.3)	1.00	-	1.00	-
	50 - 59	3,739	91 (2.4)	1.05	0.78 - 1.42	1.41	1.03 - 1.93
	60 - 69	3,042	148 (4.9)	2.16	1.65 - 2.82	2.61	1.94 - 3.50
	70 - 79	2,643	270 (10.2)	4.80	3.75 - 6.14	4.62	3.45 - 6.18
	80 +	1,813	383 (21.1)	11.30	8.89 - 14.36	8.05	5.96 - 10.88
Ethnicity	Non-white	2,058	75 (3.6)	1.00	-	1.00	-
	White	9,098	488 (5.4)	1.50	1.17 - 1.92	1.25	0.96 - 1.63
	Not known	3,881	417 (10.7)	3.18	2.47 - 4.09	2.24	1.70 - 2.94
Distant metastases at diagnosis	No	8,289	312 (3.8)	1.00	-	1.00	-
	Yes	427	156 (36.5)	14.72	11.73 - 18.47	8.41	6.49 - 10.89
	Not known	6,321	512 (8.1)	2.25	1.95 - 2.60	1.35	1.13 - 1.60
Tumour size (mm)	< 10	1.232	12 (1.0)	1.00	-	-	-
	10-19	4,089	73 (1.8)	1.85	1.00 - 3.41	-	-
	20 - 39	3,186	83 (2.6)	2.72	1.48 - 5.00	-	-
	40 - 49	2,039	86 (4.2)	4.48	2.44 - 8.22	-	-
	50 +	898	99 (11.0)	12.60	6.87 - 23.08	-	-
	Not known	3,593	627 (17.4)	21.49	12.09 - 38.20	-	-
Node status	Negative	5,587	95 (1.7)	1.00	-	-	-
	Positive	4,380	167 (3.8)	2.29	1.78 - 2.96	-	-
	Not known	5,070	718 (14.2)	9.54	7.67 - 11.86	-	-
Charlson Index (comorbidities)	0 (minor)	6,958	203 (2.9)	1.00	-	1.00	-
	1 (moderate)	407	48 (11.8)	4.45	3.19 - 6.20	2.54	1.77 - 3.65

	2+ (severe)	1,615	231 (14.3)	5.55	4.56 - 6.76	3.55	2.85 - 4.42
	Not known	6,057	498 (8.2)	2.98	2.52 - 3.52	1.10	0.90 - 1.34
Diagnosis date (In relation to Cancer Plan)	pre 2000	9,681	624 (6.4)	1.00	-	1.00	-
	2000 - 2003	4,189	292 (7.0)	1.09	0.94 - 1.26	0.90	0.75 - 1.07
	post 2003	1,167	64 (5.5)	0.84	0.65 - 1.10	0.71	0.52 - 0.98
Presentation	Screening	2,297	23 (1.0)	1.00	-	1.00	-
	Symptoms	10,294	763 (7.4)	7.91	5.21 - 12.01	3.31	2.13 - 5.14
	Incidental	592	64 (10.8)	11.98	7.37 - 19.48	3.92	2.30 - 6.66
	Not known	1,854	130 (7.0)	7.46	4.76 - 11.67	2.77	1.72 - 4.48
Surgery	No	2,002	489 (24.4)	1.00	-	1.00	-
	Yes	13,035	491 (3.8)	0.12	0.11 - 0.14	0.29	0.24 - 0.35
Radiotherapy	No	3,849	454 (11.8)	1.00	-	1.00	-
	Yes	7,335	256 (3.5)	0.27	0.23 - 0.32	0.61	0.51 - 0.74
	Not known	3,853	270 (7.0)	0.56	0.48 - 0.66	0.65	0.48 - 0.87
Chemotherapy	No	7,002	520 (7.4)	1.00	-	1.00	-
	Yes	4,403	203 (4.6)	0.60	0.51 - 0.71	1.49	1.19 - 1.86
	Not known	3,632	257 (7.1)	0.95	0.81 - 1.11	1.20	0.89 - 1.62
Tamoxifen	No	2,493	172 (6.9)	1.00	-	1.00	-
	Yes	9,231	601 (6.5)	0.94	0.79 - 1.12	0.64	0.51 - 0.80
	Not known	3,313	207 (6.2)	0.90	0.73 - 1.11	0.93	0.70 - 1.24

* Adjusted for all other factors, i.e. based on model which includes all factors

Table 4: Characteristics of women who did or did not have surgery

Patient characteristics		Surgery No Number (%)	Surgery Yes Number (%)	P-value*
Age at diagnosis (years)				
	<50	213 (10.6)	3,587 (27.5)	
	50-59	182 (9.1)	3,557 (27.3)	
	60-69	219 (10.9)	2,823 (21.7)	
	70-79	526 (26.3)	2,117 (16.2)	
	>80	862 (43.1)	951 (7.3)	< 0.001
Ethnicity				
	Non-white	238 (11.9)	1,820 (14.0)	
	White	989 (49.4)	8,109 (62.2)	
	Not known	775 (38.7)	3,106 (23.8)	0.36[a]
Distant metastases at diagnosis				
	No	680 (34.0)	7,609 (58.4)	
	Yes	151 (7.5)	276 (2.1)	
	Not known	1,171 (58.5)	5,150 (39.5)	< 0.001
Charlson index (comorbidities)				
	0	309 (15.4)	6,649 (51.0)	
	1	47 (2.3)	360 (2.8)	
	≥ 2	81 (9.0)	1,434 (11.0)	
	Not known	1,465 (73.2)	4,592 (35.2)	< 0.001
Diagnosis date				
(In relation to Cancer Plan)	pre 2000	1336 (66.7)	8345 (64.0)	
	2000 to 2003	522 (26.1)	3667 (28.1)	
	post 2003	144 (7.2)	1023 (7.8)	0.025
Presentatio				
	Screening	61 (3.0)	2,236 (17.2)	
	Symptoms	1,527 (76.3)	8,767 (67.3)	
	Incidental	117 (5.8)	475 (3.6)	
	Not known	297 (14.8)	1,557 (11.9)	< 0.001
Radiotherapy				
	No	1,014 (50.6)	2,835 (21.7)	
	Yes	339 (16.9)	6,996 (53.7)	
	Not known	649 (32.4)	3,204 (24.6)	< 0.001
Chemotherapy				
	No	1,107 (55.3)	5,895 (45.2)	
	Yes	311 (15.5)	4,092 (31.3)	
	Not known	584 (29.2)	3,048 (23.4)	< 0.001
Tamoxifen				
	No	260 (13.0)	2,233 (17.1)	
	Yes	1,315 (65.7)	7,916 (60.7)	
	Not known	427 (21.3)	2,886 (22.1)	< 0.001
	Total cases	2,002	13,035	

* P-value for comparison of proportions, excluding 'not known' category where present. For age, Charlson index and cancer plan test is for trend; for all other factors test is for heterogeneity.

[a] P-value when 'not known' category is included: < 0.001

Table 5: Crude and adjusted odds ratios and 95% confidence intervals for surgical treatment

Factor		Number of cases	Surgical cases Number (%)	Odds Ratios: Unadjusted Odds Ratio	Unadjusted Confidence Interval	Adjusted * Odds Ratio	Adjusted * Confidence Interval
Age at diagnosis (years)	< 50	3,800	3,587 (94.4)	1.00	-	1.00	-
	50 - 59	3,739	3,557 (95.1)	1.16	0.95 - 1.42	0.99	0.80 - 1.22
	60 - 69	3,042	2,823 (92.8)	0.77	0.63 - 0.93	0.73	0.59 - 0.89
	70 - 79	2,643	2,117 (80.1)	0.24	0.20 - 0.28	0.27	0.23 - 0.33
	80 +	1,813	951 (52.5)	0.07	0.06 - 0.08	0.09	0.07 - 0.10
Ethnicity	Non-white	2,058	1,820 (88.4)	1.00	-	1.00	-
	White	9,098	8,109 (89.1)	1.07	0.92 - 1.25	1.39	1.16 - 1.65
	Not known	3,881	3,106 (80.0)	0.52	0.45 - 0.61	0.93	0.77 - 1.11
Distant metastases at diagnosis	No	8,289	7,609 (91.8)	1.00	-	1.00	-
	Yes	427	276 (64.6)	0.16	0.13 - 0.20	0.16	0.12 - 0.20
	Not known	6,321	5150 (81.5)	0.39	0.36 - 0.43	0.36	0.31 - 0.40
Charlson Index (comorbidities)	0 (minor)	6,958	6,649 (95.6)	1.00	-	1.00	-
	1 (moderate)	407	360 (88.5)	0.36	0.26 - 0.49	0.70	0.49 - 0.99
	2+ (severe)	1,615	1,434 (88.8)	0.37	0.30 - 0.45	0.50	0.41 - 0.62
	Not known	6,057	4,592 (75.8)	0.15	0.13 - 0.17	0.20	0.17 - 0.23
Diagnosis date (In relation to Cancer Plan)	pre 2000	9,681	8,345 (86.2)	1.00	-	1.00	-
	2000 - 2003	4,189	3,667 (87.5)	1.12	1.01 - 1.25	1.11	0.97 - 1.27
	post 2003	1,167	1,023 (87.7)	1.14	0.95 - 1.37	0.75	0.60 - 0.94
Presentation	Screening	2,297	2,236 (97.3)	1.00	-	1.00	-
	Symptoms	10,294	8,767 (85.2)	0.16	0.12 - 0.20	0.34	0.26 - 0.45
	Incidental	592	475 (80.2)	0.11	0.08 - 0.15	0.28	0.20 - 0.40
	Not known	1,854	1,557 (84.0)	0.14	0.11 - 0.19	0.39	0.29 - 0.53

* Adjusted for all other factors, i.e. based on model which includes all factors

Table 6: Comparison of Audit cohort and registered North Thames cases

Year of diagnosis	Cancer Registry database				Breast Audit database				
	No. of registered North Thames cases	Mean (S.D.) age at diagnosis	Total deaths	Deaths within 1 year *	No. of cases submitted +	Mean (S.D.) age at diagnosis	Total deaths	Deaths within 1 year *	No. of trusts submitting
1996	4,068	61.5 (14.9)	1,829	283 (7.0%)	1,380 (33.9%)	61.6 (14.8)	577	68 (4.9%)	21
1997	4,254	61.4 (14.6)	1,734	312 (7.3%)	2,611 (61.4%)	60.8 (14.3)	1,022	161 (6.2%)	23
1998	4,121	62.0 (15.2)	1,581	325 (7.9%)	2,133 (51.8%)	61.8 (15.3)	859	144 (6.8%)	24
1999	4,269	61.7 (14.7)	1,513	332 (7.8%)	2,004 (46.9%)	61.4 (14.9)	680	130 (6.5%)	24
2000	4,100	61.7 (14.9)	1,309	372 (9.1%)	2,065 (50.4%)	61.2 (14.9)	630	159 (7.7%)	26
2001	4,086	61.8 (15.2)	1,160	328 (8.0%)	1,600 (39.2%)	61.3 (15.4)	448	120 (7.5%)	20
2002	4,006	61.6 (14.5)	922	312 (7.8%)	1,280 (32.0%)	60.1 (14.9)	280	83 (6.5%)	16
2003	4,359	61.6 (14.8)	832	331 (7.6%)	797 (18.3%)	58.7 (15.1)	149	51 (6.4%)	13
2004	4,238	61.9 (14.6)	591	316 (7.5%)	563 (13.3%)	58.4 (14.8)	81	36 (6.4%)	8
2005	3,400	61.4 (14.6)	282	220 (6.5%)	604 (17.8%)	59.0 (14.5)	39	28 (4.6%)	7
Total	40,901	61.7 (14.8)	11,753	3,131 (7.7%)	15,037 (36.8%)	60.9 (14.9)	4.765	980 (6.5%)	29

* Figures in brackets are deaths within 1 year as a percentage of total cases

+ Figures in brackets are audit cases as a percentage of total registered cases

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