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Improvements in survival for women with breast cancer in Scotland between 1987 and 1993: impact of earlier diagnosis and changes in treatment

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Abstract

We investigated changes in survival, and their causes, in women with early breast cancer diagnosed in Scotland. The Scottish Cancer Registry identified 1617 and 2077 such women, without metastases at diagnosis who underwent surgery as part of their primary treatment, diagnosed in 1987 and 1993, respectively. There was a statistically significant 11% improvement in 8-year survival between 1987 and 1993. Survival improved across almost all clinical/pathological, treatment and health care delivery/deprivation categories; improvement was not limited to those women diagnosed through the screening programme. In a multivariate model, improved survival appeared to be explained largely by screening and clinical/pathological prognostic factors. Deprivation also had an adverse effect on survival; however, the geographical variation in survival observed for women diagnosed in 1987 was not apparent by 1993. We did not demonstrate a significant independent effect of surgical caseload on survival. We conclude that survival has increased partly as a consequence of screening and earlier diagnosis, but also due to improvements in the organisation and delivery of care.

Keywords: Adjuvant treatment; Breast cancer; Breast screening; Scotland; Socio-economic status; Survival

1. Introduction

We previously presented 5-year survival analyses for all women diagnosed with operable breast cancer in Scotland in 1987 from a national, population-based survey documenting the management of breast cancer [1]. Regional variation in survival was noted, which persisted even after adjustment for known prognostic factors. Trends were apparent in line with earlier findings suggesting an effect on survival of surgical specialisation [2], caseload of the surgeon [3] and deprivation [4,5]. After adjustment for clinical/pathological prognostic characteristics, these other factors did not reach statistical significance, but were confirmed with follow-up to beyond 10 years [6].

The survey was repeated for women diagnosed in 1993, by when there had been several key changes to cancer care in the United Kingdom (UK). Most notable were the introduction of the Scottish Breast Screening Programme in 1988 [7], increased use of adjuvant systemic therapy, and greater breast awareness amongst women [8]. Also important was the reorganisation of cancer services which has continued in recent years [9,10] leading to greater surgical specialisation and women with breast cancer increasingly being managed by multidisciplinary teams [11]. All these changes may impact upon the continuing reduction in mortality from breast cancer that has been observed in both the UK and United States (US) [12,13]. Although reduction in mortality from breast cancer is the key indicator of performance in the context of a screening programme [14], examination of mortality data alone is not sufficient. The incidence of breast cancer, and survival data

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need also to be analysed to understand fully why the risk of dying from breast cancer is decreasing [15].

Here, we focus on patterns of 8-year survival in women diagnosed with early invasive breast cancer. Firstly, we examined whether the findings observed for the 1987 cohort were apparent for women diagnosed in 1993. Secondly, we quantified the improvement in 8-year survival over this period. Finally, we investigated whether it is possible to estimate the relative contributions of earlier diagnosis and better treatment to this improvement in outcome.

2. Patients and methods

2.1. Study population

National, population-based audits documenting the management of invasive primary breast cancer in Scotland were undertaken by the Scottish Cancer Therapy Network (SCTN) of women identified from the Scottish Cancer Registry diagnosed in 1987 or 1993 [16]. The current study focuses on 8-year survival for both cohorts of women. The analyses were limited to those women who had no evidence of metastases at presentation and underwent surgery as part of their primary treatment. They were selected because differences in management, both in terms of the screening programme and therapeutic strategies, are most likely to be reflected by changes in their survival. Additionally, women who do not undergo definitive surgery will not have important pathological prognostic information recorded.

Data were collected as previously described on the clinical/pathological factors, treatment and health-care delivery/demographic factors [1]. The latter included whether or not the women had their cancer detected through the screening programme that was piloted in 1987 and introduced nationally from 1988. Deprivation was defined using the Carstairs classification [17] based on the 1991 Census in Scotland, allocating patients to the least deprived quintile of the Scottish population (category 1), the most deprived (category 5) or an intermediate group (categories 2–4). Health Board (HB) was defined by residence rather than that of the site of first treatment as in our previous analyses [1,6]. This is because women identified through the screening programme are usually referred to the cancer centres based in only five of the HBs, potentially biasing the proportions of women with better prognosis tumours seen in those HBs. These biases would be observed for the 1993 cohort, but not in 1987 when very few cancers were screen-detected.

Survival data for deaths up until 30 June 2002 were obtained by probabilistic linkage [18] with the death records from the General Register Office (Scotland).

2.2. Data analysis

All the clinical/pathological, treatment and healthcare delivery/demographic factors were examined using χ^2 tests of association to investigate whether any were associated with the year of diagnosis.

Kaplan–Meier estimates of survival at 8 years were obtained for both cohorts for all clinical/pathological, treatment and health-care delivery/demographic factors to assess the effect on outcome of each of the prognostic factors separately. Two Cox's proportional hazards multivariate models were then fitted to the 1987 and 1993 cohorts separately. For both years, the first model included clinical/pathological factors and significant treatment factors; the other included clinical/pathological factors plus significant health-care delivery/demographic factors. These analyses were performed to identify whether findings were similar in the two cohorts, and whether any univariate effects on survival remained after adjustment for case mix.

For all categories of all factors, the difference in 8-year survival between the two cohorts was calculated along with an estimate of its standard error from the Kaplan–Meier analyses. The standard error (SE) for the survival difference was calculated by taking the square root of the sum of the squared SEs obtained for each of the 8-year survival estimates for the two cohorts under the assumption of independence of the two cohorts. Finally, Cox's proportional hazards modelling was then applied to the data for the two cohorts combined to examine the effect of introducing other variables into the model on the hazard ratio of death for the 1993 cohort relative to the 1987 cohort (the 'cohort effect'). This was to investigate whether the improved survival seen between the two years could be explained by factors such as case-mix, or whether it remained after adjustment for these factors.

The primary endpoint for all analyses was death from any cause 8 years after diagnosis.

3. Results

A total of 2581 and 2890 women were registered with the Scottish Cancer Registry as diagnosed with breast cancer in 1987 and 1993, respectively. As shown in Fig. 1, patients were ineligible and excluded from the current analyses if they did not fulfil the diagnostic criteria. Additionally, those women who were eligible, or potentially eligible, but whose records were inadequate/unavailable could not be included. Finally, women having metastatic disease at presentation and those who did not undergo surgery were also excluded for the reasons given above. Therefore, 1617 women diagnosed in 1987 and 2077 women diagnosed in 1993 with non-metastatic breast cancer who underwent surgery were

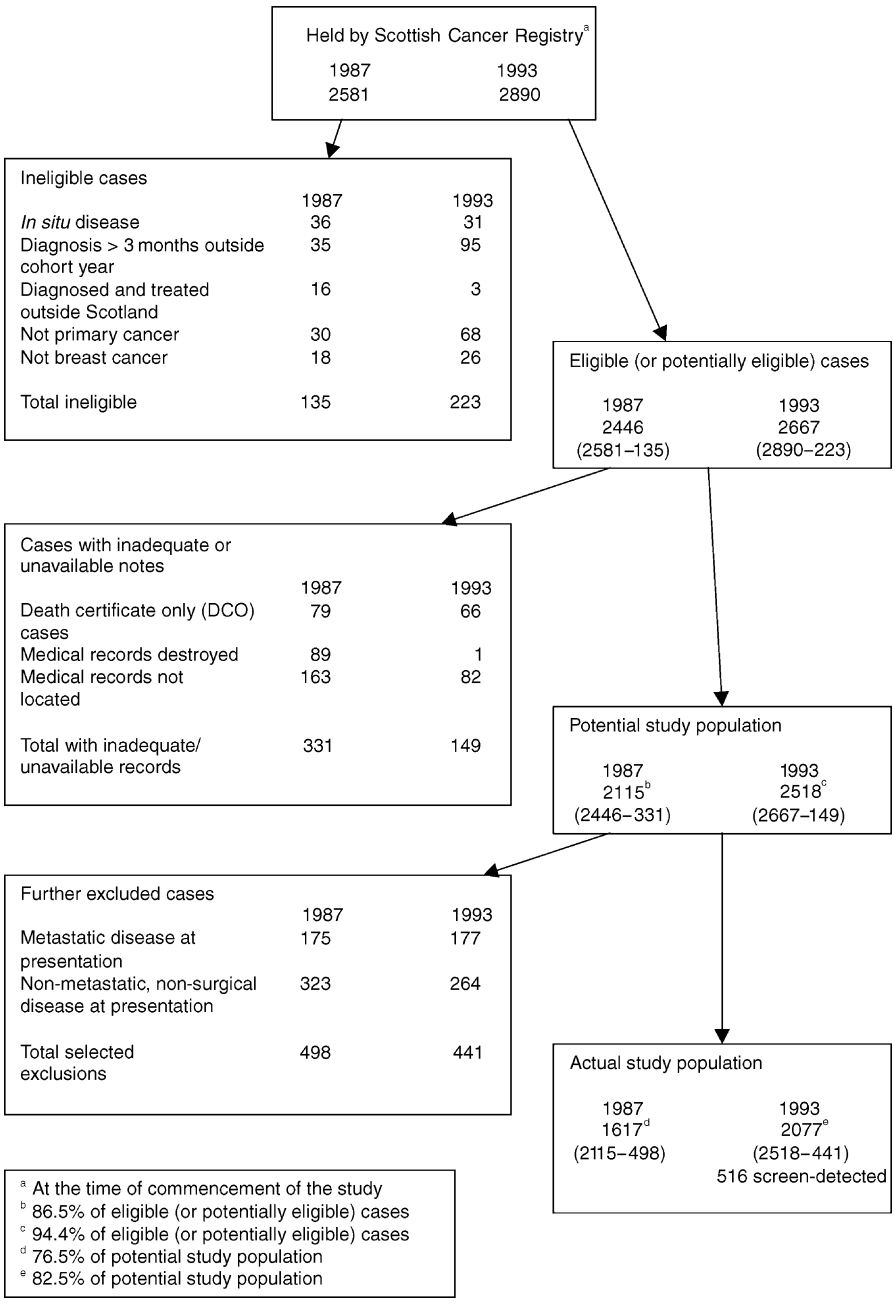

Fig. 1. Derivation of the potential and actual study populations for the 2 years.

included in this analysis. This increase between the 2 years was due largely to screening, with only 39 women diagnosed in 1987 during the pilot programme compared with 516 through the full programme in 1993. In Scotland as a whole, the European age-standardised incidence rates for breast cancer for 1987 and 1993 in all age groups were 88.8 and 105.5 per 100 000 women; age-specific rates for the screening target age group (50–64 years) were 190.8 and 263.8, respectively.

The 8-year survival for all women with invasive breast cancer for whom data were available, irrespective of whether they had metastatic disease at presentation or underwent surgery, was 46.7% in 1987 and 58.4% in 1993. In comparison, the 8-year survival figures for those in the actual study population were 57.4% and 68.3%, respectively; this represents an overall 10.9% (95% CI: 7.8–14.1%) improvement in survival from 1987 to 1993 in the study population. This equates to 689 and 658 deaths in the 1987 and 1993 study populations, respectively, eight years after diagnosis. When the 1993 cohort was limited to those women whose cancers were not screen-detected, there remained a 5.5% improvement in 8-year survival (95% CI: 2.1–8.8%).

3.1. Prognostic factors

The clinical/pathological, treatment and healthcare delivery/demographic features of the women studied in the two years are shown in Tables 1 and 2.

There were significant differences between the 1987 and 1993 cohorts for clinical/pathological prognostic factors (all $P<0.001$). Part of this was due to a reduction in the 'not known' category for all clinical/pathological factors except oestrogen receptor (ER) status. Because of the increase in screening over this period, women diagnosed in 1993 were also divided according to whether or not their tumours were screen-detected. Comparing the 1987 cohort with either the screen-detected women or the non-screen-detected women diagnosed in 1993, differences in the distribution of prognostic factors were still apparent. It appeared that tumours detected by screening in 1993 had better prognostic features than the 1987 cohort. Although the differences were smaller in magnitude, the non-screen-detected tumours in 1993 were also more likely to be clinical stage I, have pathologically confirmed node-negative disease or tumours measured pathologically as $\leqslant 2$ cm in diameter than in 1987 (all $P<0.001$). However, comparing all women diagnosed in 1987 with those diagnosed in 1993 outside of the screening programme, there was no difference in the percentage of women with node-positive disease (36.2% and 37.3%, respectively; $P=0.54$) or tumours >2 cm in diameter (40.9% and 38.6%, respectively; $P=0.17$). The main difference appears, therefore, to be a fall in the number of 'unknowns' for these categories.

The distribution of treatment and health-care delivery/demographic factors for the two cohorts are shown in Table 2. There were significant differences in all the treatment factors, surgical caseload and whether or not women were seen by an oncologist (all $P<0.001$). However, there were no differences between the two cohorts in the distribution of women by deprivation category or HB of residence ($P=0.52$ and 0.16, respectively).

3.2. Factors influencing 8-year survival within the 1987 and 1993 cohorts

3.2.1. Univariate analysis

Table 3 shows that in univariate analyses all the clinical/pathological factors had a significant effect on unadjusted 8-year survival for both years (all $P<0.001$). For women diagnosed in both 1987 and 1993 (Table 4), there were significant differences in outcome by use of adjuvant chemotherapy and type of surgery (all $P<0.01$), with those who did not receive chemotherapy or who did undergo breast conservation having better survival in both years, reflecting their having tumours with an inherently better prognosis. Additionally,

Table 1
Distribution of clinical/pathological factors for the two cohorts, with 1993 cases also shown by screening status

Variable	Level	1987 cohort ($n=1617$)		1993 cohort ($n=2077$)		1993 screen-detected cases ($n=516$)		1993 not screen-detected cases ($n=1561$)	
		Number	(%)	Number	(%)	Number	(%)	Number	(%)
Clinical/pathological factors									
Age group (years)	<50	472	(29.2)	552	(26.6)	8	(1.6)	544	(34.8)
	50–64	596	(36.9)	906	(43.6)	468	(90.7)	438	(28.1)
	65–79	474	(29.3)	499	(24.0)	40	(7.8)	459	(29.4)
	⩾80	75	(4.6)	120	(5.8)	0	(0)	120	(7.7)
Clinical stage[a]	I	308	(19.0)	715	(34.4)	300	(58.1)	415	(26.6)
	II	814	(50.3)	936	(45.1)	150	(29.1)	786	(50.4)
	III	185	(11.4)	186	(9.0)	8	(1.6)	178	(11.4)
	Not known	310	(19.2)	240	(11.6)	58	(11.2)	182	(11.7)
ER status	Positive	609	(37.7)	765	(36.8)	233	(45.2)	532	(34.1)
	Negative	389	(24.1)	350	(16.9)	58	(11.2)	292	(18.7)
	Not known	619	(38.3)	962	(46.3)	225	(43.6)	737	(47.2)
Pathological node status	Positive	586	(36.2)	690	(33.2)	108	(20.9)	582	(37.3)
	INS[b]	283	(17.5)	262	(12.6)	63	(12.2)	199	(12.7)
	Negative[c]	307	(19.0)	853	(41.1)	299	(57.9)	554	(35.5)
	Not known	441	(27.3)	272	(13.1)	46	(8.9)	226	(14.5)
Pathological tumour size	⩽2 cm	639	(39.5)	1152	(55.5)	384	(74.4)	768	(49.2)
	>2 cm	662	(40.9)	695	(33.5)	93	(18.0)	602	(38.6)
	Not known	316	(19.5)	230	(11.1)	39	(7.6)	191	(12.2)

ER, oestrogen receptor.

[a] Clinical stage was determined prior to surgery at the time of presentation of the initial examination. This means that it will be related, but will not necessarily be identical, to the pathological staging information.

[b] INS = inadequate negative sample = 1, 2, 3, unknown number taken, all negative.

[c] Negative = four or more nodes taken, all negative.

Table 2
Distribution of the treatment, health-care delivery and deprivation factors for the two cohorts

Variable	Level	1987 cohort ($n=1617$)		1993 cohort ($n=2077$)	
		Number	(%)	Number	(%)
Treatment factors					
Type of surgery	Mastectomy	949	(58.7)	970	(46.7)
	Breast Conservation	668	(41.3)	1107	(53.3)
Adjuvant radiotherapy	Given	680	(42.1)	1178	(56.7)
	Not given	937	(57.9)	899	(43.3)
Adjuvant chemotherapy	Given	124	(7.7)	387	(18.6)
	Not given	1493	(92.3)	1690	(81.4)
Adjuvant endocrine therapy	Given	1059	(65.5)	1920	(92.4)
	Not given	558	(34.5)	157	(7.6)
Adjuvant systemic therapy (chemotherapy or endocrine therapy)	Given	1145	(70.8)	1995	(96.1)
	Not given	472	(29.2)	82	(3.9)
Health-care delivery and demographic factors					
Deprivation category	Least	367	(22.7)	451	(21.7)
1991 Census	Intermediate	967	(59.8)	1282	(61.7)
	Most	281	(17.4)	344	(16.6)
	Could not be assigned	2	(0.1)	0	(0)
Surgeon caseload	1–9 cases	275	(17.0)	186	(9.0)
	10–29	678	(41.9)	423	(20.4)
	Team/$\geqslant$30	652	(40.3)	1455	(70.1)
	Unknown	12	(0.7)	13	(0.6)
Seen by oncologist	Yes	869	(53.7)	1426	(68.7)
	No	719	(44.5)	629	(30.3)
	Unknown	29	(1.8)	22	(1.1)
Health Board of Residence	Ayrshire and Arran	135	(8.3)	168	(8.1)
	Borders	31	(1.9)	55	(2.6)
	Argyll and Clyde	137	(8.5)	195	(9.4)
	Fife	121	(7.5)	115	(5.5)
	Greater Glasgow (GGHB)	281	(17.4)	320	(15.4)
	Highland	69	(4.3)	96	(4.6)
	Islands	30	(1.9)	43	(2.1)
	Lanarkshire	152	(9.4)	207	(10.0)
	Grampian	177	(10.9)	195	(9.4)
	Lothian	211	(13.0)	299	(14.4)
	Tayside	135	(8.3)	197	(9.5)
	Forth Valley	73	(4.5)	106	(5.1)
	Dumfries and Galloway	65	(4.0)	81	(3.9)
Screen-detected?	Yes	39	(2.4)	516	(24.8)
	No	1578	(97.6)	1561	(75.2)

women who received no adjuvant systemic (i.e. cytotoxic or endocrine) therapy had a significantly better outcome than those who did not if diagnosed in 1993 ($P=0.04$), but not in 1987 ($P=0.14$). There were no survival differences in relation to use of adjuvant radiotherapy ($P=0.79$ and 0.15), or endocrine therapy ($P=0.50$ and 0.87) in 1987 and 1993, respectively.

Regarding health-care delivery/demographic factors, there was significant variation in 8-year survival across the HBs for the 1987 cohort, ranging from 48% to 69% ($P=0.005$). These differences were no longer apparent in 1993 (range 61–80%; $P=0.25$). Significant differences in outcome were seen by surgical caseload for women diagnosed in either 1987 or 1993 (both $P<0.001$) with those seen by a surgeon who had a high caseload having a better outcome. In contrast, whether the woman was seen by an oncologist was not of prognostic significance in either 1987 or 1993 ($P=0.82$ and $P=0.20$, respectively). There were differences in survival between the deprivation categories in both 1987 and 1993 ($P=0.03$ and $P=0.005$, respectively), with women living in affluent areas having significantly better outcomes.

3.2.2. Multivariate analysis

When multivariate Cox models were fitted to the 1987 and 1993 cohorts separately, all the clinical/pathological factors still significantly affected survival (all $P<0.001$) for both years. After adjustment for all the clinical/pathological factors, HB of residence also influenced survival for women diagnosed in 1987 ($P=0.02$), but not in 1993 ($P=0.48$). By contrast, after allowing for clinical/pathological factors, surgical caseload no longer

Table 3
Univariate survival estimates at 8 years for the clinical/pathological factors for the two cohorts

Clinical/pathological factors	8-year figure for 1987		8-year figure for 1993		Difference (1993–1987)	
	Survival (%)	95% CI (%)	Survival (%)	95% CI (%)	Survival (%)	95% CI (%)
Age group (years)						
<50	63.4	59.0–67.7	71.0	67.2–74.8	7.7	1.9–13.4
50–64	61.6	57.7–65.5	75.8	73.0–78.6	14.3	9.5–19.0
65–79	51.3	46.8–55.8	58.9	54.6–63.2	7.6	1.4–13.9
⩾80	25.3	15.5–35.2	38.3	29.6–47.0	13.0	−0.1–26.1
Clinical stage[a]						
I	73.1	68.1–78.0	80.1	77.2–83.1	7.1	1.3–12.8
II	57.5	54.1–60.9	64.9	61.8–67.9	7.4	2.8–11.9
III	37.8	30.8–44.8	38.2	31.2–45.1	0.3	−9.6–10.2
Not known	53.2	47.7–58.8	70.0	64.2–75.8	16.8	8.7–24.8
ER status						
Positive	65.5	61.7–69.3	74.6	71.6–77.7	9.1	4.2–14.0
Negative	48.3	43.4–53.3	56.6	51.4–61.8	8.2	1.1–15.4
Not known	55.1	51.2–59.0	67.6	64.6–70.5	12.5	7.6–17.4
Pathological node status						
Positive	44.4	40.4–48.4	52.3	48.6–56.0	8.0	2.5–13.4
INS[b]	70.3	65.0–75.7	74.4	69.1–79.7	4.1	−3.4–11.6
Negative[c]	75.6	70.8–80.4	80.7	78.0–83.3	5.1	−0.4–10.6
Not known	53.7	49.1–58.4	64.3	58.7–70.0	10.6	3.3–17.9
Pathological tumour size						
⩽2 cm	67.1	63.5–70.8	77.7	75.3–80.1	10.6	6.2–14.9
>2 cm	48.6	44.8–52.4	55.0	51.3–58.7	6.3	1.0–11.6
Not known	56.0	50.5–61.5	61.7	55.5–68.0	5.7	−2.6–14.1

95% CI, 95% Confidence Interval.
[a] Clinical stage was determined prior to surgery at the time of presentation of the initial examination. This means that it will be related, but will not necessarily be identical, to the pathological staging information.
[b] INS = inadequate negative sample = 1, 2, 3, unknown number taken, all negative.
[c] Negative = four or more nodes taken, all negative.

affected the survival of the 1987 cohort ($P = 0.26$), but it did for those diagnosed in 1993 ($P = 0.03$); this effect was, however, lost when screening was also introduced into the model ($P = 0.10$). Indeed, the influence of screening on survival was highly significant after allowing for the clinical/pathological factors in 1993 ($P < 0.001$). No other factors were significant in either of these multivariate models.

3.3. Improvements in 8-year survival between 1987 and 1993

3.3.1. Univariate analysis

There was significant improvement in survival between 1987 and 1993 for nearly all categories of each of the clinical/pathological factors (Table 3). Improved survival was seen in all age groups, but was greatest (14.3%) in those targeted by screening (50–64 years). Significant improvements in survival between the two years were also observed for all categories of the treatment factors (Table 4), as well as most of the categories of the healthcare delivery/demographic factors. Specifically, improvements were observed in all deprivation categories, women not detected by screening as well as those presenting symptomatically, and across almost all HBs.

3.3.2. Multivariate analysis

We investigated the factors underlying the improvement in survival by first defining the hazard ratio of death (HR) for the 1993 cohort compared with that in the 1987 cohort (the 'cohort effect'). We then adjusted for the clinical/pathological factors (both separately and together), the treatment factors and the healthcare delivery/demographic factors (Table 5).

Without adjusting for any factors, the risk of death was significantly lower for women diagnosed in 1993 than those diagnosed in 1987 with a HR of 0.70. After adjustment for all of the clinical/pathological factors alone, the risk of death was still lower in 1993 than in 1987, but was now 0.88 instead of 0.70; the cohort effect was, however, still significant ($P = 0.025$). By contrast, adjustment for the treatment factors alone did not change the hazard ratio for the cohort effect (HR 0.68; $P < 0.001$). Addition of all the health-care delivery and demographic factors did change the risk of death to

Table 4
Univariate survival estimates at 8 years for the treatment and health-care delivery /deprivation factors for the two cohorts

	8-year figure for 1987		8-year figure for 1993		Difference (1993–1987)	
	Survival (%)	95% CI (%)	Survival (%)	95% CI (%)	Survival (%)	95% CI (%)
Treatment factors						
Type of surgery						
Mastectomy	54.5	51.3–57.7	62.8	59.7–65.8	8.3	3.9–12.7
Breast conservation	61.5	57.8–65.2	73.2	70.6–75.8	11.6	7.1–16.2
Adjuvant radiotherapy						
Given	58.2	54.5–61.9	69.7	67.1–72.3	11.5	6.9–16.0
Not given	56.8	53.6–60.0	66.5	63.4–69.6	9.7	5.3–14.2
Adjuvant chemotherapy						
Given	48.4	39.6–57.2	62.0	57.2–66.9	13.6	3.6–23.7
Not given	58.1	55.6–60.6	69.8	67.6–72.0	11.6	8.3–15.0
Adjuvant endocrine therapy						
Given	56.5	53.5–59.4	68.3	66.2–70.4	11.8	8.2–15.4
Not given	59.1	55.1–63.2	68.8	61.5–76.0	9.6	1.3–18.0
Adjuvant systemic therapy (chemotherapy or endocrine therapy)						
Given	56.0	53.1–58.9	67.9	65.8–69.9	11.9	8.3–15.4
Not given	60.8	56.4–65.2	79.3	70.5–88.1	18.5	8.6–28.3
Health-care delivery/ demographic factors						
Health Board of Residence						
Ayrshire and Arran	48.2	39.7–56.6	67.9	60.8–74.9	19.7	8.7–30.7
Borders	58.1	40.7–75.4	80.0	69.4–90.6	21.9	1.6–42.3
Argyll and Clyde	48.2	39.8–56.5	75.9	69.9–81.9	27.7	17.4–38.0
Fife	61.2	52.5–69.8	72.2	64.0–80.4	11.0	−0.9–22.9
GGHB	58.7	53.0–64.5	64.7	59.5–69.9	6.0	−1.8–13.8
Highland	56.5	44.8–68.2	61.5	51.7–71.2	4.9	−10.3–20.2
Islands	60.0	42.5–77.5	67.4	53.4–81.5	7.4	−15.0–29.9
Lanarkshire	52.6	44.7–60.6	66.7	60.2–73.1	14.0	3.8–24.3
Grampian	59.3	52.1–66.6	67.2	60.6–73.8	7.9	−1.9–17.6
Lothian	69.2	63.0–75.4	68.9	63.6–74.2	−0.3	−8.4–7.9
Tayside	57.0	48.7–65.4	64.0	57.3–70.7	6.9	−3.8–17.6
Forth Valley	49.3	37.9–60.8	68.9	60.1–77.7	19.6	5.1–34.0
Dumfries and Galloway	60.0	48.1–71.9	75.3	65.9–84.7	15.3	0.1–30.5
Surgical caseload[a]						
1-9 cases	52.4	46.5–58.3	53.8	46.6–60.9	1.4	−7.9–10.7
10-29	54.1	50.4–57.9	64.8	60.2–69.3	10.7	4.8–16.5
Team/$\geqslant$30	63.3	59.6–67.0	71.3	68.9–73.6	7.9	3.6–12.3
Seen by oncologist[b]						
Yes	57.5	54.2–60.8	69.5	67.1–71.9	12.0	7.9–16.0
No	57.4	53.8–61.0	66.0	62.3–69.7	8.5	3.4–13.7
Deprivation category[c] 1991 Census						
Least	60.8	55.8–65.8	73.4	69.3–77.5	12.6	6.2–19.1
Intermediate	58.0	54.9–61.1	67.9	65.4–70.5	9.9	5.9–14.0
Most	50.9	45.0–56.7	63.1	58.0–68.2	12.2	4.4–19.9
Screen-detected?						
Yes	82.1	70.0–94.1	84.9	81.8–88.0	2.8	−9.6–15.3
No	56.8	54.3–59.2	62.8	60.4–65.2	6.1	2.6–9.5

[a] Note that the 12 and 13 cases for the 1987 and 1993 cohorts, respectively, where the surgeon was unknown were not included in the analyses.
[b] Note that the 29 and 22 cases for the 1987 and 1993 cohorts, respectively, where the date of referral to the oncologist was unknown were not included in the analyses, as it was not possible to determine if consultation was part of the primary treatment.
[c] Note that a deprivation score could not be assigned for 2 cases in the 1987 cohort.

0.88, but again the cohort effect remained significant ($P = 0.026$). Of the healthcare delivery and demographic factors, screening appeared to make the biggest contribution, although the cohort effect remained highly significant (HR 0.84; $P = 0.001$). When adjustment was made for both the clinical/pathological factors and screening, the cohort effect was no longer significant (HR 0.94; $P = 0.27$).

Thus, the improved survival between 1987 and 1993 appears to be explained mainly by differences in clinical/pathological prognostic factors and the impact of screening. In this model, deprivation category also had an effect on survival of marginal significance ($P = 0.04$), but none of the treatment or other health-care delivery factors was significant, and did not make the hazard ratio for the cohort effect closer to unity (HR 0.93; $P = 0.24$).

Table 5
Hazard ratios for the cohort factor when forced into a Cox model with other factors

Factors	Hazard Ratio (95% CI) for 1993 versus 1987	*P* value
Cohort only (unadjusted)	0.70 (0.63–0.78)	<0.0001
Clinical/pathological factors plus cohort		
Age group + cohort	0.71 (0.64–0.79)	<0.0001
Clinical stage + cohort	0.78 (0.70–0.87)	<0.0001
ER status + cohort	0.71 (0.64–0.79)	<0.0001
Pathological node status + cohort	0.80 (0.71–0.89)	<0.0001
Pathological tumour size + cohort	0.77 (0.69–0.86)	<0.0001
All clinical/pathological factors plus cohort	0.88 (0.79–0.98)	0.025
Treatment factors plus cohort		
Type of surgery + cohort	0.73 (0.65–0.81)	<0.0001
Any radiotherapy + cohort	0.70 (0.63–0.79)	<0.0001
Any chemotherapy + cohort	0.67 (0.60–0.75)	<0.0001
Any endocrine therapy + cohort	0.69 (0.62–0.77)	<0.0001
Any adjuvant systemic therapy + cohort	0.67 (0.60–0.75)	<0.0001
All treatment factors plus cohort	0.68 (0.61–0.77)	<0.0001
Health-care delivery/demographic factors plus cohort		
Surgical caseload + cohort	0.77 (0.69–0.87)	<0.0001
Referral to oncologist + cohort	0.70 (0.63–0.78)	<0.0001
Deprivation + cohort	0.70 (0.63–0.78)	<0.0001
Health Board of Residence + cohort	0.69 (0.62–0.77)	<0.0001
Screening factor + cohort	0.84 (0.75–0.93)	0.001
All health-care delivery/demographic factors plus cohort	0.88 (0.78–0.98)	0.026
Final model		
All clinical/pathological factors plus screening factor plus cohort	0.94 (0.84–1.05)	0.27

Bold text indicates values when all of the factors of the particular categories were included in the model with the cohort factor.

4. Discussion

We have shown a statistically significant and clinically meaningful 11% improvement in the 8-year survival of women diagnosed with non-metastatic, surgically-treated invasive primary breast cancer in 1993 compared with those diagnosed in 1987. This is important in the context of a national, population-based study including over 86% of eligible women diagnosed in two recent years, over a well-defined, but heterogeneous geographical area. The Scottish Cancer Registry has high levels of ascertainment [19], and detailed information was sought directly from case notes. Indeed, we may have underestimated the improvement in survival by excluding women whose case notes could not be located or had been destroyed. Many of these women will have died, and there were more of them diagnosed in 1987 than in 1993 (252 and 83, respectively).

No single factor could be identified that fully accounted for this improvement in survival, half of which occurred in women whose cancers were detected by screening. The breast screening programme in Scotland achieves approximately 70% uptake and incorporates double-reading of 3-yearly mammograms [7]. Screening can distort comparisons of survival through lead-time bias (earlier detection of tumours that would otherwise have presented later symptomatically) and length bias (preferential detection of good prognosis cancers that spend longer in the preclinical detection phase) [20,21]. However, by studying 8-year survival, we reduced the impact of the estimated 3-year lead-time bias [21], whilst maintaining a focus on recent clinical practice and organisation of care.

The increase in 8-year survival we observed is in line with changes in death rates across England & Wales and Scotland from 1950 to 1999 (Fig. 2) and in the US [13], but the contribution of screening relative to other factors remains unclear. One UK study identified a 21% reduction in death between 1990 and 1998 for women with breast cancer aged 55–69 years, of which only 6% was directly attributed to the screening programme and 15% to other factors such as adjuvant systemic treatment and earlier presentation outside the screening programme [22]. By contrast, a fall of 19% in mortality for women aged 55–64 years has been predicted to result from screening alone [23]. However, others have challenged whether screening makes any contribution to the falling death rates [24].

Multivariate analysis suggested that 47% (from 0.70 to 0.84) of the potential improvement (from 0.70 to 1.00) in the hazard ratio of death for the 1993 cohort relative to the 1987 cohort was directly explained by screening, but a further 33% (from 0.84 to 0.94) could be attributed to clinical/pathological factors. Moreover, although the confidence interval did include 1.00, the hazard ratio did not return to this value, perhaps reflecting residual confounding factors. Indeed, there was a 5.5% increase in survival between 1987 and 1993

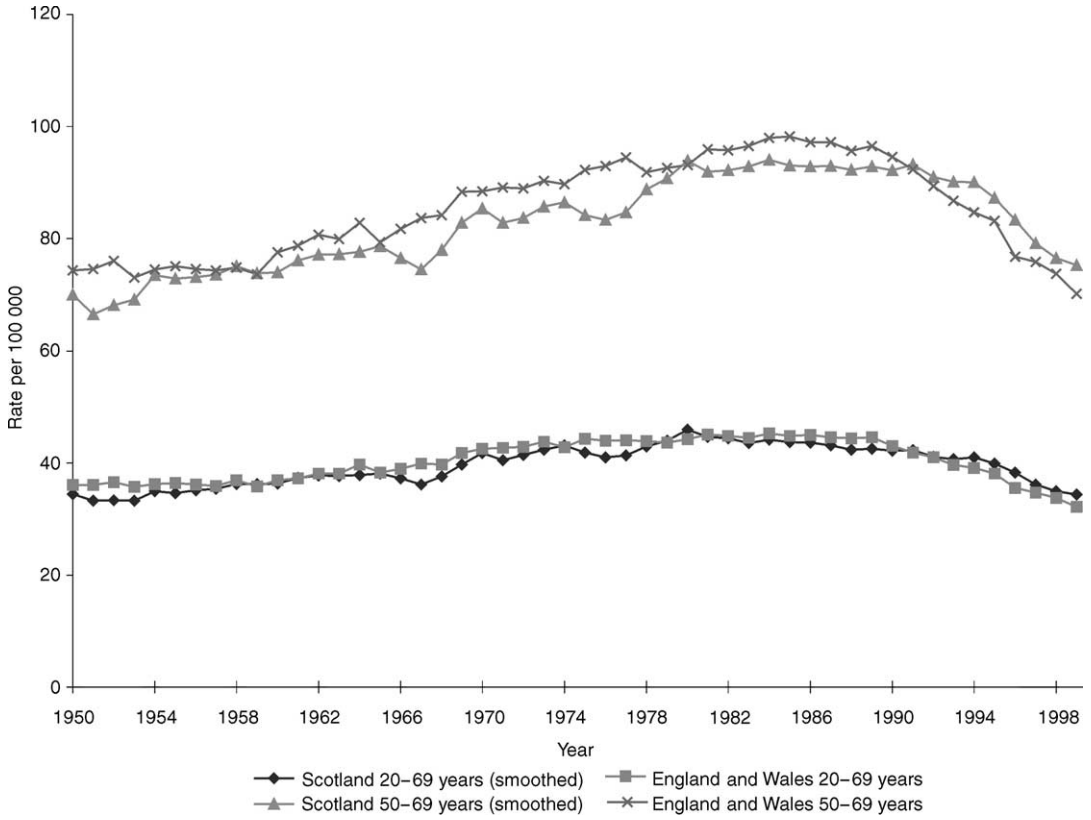

Fig. 2. European age-standardised breast cancer death rates for England & Wales (source Office for National Statistics (ONS) with correction for death certificate coding rules as described by Quinn and colleagues [12] and Scotland (source General Register Office (GRO) Scotland) 1950–1999 for age groups 20–69 years and 50–69 years; rate is smoothed over 3 years for Scotland.

for those women not detected by screening. There was an apparent improvement in some prognostic features, such as an increase in the percentage of women with tumours $\leqslant 2$ cm measured pathologically and those with pathologically confirmed node-negative disease. However, it is difficult to assess how much of this improvement is real and how much is due to better data quality with fewer women with their clinical/pathological factors being 'unknown'. Nevertheless, in the multivariate analysis, once the effect of screening had been taken into account, these prognostic factors independently influenced survival. Hence, it appears that in 1993, women presenting symptomatically did have tumours with a better prognosis than those diagnosed in 1987. Indeed, for women aged under 50 years whom the screening programme should not have directly influenced, there was an 8% improvement in survival over this period.

Between 1987 and 1993, there were substantial changes in the delivery of health-care to women with breast cancer in Scotland. During this time, the proportion of women seen by an oncologist rose from 54% to 69% ($P < 0.001$), and the proportion managed by surgeons with a higher workload or working in designated breast teams increased from 40% to 70% ($P < 0.001$). These women cared for by surgeons with higher caseloads had better 8-year survival than those managed by the 1–9 caseload surgeons (71% and 54% in 1993, respectively); this benefit was apparent in 1993 even after adjustment for case mix. However, the effect disappeared when screening, as well as the clinical/pathological factors, was taken into account. This change in practice may, in part, be an indirect effect of the screening programme resulting in many women being managed in specialist centres by surgeons with high caseloads. Similarly, in the current study across the 2 years women were more likely to receive adjuvant systemic treatment, which has a clear impact on survival [25,26], if seen by a surgeon with a high caseload rather than by other surgeons (87% versus 82%, respectively; $P < 0.001$). This emphasises the complexity of separating out these inter-related effects on survival, but reinforces the importance of the multidisciplinary team [3,27,28]. Indeed, we should probably interpret 'treatment' more widely as incorporating both specific therapies and the organisation required for their effective delivery.

In recent years, there have been important changes in the treatment of women with early breast cancer. The Northern & Yorkshire Cancer Registry & Information Service reported an effect of these changes on survival, although adjustment for stage and case mix in their study was limited considerably by missing data [29]. By

contrast, using multivariate analyses to make such an adjustment, treatment factors appeared not to influence survival in our study. However, this is not surprising in the context of observational data. Firstly, treatment is largely determined by clinical/pathological prognostic factors. For example, adjuvant chemotherapy is used more often in women at a higher risk of developing metastatic disease. Secondly, between 1987 and 1993, the proportion of women receiving adjuvant systemic therapy increased by just 25% (from 71 to 96%). Since the absolute improvement in 10-year survival of adjuvant treatment is approximately 8% [25,26], the potential benefit from increased use of adjuvant therapy in our study would be no more than a 2% survival gain. It would be wrong, therefore, to interpret the current study as showing that treatment does not influence survival. Rather, it shows that significant benefits of an intervention, clearly demonstrable in clinical trials, may not be detectable in any but the largest population studies with adequate adjustment for confounding variables.

Our earlier analysis [1] revealed variations in survival of the women diagnosed in 1987 between the HBs, even after adjustment for clinical/pathological prognostic factors. An important finding of the current study is that this geographical variability was no longer apparent in 1993, probably reflecting the more uniform use of adjuvant systemic therapy [16]. Women diagnosed in both 1987 and 1993 who lived in the most affluent areas had approximately 11% better 8-year survival than those resident in deprived areas. This may be due in part to the significantly higher incidence of ER-positive tumours in affluent women with breast cancer [30]. Indeed, after adjusting for the clinical/pathological factors by multivariate modelling, deprivation no longer significantly influenced survival in either year, but was marginally significant when the two cohorts were analysed together. Changes in deprivation did not contribute to the improvement in survival between the 2 years, but it is reassuring that between 1987 and 1993, improvements in survival were similar for the affluent and the deprived women.

The fact that survival improved for all women, irrespective of whether they had metastases at presentation or underwent surgery, suggests that care may also have improved for patients with non-curable disease. However, it was not possible to study this aspect in detail because of the absence in many cases of pathological prognostic variables in these women.

This analysis has shown the potential value of population-based cancer registry data, especially if this is expanded to include detailed clinical, pathological and treatment factors, in monitoring changes in healthcare and outcomes. The improvements in survival we report are encouraging, but improvements of around 5% were noted over time for all regions in Europe [31]. When comparison is made with European data, women diagnosed with breast cancer in 1987–1989 in the UK and Denmark appear to have a lower 5-year relative survival compared with those from Finland, Sweden and Iceland (67.8% and 80.5%, respectively). In part this may be an artefact arising from differences in methods of registration, ascertainment, completeness and quality of data [32], although some of the survival differences may have been due to patients in the UK tending to present with more advanced disease in the past, and some because of differences in the patterns of care and investment in health care services across Europe [33]. Nevertheless, it will be interesting to see whether improvements in survival such as those we observed now start to close this 'gap'.

Survival for women in Scotland diagnosed with breast cancer improved significantly between 1987 and 1993, but it is difficult to quantify the exact contributions of specific factors to this change. Over this period there have been major changes in the pattern of presentation of breast cancer, treatment itself and the organisation of how care is delivered. Our data are compatible with these changes contributing to the observed improvement in survival. Most important from the patients' point of view is that the survival improvement is genuine and substantial. Moreover, the continuing fall, in all ages, of breast cancer mortality suggests that further improvements in survival will continue to emerge.

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