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Original Paper

Entry into Clinical Trials in Breast Cancer: the Importance of Specialist Teams

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The aim of this study was to identify the factors influencing entry of women with invasive breast cancer into clinical trials in Scotland. Women diagnosed during 1987 and 1993 were identified from cancer registry data records and their case notes reviewed. Entry into clinical trials was recorded, along with clinical and demographic data for 4688 patients. In 1987, the proportion of women entering clinical trials was 12.3% and, allowing for shorter follow-up, this appeared unchanged in 1993. Patients seen by surgeons with a high case load and those referred to an oncologist were approximately seven times and three times, respectively, more likely to enter a clinical trial ($P < 0.0001$). The area of Scotland (Health Board) where the woman was first treated also influenced study entry ($P < 0.0001$), whereas social deprivation had no effect ($P = 0.93$). Older women, especially those over 80 years of age, were less likely to enter studies ($P = 0.05$). Extending the management of patients by specialist multidisciplinary teams should increase recruitment into clinical trials and help to identify better treatments for women with breast cancer.

Key words: breast cancer, clinical trials, multidisciplinary teams
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INTRODUCTION

CLINICAL TRIALS have made major contributions to the development of new and improved treatments for patients with cancer, but participation rates generally remain low. In 1979 it was estimated that, in the U.K., only 8% of all patients with breast cancer entered randomised trials [1]. This problem is not limited to the U.K. A recent survey of accrual to National Cancer Institute co-operative trials in the U.S.A. showed that phase II and III breast cancer trials accrued only 3.3% of the potentially eligible patients [2]. The potentially conflicting roles of clinician and trialist, the time and effort required from both the patient and doctor [3, 4] and the age of the patient [5] may also influence study entry. Eligibility criteria and refusal to give informed consent may limit study entry, even within a centre that is committed to the trial [6]. It is important to define more clearly the factors that influence study entry if the present rates of recruitment are to improve.

The current report addresses the issue of entry into clinical trials of all women diagnosed with invasive breast cancer in Scotland during 1987 and 1993. These women were identified from cancer registry data. However, unlike many previous studies, individual hospital case records were examined to identify entry into clinical trials. The aims were to define the proportion of patients entering clinical trials and the factors that influenced study entry.

PATIENTS AND METHODS

Patients

The study was part of a comprehensive survey of the patterns of care in patients presenting with breast cancer in Scotland. The patient population comprised all new cases of invasive breast cancer registered with the Scottish Cancer Registry in 1987 and 1993. Permission to examine case notes was obtained from the Chief Administrative Medical Officer of each Health Board and the Medical Director of each Trust

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Table 1. *Numbers of patients entering trials for early/locally advanced breast cancer and for metastatic disease in* 1987 *and* 1993

	Early/locally advanced only	Early/locally advanced and metastatic	Metastatic only	Total number of patients in trials	Total diagnosed*
1987	171†	10	83‡	264	2148
1993	219§	1	17	237	2540

*Of the total of 4187 patients who did not enter clinical trials, 260 had metastatic disease. †Including 7 patients in two trials for early/locally advanced disease only. ‡Including 2 patients in two trials for metastatic disease only. §Including 1 patient in two trials for early/locally advanced disease only.

Hospital. Case notes were examined by Scottish Cancer Therapy Network (SCTN) staff. Entry to clinical trials was recorded and clinical trials databases held at SCTN checked to ensure that all relevant trial entries had been identified. Trials were categorised as for either early/locally advanced disease or metastatic breast cancer. Information on disease characteristics at presentation, including clinical stage, pathological tumour size, oestrogen receptor (ER) status and nodal status, was collected. Demographic data included age, social deprivation [7] and the area of Scotland within which the patient was first managed. Healthcare in Scotland is structured around 15 Health Boards based on geographical areas. Surgeons were classified according to case load as previously described [8], modified to include surgeons working in breast clinic teams in the group treating at least 30 women with breast cancer each year. Those working in surgical teams were identified prior to analysis. Referral to an oncologist within 3 months of diagnosis was recorded.

Statistical methods

Chi-squared tests were used to compare the clinical features of patients entering and not entering clinical trials. An initial univariate analysis examined the effect of each demographic factor on trial entry. Because of possible confounding effects, multivariate logistic regression was then used to assess these effects further. In this analysis, all variables were entered as unordered categorical factors. The effect of trial entry on survival, adjusted for other factors, was investigated using a Cox's proportional hazards regression model [9].

RESULTS

Case notes were located for 89% and 97% of registered patients diagnosed in 1987 and 1993, respectively. The total population studied was 2148 patients from 1987 and 2540 from 1993. Patients entered 34 clinical trials, 18 for early or locally advanced disease, 14 for metastatic disease, with two open to patients with either category of disease. The trials included two phase I and five phase II studies of new agents, as well as 27 randomised phase III studies. Only seven of the studies were sponsored by the pharmaceutical industry; the rest were supported by local funds or by trials groups such as the EORTC. Fifteen trials were local (i.e. a single cancer centre), eight were national U.K. studies and 11 were international. Patients were entered into trials from 21 hospitals; five of these were the Scottish cancer centres and, overall, they enrolled 78% of the trial entries. The proportion of patients first seen at one of these five centres who were entered into trials was higher than that of patients treated elsewhere (18.1% and 3.3%, respectively). Interestingly, the 37 women treated privately appeared as likely to enter trials as those treated within the National Health Service (10.7% and 10.8%, respectively).

Table 1 shows the number of patients entering trials for early/locally advanced disease or metastatic breast cancer in both years. A total of 501 women entered trials, 12.3% of those diagnosed in 1987 and 9.3% of those diagnosed in 1993. Between 1987 and 1993, the absolute number of women entering trials for early or locally advanced disease increased, but the proportion was almost identical (8.4% and 8.7%, respectively). The pattern of entry into trials did, however, change between the two years. Entry into trials primarily addressing issues of local disease control (conservation surgery and radiotherapy or axillary surgery) fell from 103 in 1987 to 62 in 1993. By contrast, entry into studies of adjuvant or neo-adjuvant systemic treatment rose from 78 in 1987 to 158 in 1993.

As the proportion of women entering trials for early or locally advanced disease was the same in 1987 and 1993, the features of women in both years who did and did not enter these trials were compared together. Table 2 shows that women who entered these trials had their disease more accurately staged. For example, axillary node status was not

Table 2. *Clinical features of women with non-metastatic disease entering and not entering clinical trials for early/locally advanced disease* (n = 4321)

	Number in trial (%)*	Number not in trial (%)	*P* value†
Clinical stage			< 0.0001
I	97 (24.6)	977 (24.9)	
II	217 (55.1)	1726 (44.0)	
III	58 (14.7)	589 (15.0)	
Unknown	22 (5.6)	635 (16.2)	
Node status			< 0.0001
Positive	136 (34.5)	1153 (29.4)	
Negative	197 (50.0)	1531 (39.0)	
Unknown	61 (15.5)	1243 (31.7)	
ER status			< 0.0001
Positive	189 (48.0)	1251 (31.9)	
Negative	84 (21.3)	697 (17.7)	
Unknown	121 (30.7)	1979 (50.4)	
Tumour size			< 0.0001
≤ 2 cm	208 (52.8)	1600 (40.7)	
> 2 cm	92 (23.4)	1279 (32.6)	
Unknown	94 (23.9)	1048 (26.7)	

ER, oestrogen receptor.

*401 patients were entered into trials for early/locally advanced disease only ($n = 390$) or both early/locally advanced and metastatic disease ($n = 11$). 7 patients were found to have metastases and were excluded from the above analysis, giving a total of 394 patients. †χ^2 test for association.

known for twice as many of the patients who did not enter clinical trials. However, because entry into trials is largely defined by eligibility criteria based on these clinical characteristics, their effect on study entry was not examined further.

In a univariate analysis, the demographic factors (age, referral to an oncologist, surgical case load, deprivation category and Health Board of first treatment) all had a significant effect on trial entry (Table 3). The multivariate logistic regression analysis showed that referral to an oncologist ($P < 0.0001$), surgical case load ($P < 0.0001$) and Health Board of first treatment ($P < 0.0001$) were significant determinants of trial entry. Women referred to an oncologist were significantly more likely to enter a clinical trial (adjusted odds ratio 3.06, 95% confidence interval (CI) 2.30–4.07) as were those treated by a surgeon with a high case load (adjusted odds ratio 7.39, 95% CI 4.75–11.49). The adjusted odds ratios for trial entry compared with Greater Glasgow Health Board varied widely across the Health Boards from 0.13 (95% CI 0.05–0.37) to 1.4 (95% CI 1.01–1.83). Age was marginally significant in the multivariate analysis, with women over 65 years of age less likely to enter a trial ($P = 0.05$; adjusted odds ratio 0.76, 95% CI 0.57–1.00). This effect was more pronounced, and statistically significant, for women over 80 years of age ($P = 0.01$; adjusted odds ratio 0.43, 95% CI 0.22–0.84). The effect of deprivation on trial entry in the univariate analysis was mainly due to a higher proportion of the least deprived women entering studies with no clear trend across the full range of deprivation categories. In the multivariate analysis, deprivation had no effect on entry into clinical trials ($P = 0.93$).

Survival was evaluated in the 1987 cohort of women without metastatic disease at presentation, in whom initial management may reasonably be expected to influence outcome. At the time of this analysis, 844 of these women had died, of whom 58 had entered trials for early or locally advanced disease. There was a trend for adjusted survival to be better in the women treated in these clinical trials, although this did not reach statistical significance ($P = 0.10$; Hazard ratio 0.79, 95% CI 0.59–1.04).

Table 3. *Factors influencing study entry into clinical trials for early/locally advanced disease in women with non-metastatic disease in univariate analyses* (n = 4321)

	% in trial (observed)	*P* value*
Age (years)		< 0.0001
< 50	12.2	
50–69	11.0	
65–79	6.7	
≥ 80	2.3	
Seen by oncologist		< 0.0001
Yes	12.3	
No	4.3	
Deprivation category		0.016
1 (least deprived)	11.2	
2	6.9	
3	8.4	
4	9.9	
5 (most deprived)	9.1	
Health Board ($n = 13$)†	0, 0, 0, 1.2, 1.5, 2.5, 3.0, 3.1, 3.5, 11.0, 13.1, 15.7, 17.8	< 0.0001
Surgical case load		< 0.0001
1–9	2.8	
10–29	1.3	
≥ 30 or team	14.8	

*χ^2 test for association. †Because of their small numbers and geographical similarities, the Orkney, Shetland and Western Isles Health Boards were analysed as a single group.

DISCUSSION

To our knowledge, this is the first study to address issues of trial recruitment through a nationwide review of individual case records identified from a population-based registry rather than clinical trials databases alone. The most important finding of the current study is that, after allowing for other factors in the multivariate analysis, patients seen by a specialist surgeon or oncologist are significantly more likely to enter clinical trials. A woman seen by a surgeon with a large case load is approximately seven times more likely to be treated in a clinical trial. Similarly, women referred to an oncologist are approximately three times more likely to enter trials.

In Scotland, approximately 12% of patients with breast cancer enter clinical trials. The apparent reduction in clinical trial entry between 1987 and 1993 is due to fewer patients in the latter cohort having relapsed and entered studies of metastatic disease by the time the data were collected. The proportion of women entering trials for early or locally advanced disease was the same in both years. The figure of 12% compares with over 50% of children who have acute lymphoblastic leukaemia being treated in Medical Research Council studies. However, this level of recruitment is seen only in childhood malignancies where entry into a clinical trial is itself associated with improved survival [10]. It is not surprising that in our study no significant survival benefit was observed. With many patients entering trials examining local control, which is unlikely to affect survival, and only 58 deaths amongst women entering trials for early or locally advanced disease, the current study had little statistical power to detect such an effect.

Women entering clinical trials consistently had their disease staged more comprehensively. Axillary node status is the single most important prognostic factor in women with breast cancer and an important determinant of adjuvant systemic treatment. Women entering a trial were significantly more likely to have their axillary status defined. Similarly, ER status, clinical stage and pathological tumour size were all recorded in a higher proportion of women entering clinical trials. These patients may receive more appropriate treatment. Clinical trial eligibility criteria probably explain, at least in part, the significantly lower recruitment of older women. Their management is, however, often suboptimal [5] and unlikely to improve until they are recruited into trials addressing issues relevant to their care. By contrast, it is encouraging to note that social deprivation did not influence study entry in the multivariate analysis. This is important, as patients entering clinical trials should be representative of the general population.

The current study has highlighted important demographic factors that contribute to variability in entry into clinical trials. Referral to a surgeon with a large case load or to an oncologist are particularly important. In the unadjusted analysis, women seen by a surgeon with a case load of less than 30 per year and who did not see an oncologist had the lowest rate of trial entry (0.3%), whereas those seen by both a high case load surgeon and an oncologist were most likely to enter a trial (19.7%). Patients seen by either a high case load

surgeon *or* an oncologist had an intermediate rate of trial entry (5.0%). In the multivariate analysis, both surgical case load and referral to an oncologist were highly significant in a multivariate analysis of factors predicting trial entry.

The Health Board of first treatment also had a significant effect on the likelihood of patients entering clinical studies in the multivariate analyses. Not surprisingly, when the Health Boards were ranked according to the percentage of patients entering clinical trials, the top four positions were occupied by the Health Boards with teaching hospitals. Similarly, patients first seen at one of the five regional cancer centres were more likely to be entered into trials than those treated elsewhere. The local availability of resources for undertaking clinical trials is likely to be an important factor determining the geographical variability in entry into trials. In particular, non-surgical oncologists are based predominantly in these cancer centres. As in the rest of the U.K., the small number of senior non-surgical oncologists in Scotland (32 in 1987 and 37 in 1993) may limit their ability to enter patients into trials, even within the major centres.

This study has important implications both for the delivery of cancer services and clinical trials in the future. The development of cancer services in cancer units linked to larger cancer centres is a central theme of plans proposed by the Expert Advisory Group on Cancer, U.K. [11]. As only half of all patients with cancer see an oncologist at present in Britain [12], the reorganisation of cancer services should also increase recruitment to clinical trials. However, a working party from the United Kingdom Coordinating Committee on Cancer Research recently warned that changes in the National Health Service may threaten research because of the excess costs incurred [13]. In the U.S.A., concerns have been voiced that the treatment of an increasing proportion of patients with Hodgkin's disease in smaller units may compromise accrual to clinical trials [14]. The current study emphasises the importance of the organisation of cancer services into specialist teams in recruitment into cancer trials. It is essential that the increasing number of U.K. oncologists based at cancer units [15] are integrated into teams with specialist surgeons and have access to the resources necessary for clinical trials. The effect of a Health Board on trial entry highlights the need to address geographical variation in patterns of treatment and clinical research. Finally, there is a need for clinical trials to address issues relevant to the management of older women with breast cancer.

It is vital that more patients enter studies to identify improved treatments for women with breast cancer. The management of patients by specialist multidisciplinary teams committed to the development of better care for women with breast cancer should facilitate entry into clinical trials.

1. Tate HC, Rawlinson JB, Freedman LS. Randomised comparative studies in the treatment of cancer in the United Kingdom: room for improvement? *Lancet* 1979, **ii**, 623–625.
2. Friedman MA, Cain DF. National Cancer Institute sponsored cooperative clinical trials. *Cancer* 1990, **65**, 2376–2382.
3. Swanson GM, Ward AJ. Recruiting minorities into clinical trials: toward a participation-friendly system. *J Natl Cancer Inst* 1995, **87**, 1747–1759.
4. Macbeth F, Stephens R. Marketing clinical trials. *Lancet* 1996, **348**, 111–112.
5. Fentiman IS, Tirelli U, Monfardini S. Cancer in the elderly: why so badly treated? *Lancet* 1990, **335**, 1020–1022.
6. Jack WJL, Chetty U, Rodger A. Recruitment to a prospective breast conservation trial: why are so few patients randomised? *Br Med J* 1986, **301**, 83–85.
7. Carstairs V, Morris R. *Deprivation and Health in Scotland*. Aberdeen, Aberdeen University Press, 1991.
8. Sainsbury R, Haward B, Rider L, Johnston C, Round C. Influence of clinician workload and patterns of treatment on survival from breast cancer. *Lancet* 1995, **345**, 1265–1270.
9. Armitage P, Berry G. *Statistical Methods in Medical Research*, 3rd edition. Oxford, Blackwell Scientific, 1994.
10. Stiller CA. Centralised treatment, entry to clinical trials and survival. *Br J Cancer* 1994, **70**, 352–362.
11. Expert Advisory Group on Cancer. *A Policy Framework for Commissioning Cancer Services*. London, Department of Health, 1995.
12. Richards MA, Parrott JC. Tertiary cancer services in Britain: benchmarking study of activity and facilities at 12 specialist centres. *Br Med J* 1996, **313**, 347–349.
13. Smyth JF, Mossman J, Hall R, *et al.* on behalf of the United Kingdom Coordinating Committee on Cancer Research. Conducting clinical research in the new NHS: the model of cancer. *Br Med J* 1994, **309**, 457–461.
14. Rosenburg SA. Hodgkin's disease: no stage beyond cure. *Hosp Pract* 1986, **21**, 91–108.
15. McIllmurray MB, Gorst DW, Holdcroft PE. A comprehensive service in a district general hospital. *Br Med J* 1986, **292**, 669–671.

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