Changes in long term prognosis for breast cancer in a Dutch cancer registry

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Abstract

Objectives—To assess whether the long term survival of patients with breast cancer has changed with time.

Design—Population based descriptive study.

Setting—Eindhoven Cancer Registry in south east Netherlands.

Subjects—2052 patients with first primary breast cancer diagnosed between 1955 and 1974.

Main outcome measures—Overall survival and relative survival.

Results—Overall survival was 35% (727 patients) after 10 years, 21% (267) after 20 years, and 15% (25) after 30 years. The corresponding relative survival rates were 43%, 34%, and 34%, respectively. Survival improved from 1955 onwards for all ages and all tumour stages. Improvement was observed in both overall and relative survival. Prognosis was strongly related to the stage at diagnosis in the first 10 years of follow up but independent of stage after 10 years. Survival of patients still alive after 19 years became similar to that of the general female population.

Conclusions—Both short and long term survival improved considerably in all age groups. This improvement was most marked for patients who were diagnosed with a localised tumour. Patients who survive for 19 years may be considered cured.

Introduction

Breast cancer is the most common malignancy in Dutch women. It makes up about 30% of all new primary cancers¹ and 22% of cancer deaths in women.² Over the past 30 years the incidence of breast cancer in south east Netherlands has roughly doubled in all age groups, with a clear trend towards an earlier stage at diagnosis.³ Simultaneously, breast cancer mortality has remained unchanged in women aged under 60 and increased slightly in older women. These differing trends between incidence and mortality, which have been observed in many countries,^{4,7} suggest increasing survival rates with time. However, most reports on improved survival for breast cancer patients have only a short follow up^{5,9} or do not control for the influence of tumour stage on survival outcome.^{7,10}

We investigated trends in long term overall and relative survival of 2052 women in whom breast cancer had been diagnosed between 1955 and 1974.

Patients and methods

The study included all women with a first primary breast cancer diagnosed between 1955 and 1974 in south east Netherlands, who were followed up until 1991. Data came from the Eindhoven Cancer Registry, which was founded in 1955 and has been part of the Comprehensive Cancer Centre South Netherlands since 1983.¹ The data were derived from copies of pathologists' records, patients' files in community hospitals, and the regional radiotherapy institute. The registry covered an area in south east Netherlands with

about 300 000 inhabitants in 1955 and over 900 000 since 1970; this increase was largely due to expansion of the area covered by the registry in 1970. Patients from the newly included area had a similar age distribution to patients in the original region at the time of the expansion. The incidence of breast cancer in this population could be estimated from 1960 onwards.^{3,11}

From 1955 to 1974 the registry collected data on 2098 new breast cancer patients, and for 2052 of these patients information about vital status was obtained from population administrations for up to 1 July 1991. A total of 100 women were lost to follow up after varying periods, and in analyses these patients were considered to have withdrawn alive.

Tumour stage at diagnosis was recorded on the basis of clinical examination supplemented by pathologists' reports and was classified into three categories: localised (cancer confined to the breast regardless of size), regional (cancer spread beyond breast but still in its immediate neighbourhood or extended to the regional lymph nodes), and distant (cancer having involved tissues beyond those immediately draining or neighbouring the breast). In 137 patients tumour stage could not be classified into one of these categories.

Survival was calculated as overall and relative survival, relative survival being the ratio of the observed rates to the expected rates. Expected survival rates were calculated from life tables (supplied by the Netherlands Central Bureau of Statistics) compiled according to five year age groups and year of diagnosis for the regional female population.¹² Actuarial survival curves were computed,¹³ according to age category (≤ 50 , 51-65, and > 65), year of diagnosis (1955-9, 1960-4, 1965-9, 1970-4), and tumour stage. The log rank test was used to assess the significance of differences in survival. The prognostic value for the overall survival of several factors simultaneously was assessed using the Cox proportional hazards model.¹⁴

MORTALITY DUE TO BREAST CANCER

Excess risk of death due to breast cancer was modelled with a program of the Finnish Cancer Registry.¹⁵ In this model the annual excess mortality was allowed to depend simultaneously on age, tumour stage, and year of diagnosis. Excess mortality was the difference between observed mortality and expected mortality. Expected mortality was determined by the age of the patients and the time of diagnosis. The excess mortality presumably reflected deaths due to breast cancer. In both analysis methods we assumed that the various factors had a proportional effect on the outcome. As this assumption appeared to be violated when the total follow up after diagnosis was considered, separate analyses were performed for the first and second five year periods of follow up and for the next 10 year period of follow up. This was achieved by considering only patients who were alive at the beginning of each period, while patients who survived to the end of the period were considered as withdrawn from the study (censored).

In all analyses all variables were initially taken to be

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categorical, but we found that the factor of primary interest, year of diagnosis, had estimated effects that were roughly linear with more recent diagnosis. Therefore this factor was introduced in the models with the numerical codes 0, 1, 2, and 3 for the times of diagnosis (1955-9, 1960-4, 1965-9, and 1970-4), thereby allowing tests for linear trend to be performed. Within each of the three periods of follow up considered we investigated whether the effect of the time of diagnosis depended on tumour stage or age of patients at diagnosis by incorporating appropriate interaction terms in the models. In the final model, after adjustments for age and tumour stage, the death rate among patients whose cancer was diagnosed in one five year period was compared with the death rate in the next five year period of diagnosis as an indicator of the change in prognosis over time. Other statistical methods were used as indicated in the text, and significance was set at the 5% level.

Results

The age distributions of the patients (mean age 56.5 years, range 22-95) did not differ significantly between the four sets of patients grouped according to time of diagnosis (Kruskal-Wallis test, $P=0.7$) (table I). Tumour stage tended to be more favourable with more recent diagnosis (χ^2 test for trend, $P=0.04$). Patients' age did not correlate with tumour stage at diagnosis. Primary treatment for localised tumours showed a slight shift from combined surgery and radiotherapy to surgery only. The proportions of patients treated by adjuvant chemotherapy and hormonal therapy (including ovariectomy) increased slightly from none and 1% (2) respectively of those whose concerns were diagnosed in 1955-9 to 2% (24) and 2% (27) of those with cancers diagnosed in 1970-4. In addition, the proportions of patients treated by secondary chemotherapy and secondary hormonal treatment rose from 2% (4) and 2% (5) respectively among those with cancer diagnosed in 1955-9 to 13% (152) and 19% (223) respectively among those with cancer diagnosed in 1970-4.

In total 1172 (52%) patients survived five years after diagnosis, 727 (35%) survived 10 years, 267 (21%) survived 20 years, and 25 (15%) survived 30 years. The corresponding relative survival percentages were 57%, 43%, 34%, and 34% respectively. Prognosis was considerably worse for patients with distant metastases at diagnosis, and so survival of such patients was analysed separately.

OVERALL SURVIVAL

For patients without distant metastases at diagnosis 10 year survival rates were 26%, 31%, 34%, and 39% for patients with cancers diagnosed in 1955-9, 1960-4, 1965-9, and 1970-4 respectively. Cox regression analysis showed that, during the first five years of follow up, tumour stage was an important prognostic

TABLE II—Age adjusted death rate ratios (SE) for patients with breast cancer during different periods of follow up according to tumour stage and time of diagnosis. Values calculated by Cox regression, and only patients with localised and regional disease included

	Period of follow up		
	Years 1-5 (n=1806)	Years 6-10 (n=923)	Years 11-20 (n=602)
<i>Regional stage of tumour*</i>			
Patient's age (years):			
22-50	2.6 (0.6)	1.8 (0.2)	1.1 (0.2)
51-65	2.3 (0.5)		
> 65	1.1 (0.2)		
<i>Time of diagnosis†</i>			
Tumour stage:			
Localised	0.77 (0.05)	0.95 (0.05)	0.8 (0.06)
Regional	0.93 (0.03)		

*Localised disease used as reference category and given value of 1 for each follow up period. Rate ratios significantly dependent on age for first follow up period and represent effect of tumour stage for first period of diagnosis (1955-9): for each subsequent diagnostic period rate ratios increased by 21% because of greater improvement in survival for localised disease compared with regional disease.

†1960-4 v 1955-9, 1965-9 v 1960-4, and 1970-4 v 1965-9. Rate ratios significantly dependent on tumour stage for first follow up period.

TABLE III—Age adjusted ratios (SE) of excess risks of death for patients with breast cancer during different periods of follow up according to tumour stage and time of diagnosis. Only patients with localised and regional disease included

	Period of follow up		
	Years 1-5 (n=1806)	Years 6-10 (n=923)	Years 11-20 (n=602)
<i>Regional stage of tumour*</i>			
	2.1 (0.5)	2.3 (0.3)	1.2 (0.3)
<i>Time of diagnosis†</i>			
Tumour stage:			
Localised	0.72 (0.07)	0.98 (0.07)	0.77 (0.09)
Regional	0.93 (0.04)		

*Localised disease used as reference category and given value of 1 for each follow up period. Excess risk for first follow up period represents effect of tumour stage for first period of diagnosis (1955-9): for each subsequent diagnostic period excess risk increases by 29% because of greater improvement in survival for localised disease compared with regional disease.

†1960-4 v 1955-9, 1965-9 v 1960-4, and 1970-4 v 1965-9. Excess risk significantly dependent on tumour stage for first follow up period.

factor that significantly depended on age ($P<0.001$), with the prognostic value of stage being highest in the youngest patients (table II). Survival improved with more recent diagnosis for both localised and regional tumours ($P<0.05$), although improvement was greater for localised disease (table II).

In the second five years of follow up, tumour stage at diagnosis was again an important independent prognostic factor (table II). The improvement in overall survival in this follow up period was small and not significant ($P=0.3$). In the second 10 years of follow up survival did not differ between patients with different tumour stage at diagnosis. In this period survival improved substantially with more recent diagnosis ($P<0.05$), but this improvement was not significantly different from that seen in the second five years of follow up. Unsurprisingly, overall mortality was strongly related to age in all the periods of follow up.

Median survival of the group of 109 patients with distant disease at diagnosis was 0.9 years. Of these patients, 29 survived for two years, and only nine survived for more than five years. Age adjusted death rates declined by 20% compared with diagnoses made five years earlier ($P<0.01$), and this improvement in survival was apparent in all age groups.

RELATIVE SURVIVAL

Relative survival improved with more recent diagnosis, particularly for patients with localised tumours at diagnosis (fig 1). Table III shows that, in contrast to overall survival (table II), the excess risk of dying in the first five years of follow up in relation to stage at diagnosis did not differ significantly between the

TABLE I—Number (percentages) of patients with breast cancer according to age, tumour stage, and primary treatment. Data are grouped according to time of diagnosis

	1955-9 (n=240)	1960-4 (n=273)	1965-9 (n=393)	1970-4 (n=1146)	Total (n=2052)
Age (years):					
22-50	101 (42)	102 (37)	138 (35)	451 (39)	792
51-65	77 (32)	103 (38)	154 (39)	382 (34)	716
> 65	62 (26)	68 (25)	101 (26)	313 (27)	544
Tumour stage:					
Localised	67 (28)	84 (31)	154 (39)	392 (34)	697
Regional	143 (60)	174 (64)	206 (52)	586 (51)	1109
Distant	17 (7)	10 (3)	17 (4)	65 (6)	109
Unknown	13 (5)	5 (2)	16 (4)	103 (9)	137
Primary treatment:					
Surgery	49 (20)	45 (17)	96 (24)	412 (36)	602
Radiotherapy	18 (8)	29 (9)	23 (6)	73 (6)	138
Surgery and radiotherapy	169 (70)	200 (73)	270 (69)	638 (56)	1277
Other or none	4 (2)	4 (2)	4 (1)	23 (2)	35

FIG 1—Percentage relative survival of patients with breast cancer diagnosed between 1955 and 1974

FIG 2—Annual relative survival rates of patients with breast cancer diagnosed between 1955 and 1974

various age groups. In this period of follow up the reduction in the excess death rates for patients with localised disease was 28% ($P < 0.01$) compared with patients diagnosed five years earlier: for patients with regional disease this figure was significantly less at 7% ($P = 0.08$).

In the second five years of follow up excess risk of dying also depended significantly on tumour stage at diagnosis and not significantly on the period of diagnosis. In the second 10 years of follow up the excess risk of dying did not depend on tumour stage at diagnosis, and in this follow up period the reduction in excess death rates was 23% ($P < 0.01$) compared with

patients diagnosed five years earlier. Excess mortality was not significantly related to the age of patients in any of the follow up periods.

For patients with distant disease at diagnosis, the excess death rates decreased significantly by 22% ($P < 0.01$) compared with patients diagnosed five years earlier.

Annual relative survival rates for the patients gradually increased and reached 100% at 19 years, implying that the subsequent survival rate of patients who survive that long does not differ from that of women of a similar age in the general population of the study region (fig 2).

Discussion

The prognosis for patients in south east Netherlands with a diagnosis of breast cancer improved substantially between 1955 and 1974. This improvement occurred in both short and long term survival and was present at all ages. The improvement in relative survival (table III) was similar to that for overall survival (table II) and showed that improvement was greatest for patients with localised tumours at diagnosis. The improved survival we found is consistent with the report of increased incidence of localised and distant tumours but stable mortality in south east Netherlands in the same period.³ Possible reasons for the improved survival include better treatment, earlier detection, and diagnosis of less aggressive tumours.

Since the 1960s various claims have been made about more effective treatments consisting of hormonal and cytotoxic treatment. Cytotoxic treatment, which was introduced in the study region in the 1970s and mostly given for recurrence, possibly contributed slightly to the improvement of survival. Supportive care such as prevention of complications and treatment of comorbidity may also have improved, thereby helping to improve the prognosis of breast cancer. Although we adjusted for tumour stage, the trend towards earlier detection may nevertheless have had an impact on the results, since within the three robust stage groups a trend is also likely. For example, localised tumours detected in the 1970s were probably generally smaller than localised tumours detected in the 1950s (residual confounding). However, the substantial improvement in relative survival was also observed when we used the

Clinical implications

- For decades many countries have observed an increase in incidence of breast cancer combined with relatively stable mortality, suggesting increased survival rates
- However, studies reporting improved survival of patients with breast cancer have generally had short follow up or have not controlled for the effects of tumour stage
- In this study of patients in south east Netherlands with breast cancer diagnosed between 1955 and 1974 we found that both short and long term survival improved considerably during study period
- This improvement occurred in all age groups and was greatest for patients with localised tumours at diagnosis
- At 19 years after diagnosis patients' survival was similar to that of the general female population, indicating that such patients could effectively be regarded as cured

more refined staging of the tumour, node, metastases (TNM) classification to analyse the results for the 1396 patients for whom suitable information was available (data not shown). Alternatively, increasing numbers of patients may have been allocated to higher tumour stages because of more extensive staging procedures,¹⁶ resulting in a more favourable outcome in all stages.¹⁷ An increase in the proportion of less aggressive tumours is also possible.¹⁸

While some reports have shown that patients with breast cancer have increased mortality compared with the normal population for as long as they are followed up,¹⁹⁻²¹ other studies have found that such patients' mortality approaches or equals that of the normal population after varying intervals.²²⁻²³ In our study breast cancer patients had the same mortality as the general female population after 19 years and might therefore be considered cured after that time.

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Pursuit and practice of complementary therapies by cancer patients receiving conventional treatment

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See editorial by Oh

Abstract

Objectives—To determine what proportion of oncology patients receiving conventional medical treatment also use complementary treatments; to assess which complementary treatments are the most popular and to assess patients' motivation for using them; to evaluate associated advantages and risks.

Design—Postal screening questionnaire followed by semistructured interview.

Setting—Two hospitals in inner London.

Subjects—600 unselected oncology patients aged 18 or over who had known their diagnosis of cancer for at least three months.

Main outcome measures—Prevalence and demography of use of complementary therapies; patients' motivation and expectations of complementary therapies; areas of satisfaction and dissatisfaction associated with conventional and complementary therapies.

Results—415 (69%) patients returned the questionnaire. 16% had used complementary therapies. The most popular were healing, relaxation, visualisation, diets, homoeopathy, vitamins, herbalism, and the Bristol approach. Patients using complementary therapies tended to be younger, of higher social class, and female. Three quarters used two or more therapies. Therapies were mostly used for anticipated antitumour effect. Ill effects of diets and herb treatments were described. Satisfaction with both conventional and complementary therapies was high,

although diets often caused difficulties. Patients using complementary therapies were less satisfied with conventional treatments, largely because of side effects and lack of hope of cure. Benefits of complementary therapies were mainly psychological.

Conclusions—A sizeable percentage of patients receiving conventional treatments for cancer also use complementary therapies. Patient satisfaction with complementary therapies, other than dietary therapies, was high even without the hoped for anticancer effect. Patients reported psychological benefits such as hope and optimism.

Introduction

Complementary or alternative medicine are the names given to a system of health care which lies for the most part outside the mainstream of conventional medicine. It has been described as the growth industry of the 1980s and is predicted to be even more popular in the 1990s. In 1983 the British Medical Association's Board of Science and Education commissioned a working party to assess the practice of complementary or alternative therapies.¹ The report, published in 1986, identified the dissatisfaction of the general public with the increasingly technical approach to medicine, the fragmentation of care due to specialisation, and the loss of bedside skills as contributory factors to the increased popularity of complementary therapies. It noted the heightened expectations of the public caused

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