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Long-term survival of women with breast cancer in New South Wales

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Abstract

Several long-term studies of breast cancer survival have shown continued excess mortality from breast cancer up to 20–40 years following treatment. The purpose of this report was to investigate temporal trends in long-term survival from breast cancer in all New South Wales (NSW) women. Breast cancer cases incident in 1972–1996 (54,228) were derived from the NSW Central Cancer Registry—a population-based registry which began in 1972. All cases of breast cancer not known to be dead were matched against death records. The expected survival for NSW women was derived from published annual life tables. Relative survival analysis compared the survival of cancer cases with the age, sex and period matched mortality of the total population. Cases were considered alive at the end of 1996, except when known to be dead. Proportional hazards regression was employed to model survival on age, period and degree of spread at diagnosis. Survival at 5, 10, 15, 20 and 25 years of follow-up was 76 per cent, 65 per cent, 60 per cent, 57 per cent and 56 per cent. The annual hazard rate for excess mortality was 4.3 per cent in year 1, maximal at 6.5 per cent in year 3, declining to 4.7 per cent in year 5, 2.7 per cent in year 10, 1.4 per cent in year 15, 1.0 per cent for years 16–20, and 0.4 per cent for years 20–25 of follow-up. Relative survival was highest in 40–49 year-olds. Cases diagnosed most recently (1992–1996) had the highest survival, compared with cases diagnosed in previous periods. Five-year survival improved over time, especially from the late 1980s for women in the screening age group (50–69 years). Survival was highest for those with localised cancer at diagnosis: 88.4 per cent, 79.1 per cent, 74.6 per cent, 72.7 per cent and 72.8 per cent at 5, 10, 15, 20 and 25 years follow-up (excluding those aged $\geqslant$70 years). There was no significant difference between the survival of the breast cancer cases and the general population at 20–25 years follow-up. Degree of spread was less predictive of survival 5–20 years after diagnosis, compared with 0–5 years after diagnosis, and was not significant at 20–25 years of follow-up. Relative survival from breast cancer in NSW women continues to decrease to 25 years after diagnosis, but there is little excess mortality after 15 years follow-up, especially for those with localised cancer at diagnosis, and the minimal excess mortality at 20–25 years of follow-up is not statistically significant.

Keywords: Breast neoplasm; Long-term survival; Population study; Excess mortality; Relative survival analysis; Annual hazard rate

1. Introduction

Several long-term studies of breast cancer survival have shown continued excess mortality from breast cancer up to 20–40 years following treatment [1–10]; these would not have received adjuvant chemotherapy as part of primary treatment. Some studies suggest improvement of long-term survival for cases diagnosed more recently (in women who would have received adjuvant chemotherapy), and the possibility of cure—defined as the disappearance of excess mortality at extended periods of follow-up in cancer cases compared with the age, sex and period matched general population. A Dutch study [11,12] reported that relative survival for breast cancer reached a plateau at 19 years after diagnosis, but data from Sweden [13] and the United States [14] suggest a continued fall in relative survival after 15 years post-diagnosis.

Studies of long-term survival for localised breast cancer have indicated good survival and a very low risk of recurrence after 10 years, which suggests that node-negative breast cancer is a curable disease [15–17].

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Analyses of predictors of breast cancer survival generally have found less effect of prognostic indicators for long-term than short-term survival and demonstrated significant effects of age and stage on long-term survival [18].

The purpose of this study was to examine long-term survival in New South Wales (NSW) women diagnosed with breast cancer from 1972 to 1996, and to determine whether there are groups defined by age and degree of spread at diagnosis that can be considered cured. Previous population studies of breast cancer survival in NSW and Australia have been mostly limited to five-year follow-up [19–25].

2. Patients and methods

2.1. Study

The study is a longitudinal, population-wide study of breast cancer survival using the relative survival (excess mortality) method [26,27]. The outcome factor is breast cancer survival or odds of death from breast cancer. The study factors are age group, period of diagnosis and degree of spread of the cancer at diagnosis.

2.2. Data

2.2.1. Breast cancer cases

Breast cancer cases were derived from the NSW Central Cancer Registry (NSW CCR), a population-based registry that began data collection in January 1972. The notification of malignant neoplasms has been a statutory requirement for all NSW public and private hospitals, radiotherapy departments and nursing homes since 1972, and for pathology and outpatients departments since 1985 [28]. Measures of data quality do not suggest significant under-enumeration, and data from the NSW CCR are accepted by the International Agency for Research on Cancer (IARC) for publication in *Cancer Incidence in Five Continents* [29].

The histological verification rate for breast cancer in the NSW has improved from 77 per cent in 1973–1977 to 96 per cent for 1988–1991. Lower rates of histological verification in earlier periods are most likely due to the voluntary nature of pathology notification in NSW before, rather than less histological diagnoses. Cases notified by death certificate only (DCO) varied from 1.3% in earlier time periods to 0.3% in the most recent data. All invasive breast cancer cases notified to the CCR as diagnosed in NSW women from 1972 to 1996 were included in this analysis (including DCO notifications); survival follow-up extended to the 31 December 1996 for all cases. Incident cases in 1996 had a maximum of one year follow-up. In situ breast neoplasms were not included. Data on degree of spread of tumour were recorded from hospital and radiotherapy notifiers as: (a) localised to tissue of origin (localised); (b) invasion of skin or underlying muscle (locally advanced), or regional lymph nodes; (c) distant metastasis (metastatic); and (d) unknown (no information available); see Table 1. The information was 78 per cent complete for 1972–1976, and this rate improved to 87 per cent for 1987–1991.

This method of classification of cancer spread is also used by several major cancer registries around the world, such as the Surveillance, Epidemiology and End-results (SEER) programme in the USA (which groups nine US population-based registries) [30–32], and the Danish cancer registry [33]. Although not ideal, it has been possible to implement this classification for a high proportion of cancers on a population-wide basis [34]. From a study of breast cancers in patients resident and treated in western Sydney during 1992 [35] enumerated by the NSW CCR, but added to by a detailed review of the clinical records (and information from treating doctors where necessary), it was found that 90 per cent of breast cancers designated as 'localised' by the NSW CCR were truly localised according to detailed TNM staging (pathological clinical); and 96 per cent designated as 'regional' were, in fact, regional spread according to the TNM staging. Numbers were too small to evaluate the distant spread category. Among the cases with unknown spread, around 60 per cent were found to be localised cancers and 40 per cent to have regional spread.

2.2.2. Deaths in breast cancer cases

The NSW CCR enumerates breast (or other) cancer deaths in breast cancer cases in NSW. Cancer registries in Australia regularly exchange information on deaths in cancer patients and cases are allocated to the state where the cancer was incident. All cases of breast cancer not known to be dead by the NSW CCR were matched against the death records from the NSW Registrar of Births, Deaths and Marriages (BDM), enhanced by information obtained from the Australian Bureau of Statistics (ABS). Since there is no unique number, record linkage in Australia must depend on the use of standard identifiers such as names, sex and date of birth. Record linkage was accomplished by in-house deterministic procedures and probabilistic matching [36–39]. Equivocal matches were investigated by individual examination of the details available. It was assumed that those women not known to be dead were alive on 31 December 1996 (passive follow-up).

2.2.3. Underlying female mortality

The expected survival for age and period-matched NSW women was derived from published annual, unabridged (single year of age) life tables for each sex produced by ABS for 1972–1996 and available on

Table 1
Breast cancer by degree of spread and period at diagnosis, NSW women age <70 years

Degree of spread[a]	Period of diagnosis				
	1972–1976	1977–1981	1982–1986	1987–1991	1992–1996
Localised					
Cancers	2472	2808	3337	4413	5921
%	42.5	44.6	47.3	48.7	51.6
% excl unkn [b]	54.4	54.1	54.0	54.8	59.0
Regional spread and/ or, locally advanced					
Cancers	1764	2061	2471	3297	3801
%	30.3	32.7	35.0	36.4	33.1
% excl unkn [b]	38.8	39.7	40.0	41.0	37.9
Metastatic					
Cancers	307	325	372	340	312
%	5.3	5.2	5.3	3.7	2.7
% excl unkn [b]	6.8	6.3	6.0	4.2	3.1
Unknown spread					
Cancers	1277	1108	870	1017	1438
%	21.9	17.6	12.3	11.2	12.5
Total	5820	6302	7050	9067	11,474

[a] Localised: cancer localised to the breast without local involvement of skin or muscle. Regional spread ± locally advanced: regional lymph node involvement and /or local invasion of muscle or skin.
[b] Excluding patients with unknown degree of spread of cancer at diagnosis

microfiche and electronically. The probability of dying (q_x) in one year and the life expectancy (e_x), for exact single years of age (0–99), were extracted from published tables.

2.3. Analysis

Relative survival compares the survival of women with cancer with the age, sex and period matched mortality of the total population; the advantage is that a single specific cause of death need not be assigned, and end-points can be obtained by linkage with death certificates [26,40]. Relative survival was calculated based on the period between diagnosis (date of 'first definitive treatment') and death (from any cause) for every case, and the age-and period-matched survival for all NSW women [26,27]. Women were considered alive at the end of 1996, except when known to be dead through death certificate linkage. Absolute survival was calculated according to the actuarial method. The relative survival analysis was carried out using a programme designed by the Finnish Cancer Registry and Newcastle University (NSW), Australia [40,41], which incorporates a correction for heterogeneity in the patient's follow-up times [40,42].

In order to preserve numbers in cross-classifications, categories were aggregated based on a similar relative survival. Age was classified as: 0–39 years, 40–49 years, 50–69 and ⩾70 years; and year of diagnosis was grouped as: 1972–1976, 1977–1986; 1987–1991, 1992–1996 (for survival analyses). Preliminary analysis indicated an increase in cumulative relative survival in women aged ⩾70 years at diagnosis after 10 years of follow-up, and this age group was excluded from analyses that included ⩾10 years of follow-up. Annual relative survival was averaged over five-year follow-up categories by meta-analysis, to obtain more stable estimates at extended periods of follow-up [43].

Proportional hazards regression analysis was performed in GLIM (Generalised Linear Interactive Modelling) [44] using the macro written by Hakulinen [41,45]. The statistical significance of including each of these variables was assessed from the change in deviance and degrees of freedom, approximated by a chi square (χ^2) distribution. Confidence intervals (95 per cent) were derived from the regression coefficients and their standard errors. Annual hazard rate for excess mortality was derived from the model. Sparsity of data necessitated the modelling of hazard rates for the 15–19 year and 20–25 year follow-up over the five-year period rather than annually in order to achieve convergence. Models of the effect of stage were constructed for each five-year period of follow-up. The advantage of this multiple regression is that it allows for the control of confounding by age, period of diagnosis and degree of spread, which occurs in the univariate relative survival calculations.

3. Results

Relative survival at 5, 10, 15, 20 and 25 years of follow-up was 76 per cent, 65 per cent, 60 per cent, 57 per cent and 56 per cent. The annual hazard rate for excess mortality for all cases was 4.3 per cent in year 1, maximal at 6.5 per cent in year 3, declining to 4.7 per cent in year 5, 2.7 per cent in year 10, 1.4 per cent in year 15, 1.0 per cent for years 16–20, and 0.4 per cent for years 20–25 of follow-up. Annual hazards for localised breast cancer and locally advanced and/or, regional spread are given in Fig. 1. At 20–25 years of follow-up, the small excess mortality hazard is the same for localised cancers and those with regional spread (or locally advanced) at diagnosis, and this is not statistically significant.

Relative survival was highest in the age group 40–49 years. Localised cancer had the highest relative survival, with little change after 15 years (75 per cent). Cases diagnosed more recently had the highest survival at 5, 10 and 15 years; survival to 20 years was higher in those diagnosed in 1977–1986 than in those diagnosed in 1972–1976, but the 95 per cent confidence limits overlap (Fig. 2). The proportion of cancers localised at diagnosis increased only during the most recent period, 1992–1996, associated with reductions in the proportion that were regional and metastatic (Table 1. Fig. 3).

Annual relative survival at diagnosis (1972–1996) was significantly less than the age- and period-matched female population of NSW to 19 years of follow-up, as judged by the 95 per cent confidence intervals. When aggregated into five-year follow-up periods, the annual excess risk for breast cancer patients is quite small (<0.5 per cent) at 20–25 years of follow-up and 95 per cent confidence intervals indicate no significant difference from the general population. At 15–20 years of follow-up, the excess annual mortality risk is 1 per cent for all patients, 0.5 per cent for women with localised breast cancer, and 2 per cent for women with locally advanced and/or regional spread at diagnosis (Table 2).

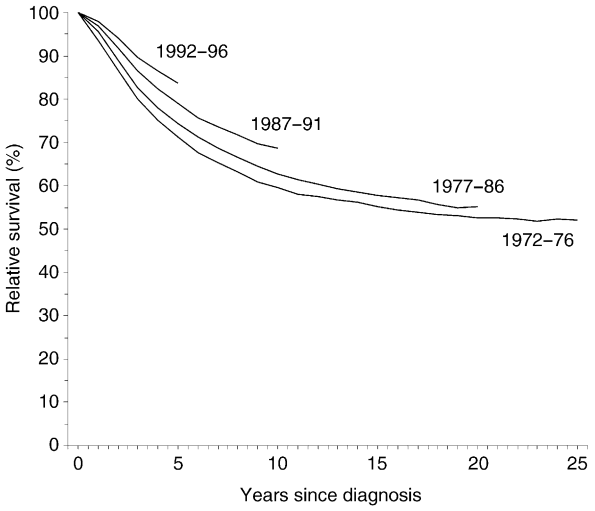

Fig. 2. Breast cancer relative survival in NSW women 1972–1996, by period, age <70 years at diagnosis.

The conditional relative survival for localised breast cancer and the local and/or regional spread category is given in Table 3. Women with localised cancer who survive five years have a near 90 per cent chance of surviving breast cancer over the next five years. For women with locally advanced and/or regional spread at diagnosis, breast cancer survival over the next five years of $\geqslant 90$ per cent is reached only after 15 years of follow-up.

The effect of degree of spread at diagnosis on excess mortality was less with follow-up of 5–20 years, than after 0–5 years, as evidenced by other smaller RRs for excess mortality in those with non-localised cancers at diagnosis (Table 4). Stage at diagnosis was not significant

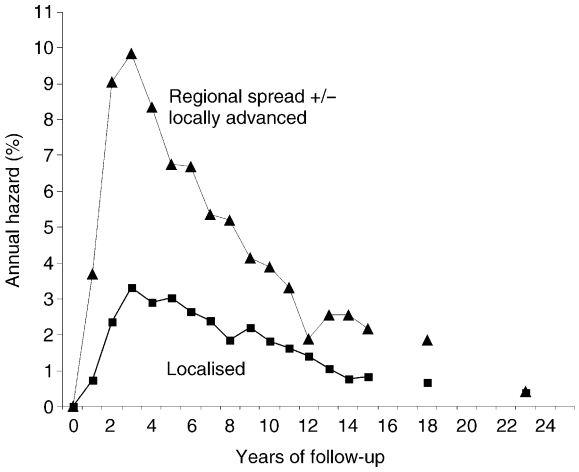

Fig. 1. Annual mortality hazard for breast cancer in NSW women 1972–1996, age <70 years at diagnosis.

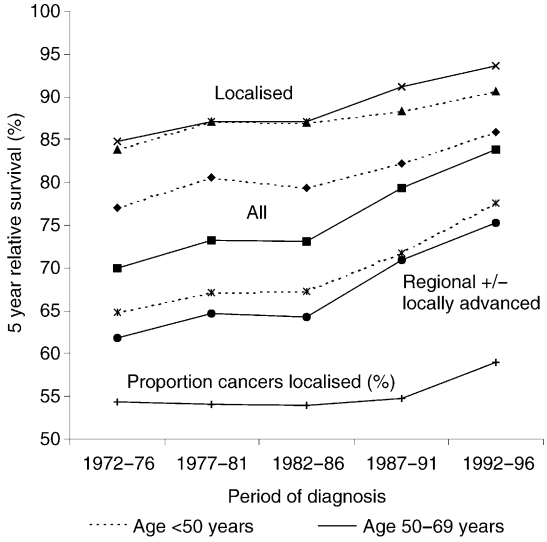

Fig. 3. Breast cancer five-year survival in NSW women 1972–1996 aged <50 and 50–69 years.

Table 2
Breast cancer survival to 25 years in NSW women aged <70 years at diagnosis, 1972–1996

Follow-up (years)[ab]	Breast cancer deaths	Average annual relative survival (%)	
		Survival ratio[c]	95% CIs
All			
0–5	7618	94.62	93.66–95.59
5–10	3394	96.72	96.17–97.27
10–15	1328	98.35	97.99–98.70
15–20	646	98.94	98.68–99.20
20–25	174	99.70	99.10–100.31[d]
Localised			
0–5	2289	97.57	96.51–98.64
5–10	1395	97.79	97.49–98.09
10–15	642	98.80	98.47–99.14
15–20	307	99.46	99.14–99.79
20–25	90	99.63	99.30–100.64[d]
Regional spread and/or, locally advanced			
0–5	3854	92.70	90.33–95.13
5–10	1354	95.03	94.12–96.00
10–15	431	97.48	96.98–98.00
15–20	195	98.04	97.45–98.64
20–25	39	98.44	95.32–101.67[d]

[a] Localised: cancer localised to the breast without local involvement of skin or muscle. Regional spread±locally advanced: regional lymph node involvement and/or local invasion of muscle or skin.
[b] Follow-up categories (years) are given from the beginning of one interval to the beginning of the next interval.
[c] Survival compared with age and period matched NSW women.
[d] Confidence limits (95%) of average annual relative survival for all categories above overlap 100% at 20–25 years follow-up.

in the regression model for excess mortality at 20–25 years of follow-up.

Five-year relative survival improved over the five periods of diagnosis, especially from the late 1980s onwards, for all breast cancers, and for the separate localised and regional (including locally advanced) categories separately (Fig. 3).

Table 4
Breast cancer survival in NSW women aged <70 years at diagnosis, 1972–1996 (The effect of stage at various periods of follow-up)

Follow-up (years)[a]	Effect of stage[b]		Relative risk (95% CIs) for excess mortality[c]	
	Chi Sq (2 df)	*P* value	Localised	Regional spread and/or locally advanced
0–5	2228	<0.001	1.00	3.79 (3.05–4.72)
5–10	301	<0.001	1.00	2.34 (2.10–2.62)
10–15	42	<0.001	1.00	2.08 (1.63–2.64)
15–20	18	<0.001	1.00	2.74 (1.74–4.33)
20–25	0.1	NS	1.00	0.89 (0.10–7.81)[d]

The effect of stage adjusted for five-year follow-up, period and age, except for 20–25 years follow-up where only stage could be modelled. Relative risks for the metastatic/unknown category not shown.
[a] Follow-up categories (years) are given from the beginning of one interval to the beginning of the next interval.
[b] df, Degrees of freedom; NS, non-significant.
[c] Localised: cancer localised to the breast without local involvement of skin or muscle. Regional spread±locally advanced: regional lymph node involvement and /or local invasion of muscle or skin.
[d] 95% CIs overlap 1.00.

4. Discussion

This study has included all women diagnosed with invasive breast cancer in New South Wales from 1972 to 1996, with follow-up to the end of 1996. Survival status was determined by automated record linkage between the State cancer registry and death register. Relative survival was calculated compared with the general mortality of NSW women matched for age and period.

Table 3
Breast cancer survival in NSW women aged <70 years at diagnosis, 1972–1996 (Conditional relative survival by five year follow-up for localised and locally advanced and/or regional spread)

	Relative survival (%)					
	Year of follow-up					
	0	5	10	15	20	25
Localised						
Relative survival to year of follow-up		88.4	79.1	74.6	72.7	72.8
Relative survival for next 5 years from year of follow-up	88.4	89.4	94.2	97.2	100.3	
Relative survival for next 10 years from year of follow-up	79.1	84.3	91.5	97.5		
Regional spread and/or, locally advanced						
Relative survival to year of follow-up		68.5	53.1	46.9	42.8	41.8
Relative survival for next 5 years from year of follow-up	68.4	77.5	88.0	90.7	97.8	
Relative survival for next 10 years from year of follow-up	53.1	68.3	79.9	88.8		

Localised: cancer localised to the breast without local involvement of skin or muscle. Regional spread±locally advanced: regional lymph node involvement and/or, local invasion of muscle or skin.

Women aged $\geqslant 70$ years at diagnosis manifested unrealistic relative survival at $\geqslant 10$ years follow-up (when aged $\geqslant 80$ years). This is most likely due to an under-ascertainment of deaths, with linkage procedures less successful because of less detail and reliability of identifiers recorded at both cancer and death registration at advanced ages. Since this study was concerned primarily with long-term survival, patients aged $\geqslant 70$ years at diagnosis were excluded from most of the calculations because of a probable ascertainment bias, and at 15 years of follow-up they would be at least 85 years old.

The study shows previously documented better survival in those aged 40–49 years at diagnosis than other ages, higher survival with a reduced degree of spread at diagnosis, and improved survival for more recent periods of diagnosis.

The debate continues as to whether breast cancer is a curable disease since recurrences may occur many years after diagnosis and treatment, and some long-term follow-up studies have documented continual excess mortality in patients compared with the general population to the limit of the follow-up in those studies [1–10,13,14]. This study shows excess mortality in women with breast cancer compared with the general population of NSW women up to 20–25 years of follow-up. However, the annual excess risk for breast cancer patients is quite small (<0.5 per cent) at 20–25 years of follow-up and the 95 per cent confidence intervals indicate no significant difference from the general population. At 20–25 years of follow-up, the small excess mortality hazard is the same for localised cancers and those with regional spread (or locally advanced) at diagnosis, and this is not statistically significant. These cases can be considered as cured. At 15–20 years of follow-up, the excess annual mortality risk is 1 per cent for all patients, 0.5 per cent for women with localised breast cancer, and 2 per cent for women with locally advanced and/or regional spread at diagnosis. Since designation of localised cancers in cancer registry material is not entirely accurate, the annual excess mortality for patients with truly localised breast cancer could be lower.

Women with localised cancer who survive five years have a near 90 per cent chance of surviving breast cancer over the next five years. For women with locally advanced and/or regional spread at diagnosis, breast cancer survival over the next five years of $\geqslant 90$ per cent is only reached after 15 years of follow-up. Although effective cure of breast cancer (defined by a mortality the same as the general population) occurs at extended follow-up (after 15 years), it has been pointed out that such periods are at or beyond the life expectancy of most patients, and that breast cancer is thus effectively incurable [10].

Similar to previous studies [10–12] the effect of stage as a predictor of excess mortality is less after five years of follow-up than during the first five years, and it is not significant at 20–25 years.

Secular trends indicate improvements in breast cancer survival since 1972, except for a plateau during 1977–1981 and 1982–1986. This improvement is evident for all breast cancer cases, and separately for localised cancers and those with regional spread (and/or locally advanced cancers). It is unlikely that this is due to any artefacts of the data from changes in enumeration of cancer or death linkage. The explanations are likely to result from earlier diagnosis and improvement in therapy.

Earlier diagnosis is a consequence of increased awareness of breast symptoms (and subsequent medical assessment) and screening of asymptomatic women, including through formal mammographic screening programmes. Earlier diagnosis (especially screening) will extend survival through 'lead time' bias because cancers are diagnosed earlier than they would have been, even with unchanged stage-specific survival. Furthermore, the initial screening examination detects more cancers than subsequent screens, and some of these prevalent cancers are slow-growing, and thus produce 'length-time' bias'. Informal mammographic screening occurred in NSW during the late 1980s, as evidenced by the increase in mammograms through Medicare (Health Insurance Commission) [46], and two pilot population-screening sites were established. However, population-based screening programmes were not started until 1992, and only by 1996 had the public mammographic screening programme evolved so that the entire population of NSW women notionally had access. Thus both 'lead-time' and 'length-time' bias would be expected to have operated increasingly over the two time periods of 1987–1991 and 1992–1996. Data on the proportion of cancers by degree of spread indicate that definite increases in the proportion that were localised did not occur until 1992–1996 when population-based mammographic screening was introduced progressively. Neither length-time nor lead-time bias should result in a reduced long-term cumulative survival, especially after 10 years, since they merely shift the mortality to later years of follow-up.

The real purpose of an earlier diagnosis of breast cancer is to improve survival by applying treatment that has a greater efficacy at an earlier stage of the disease. In this instance, stage-specific survival need not change. The data presented in this report indicate survival improvement for both localised breast cancers and for cancers with regional spread (and/or locally advanced) which may suggest that treatment has improved stage-specific outcome. However, localised and regional spread (and/or locally advanced) are broad categories, and the temporal improvement in survival could well be due to a reduction in the size of breast cancers in the localised group, and a reduced spread of cancers in the regional (and/or locally advanced) group over time. Furthermore, more intensive diagnostic assessment over time could improve the survival outcome of both groups by moving non-localised cancers with minimal spread

from the localised to the regional (and/or, locally advanced) category, and moving occult metastatic cancers out of the localised and regional categories. Although the proportion of cancers localised at diagnosis did not definitely increase until the latest time period (1992–1996), coinciding with the introduction of widespread mammographic screening, there might have been trends for smaller or less advanced tumours within the localised and regional categories during the prior time period (1987–1991).

The other important explanation to consider is the effect of improved stage-specific treatment on survival. The introduction of national universal medical insurance in late 1975 might have improved access to treatment for many patients in 1997–1981, over patients in 1972–1976. The advent of chemotherapy for node-positive breast cancer in the late 1970s might have been associated with improvements in survival for patients with regional spread in 1977–1981 over patients in 1972–1976. Increasing use of radiotherapy in the 1980s might have been associated with the improvement of survival from 1982–1986 to 1987–1991, although this period also witnessed informal and pilot mammographic screening and increased diagnostic activity. Some of the improvement in survival from 1987–1991 to 1992–1996 may be associated with the increasing use of adjunctive chemotherapy for node-negative patients in the localised category.

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