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Survival and Age at Diagnosis of Breast Cancer in a Population-based Cancer Registry

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From the population covered by the Lombardy Cancer Registry, Italy, 1991 female breast cancer patients diagnosed from 1976 to 1981 were followed up until May 1987. Relative survival was 69% at 5 years and 58% at 10 years; median survival was 8.8 years. Ages 40–49 showed the best survival; ages 25–34 were 20% lower. From age 50 onwards, survival decreased progressively, with the exception of age group 65–74. We suggest that the best prognosis for ages 40–49, followed by the survival fall in subsequent ages, could be related to an anticipation of diagnosis in ages near menopause. The death hazard function showed a bimodal pattern, with a first peak in the first years after diagnosis, and a second one between the seventh and eighth years. The death hazard rate decreased by about 1% per year at each subsequent calendar year of diagnosis. When such an estimated calendar effect was taken in account, there were no considerable survival differences among Western countries covered by population-based cancer registries.
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INTRODUCTION

THE AIM of this study was to analyse breast cancer survival in an Italian population covered by a cancer registry. The results of this work have also been applied to estimate breast cancer incidence and prevalence in the whole country by means of a mathematical model using survival and mortality [1].

The main prognostic factors analysed in this study are age at diagnosis and calendar period of diagnosis. Other important clinical prognostic indicators such as tumour stage and histotype are more difficult to analyse in a cancer registry, as the relevant information usually derives from different sources which are not standardised. However, population-based studies are able to give a picture of the impact of the disease on the entire population and provide information on the overall effectiveness of the health facilities existing in a defined area.

PATIENTS AND METHODS

The Lombardy Cancer Registry (LCR) provides incidence of cancer in the province of Varese, Northern Italy [2, 3], since 1976 and covers a population of approximately 380 000 males and 410 000 females [4].

2042 cases of invasive breast cancer (ICD-9 174) [5] which occurred in the 6 years from 1976 to 1981 were considered in this study. 47 cases (2.3%) known to the registry only through their death certificates were excluded from the survival analysis; 31 of them were aged 75 or more. 4 cases (0.2%) could not be traced for follow-up and were excluded from the study. The total number of study subjects was therefore 1991.

A mixed active and passive follow-up was performed. The municipalities of the Varese province periodically send the death certificates of all the residents to the LCR, regardless of the cause of death. The date of death is then linked to LCR records. For patients for whom no death certificate had arrived at the registry, the municipalities of residence were directly contacted and the life status of patients on 31 May 1987 was checked; length of follow-up, therefore, ranged from 6 to 11 years. By this procedure, we were unable to trace 4 patients (0.2%), who were excluded from the analysis. 11 patients (0.6%) whose life status on 31 May 1987 was unknown were considered withdrawals at the last date at which some clinical information was available.

The index date for computing incidence and survival is the date of first hospital admission for breast cancer. For 81 patients suffering from a bilateral breast cancer we considered the date of the first tumour occurrence.

The Kaplan–Meier method [6] was used to obtain breast cancer survival figures. Relative survival was computed by dividing the observed survival by the expected survival for the same age group in the overall population of Lombardy [7]. Observed and relative survival were also computed using the Cox model [8], in order to take into account the calendar period of diagnosis. The hazard rate was computed dividing the number of deaths in a given year by the total number of subjects at risk in the same year.

RESULTS

Figure 1 shows the observed probability of survival for the entire study population. The number of subjects at risk at 1 year intervals is also shown. Overall observed survival decreased progressively during the follow-up period: at 1 year it was 91%

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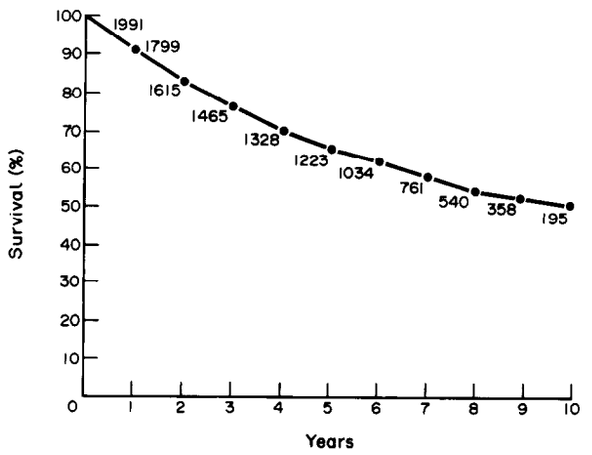

Fig. 1. Observed survival by time for breast cancer (LCR, 1976–1981). ● = No. of subjects at risk.

Table 1. Observed survival by age and follow-up time

Age	Cases	Survival (year) % 1	2	3	5	7	9	10
25–34	50	94.00	80.00	72.00	60.00	58.00	58.00	58.00
35–39	94	95.74	90.43	82.98	69.02	61.52	58.48	55.04
40–44	165	95.76	93.33	90.87	84.12	75.53	73.23	73.23
45–49	240	96.67	91.25	88.33	79.16	71.95	65.06	63.99
50–54	221	97.27	89.55	81.37	72.73	67.92	62.18	59.79
55–59	236	94.07	83.43	76.59	65.38	56.71	52.93	51.27
60–64	214	90.65	80.37	70.94	57.93	51.55	43.11	40.17
65–69	259	91.09	82.94	75.93	61.48	53.85	44.54	42.15
70–74	226	84.87	78.57	71.35	58.24	47.55	34.34	32.05
75+	286	77.40	60.57	48.12	34.22	24.18	19.01	16.29
All	1991	91.22	83.21	76.27	65.65	58.12	52.19	50.22

[95% confidence interval (C.I.) 90–93], at 3 years 76% (C.I. 74–78) at 5 years 66% (C.I. 63–68) and at 10 years 50% (C.I. 43–57); median survival was 8.8 years.

Figure 2 shows the hazard rate for three age groups (25–39, 40–59 and 60+). The hazard rate indicates the probability of dying during a given year for patients who survived until that year. Figure 2 shows a bimodal behaviour of the hazard function in all the age groups: there is a first maximum in the early period after diagnosis and a second maximum between the seventh and eighth year.

Tables 1 and 2 show the observed and relative probability of survival according to age at diagnosis during the 10 years of follow-up analysed by the Kaplan–Meier method and the number of cases in each age group. Age was classified in 5-year groups, except for the first two groups which were combined in the 25–34 category, as there was only 1 patient in the 25–29 age group.

A complex survival pattern was shown. Younger patients had a poor prognosis over the whole study period. From the second year to the end of follow-up, patients belonging to the 40–44 age group showed the best prognosis of the entire study population. The subsequent age group, 45–49, showed a slightly lower survival, but, on the whole, patients aged between 40 and 49 had the best survival. The survival probability decreases progressively in the older age groups, up to 60–64 years; a slight increase is noticeable between 65 and 74 years. Finally, age group 75 and over shows the poorest prognosis, even after allowing for general mortality. The general age trend of survival is already clear in the second year after diagnosis, and becomes more evident later on.

Table 3 contains the results of the survival analysis carried out using the Cox model. It shows the relative death risk for each age group with reference to the 55–59 age group, and the 95% confidence intervals of relative risk.

The regression analysis confirms the age pattern obtained by the Kaplan–Meier method. Moreover, Cox regression shows that during the 1976–1981 study period there was a protective effect due to the calendar period of diagnosis: relative risk according to the calendar year of diagnosis is 0.96 (C.I. 0.92–1.00), meaning that hazard decreased by 4% every year. At the same time, the general mortality of the Varese female population with the same age distribution of the LCR breast cancer patients decreased by 2.7% per year [7]. Therefore, during the study period there was a slight reduction (about 1%)

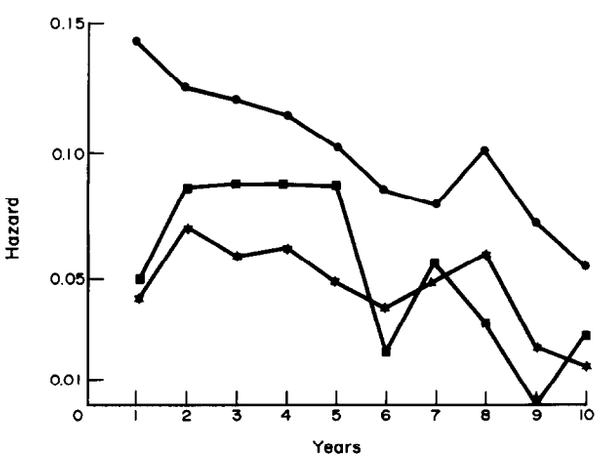

Fig. 2. Death hazard trend by age for breast cancer (LCR 1976–1981). ■ = 25–39 and ★ = 40–59 years, ● = 60+.

Table 2. Relative survival by age and follow-up time

Age	Survival (year) (%) 1	2	3	5	7	9	10
25–34	94.05	80.09	72.12	60.18	58.27	58.37	58.44
35–39	95.82	90.60	83.23	69.41	62.06	59.23	55.87
40–44	95.91	93.63	91.33	84.91	76.65	74.82	75.13
45–49	96.91	91.74	89.09	80.46	73.79	67.42	66.70
50–54	97.70	90.37	82.52	74.59	70.61	65.75	63.86
55–59	94.74	84.62	78.26	68.09	60.44	57.99	57.08
60–64	91.66	82.24	73.55	61.92	57.20	50.10	48.00
65–69	92.72	86.08	80.56	68.72	64.30	57.83	57.57
70–74	87.55	83.94	79.28	71.16	65.86	56.16	57.95
75+	81.71	68.07	58.13	49.34	43.73	45.64	46.12
All	92.18	82.50	78.22	68.63	62.91	60.07	58.08

Table 3. Relative risk of dying

Age	Relative risk	95% CI
25–34	0.98	0.61–1.63
35–39	0.84	0.58–1.22
40–44	0.49	0.34–0.70
45–49	0.62	0.46–0.83
50–54	0.75	0.56–1.00
55–59*	1	–
60–64	1.27	0.97–1.66
65–69	1.17	0.90–1.51
70–74	1.45	1.12–1.87
75+	2.76	1.18–3.49
Period	0.96	0.92–1.00

Analysis by the Cox model.
CI = confidence intervals.
*Reference category.

in the annual death risk. This 1% estimate is consistent with data from other cancer registries which analyse breast cancer survival according to calendar periods [9–12].

DISCUSSION

Our study emphasises a poor prognosis for patients aged less than 35 and a higher survival for patients aged between 40 and 50, with the best survival for the 40–44 age group. These results are in accordance with other clinical [13, 14] and population-based [9, 15, 16] studies. Studies which provided survival rates only for relatively large age classes showed a better prognosis for younger patients than older ones [17, 18], or for premenopausal patients compared with menopausal ones [17, 19]. In young patients a recent pregnancy was associated with a worse prognosis, suggesting that hormonal levels have an influence on survival [13]. Two clinical studies [14, 20] found that early menopausal status (within 5 years of amenorrhea) at diagnosis was predictive of lower survival, controlling also by other factors such as stage and age at diagnosis. Although in our study we could not analyse menstrual status at diagnosis, a recent survey in the overall population of the Varese province showed that 95% of women aged 40–44 still had their menses. The observed gradual survival decrease after 45 years could, therefore, be related to an early menopausal status at diagnosis.

In many western countries, there is a breast cancer incidence peak between 45 and 55 years of age, followed by a slight decrease in subsequent ages, the so-called "Clemmesen's hook" [22]. This phenomenon has been interpreted as a biological effect resulting from hormonal changes in the years near menopause, or as a cohort effect due to different reproductive behaviours. It may also be partially related to an anticipation of diagnosis: because of the increasing risk in these ages, more attention could be paid by physicians and by the women themselves to the discovery of a breast tumour. Also, the breast tissue modifications due to ageing might facilitate the discovery of small lumps in this period. The resulting anticipation of diagnosis could lie behind both the Clemmesen's hook and the high survival between 40 and 50 years of age. If this menopausal incidence pattern reflected a real risk, there should be a corresponding behaviour in mortality curves. Actually, in western countries breast cancer mortality rates [23–25] rise in menopausal ages, without showing any hook, supporting the interpretation of the incidence peak as an anticipation of diagnosis. This interpretation is not supported by studies finding that the survival differences by age are present in all stages [10, 13, 18].

After menopause, both incidence and mortality increase at a lower pace with respect to the ages around menopause. This pattern is likely to result from the oestrogen and progestogen depletion occurring at menopause [26]. Hormonal levels may also affect survival, perhaps through a lower tumour growth rate; this might explain the relatively good relative survival of women aged between 65 and 74. This interpretation is also consistent with the observation that obese women, who keep hormonal serum levels longer, have both higher breast cancer incidence in postmenopause [26] and lower survival rates [27, 28].

Death hazard shows a gradual decrease from the fourth year after diagnosis, but between the seventh and eighth year another hazard peak is noticeable and this pattern is similar to that recorded by another population-based study [16]. In order to interpret the meaning of this late hazard peak, we studied the hazard function according to histotype and causes of death indicated in the death certificates.

Ductal carcinomas (75% of all cases) resembled the overall hazard pattern; the two risk peaks were higher in lobular carcinomas; and the later peak was more evident in tubular carcinomas (3% of all cases). However, their exclusion from the analysis did not change the overall hazard pattern. More specific studies on the repeatability of histological classifications should be envisaged to assess the prognostic role of breast cancer histotype.

Presuming that the second hazard peak may be related to a late cardiac toxicity of radiotherapy [29], we reviewed the death certificate of all the patients who died after the sixth year after diagnosis. The proportion of death certificates mentioning cardiovascular pathology (ICD code 410–414) was higher among women who died between the seventh and eighth year after diagnosis in comparison with those who died during the sixth year and during the ninth or tenth year. However, the hazard pattern showed only a minor change when the deaths due to cardiovascular disease were excluded from the analysis.

In Table 4 LCR relative survival is compared to that of other cancer registries. Breast cancer survival shows a considerable variability according to incidence period. On the whole, an improvement is noticeable from past to recent years: 5-year survival is 49% in the New Zealand Cancer Registry (study period: 1950–54) [15] and 73% in The Netherlands (study period: 1980–1985) [30]. Therefore, to make comparisons among countries, it is necessary to take the period effect into account. Considering a hazard decrease of approximately 1% per year for all countries, as suggested above, in 1979, which is the mid year of the LCR study, the expected 5-year relative survival pattern would be as follows: New Zealand 61%, Sweden [16] 71%, Norway [10] 69%, UK [31] 60%, USA [9] 73%, Switzerland [32] 73%, France [33] 70%, Finland [12] 70% and The Netherlands 72%. After this adjustment, the countries considered, apart from the UK and New Zealand, have a similar survival rate ranging between 69% and 73%.

Apart from the incidence period effect, survival variability between countries could be due to other reasons. Screening policies carried out in some countries could lead to early diagnosis, and consequently to an apparently better survival. Even without any screening campaigns, the availability of improved diagnostic techniques can lead to the discovery of early cancers. The inclusion criteria of cases vary among the registries; for instance, the inclusion of non-invasive cancers could be the

Table 4. Relative survival for breast cancer in some cancer registries

Country	Incidence period	Follow-up (yr) 1	3	5	10
New Zealand, National Cancer Registry	1950–1954			49	38
Sweden, National Cancer Registry	1960–1978			68	56
Norway, National Cancer Registry	1968–1975	91	76	67	
England and Wales	1971–1973			57	
USA (SEER)* Whites	1973–1979	94	82	72	
Switzerland, Geneva Cancer Registry	1970–1986	94		73	
France (EPC)†	1975–1981	93	80	70	
Finland, National Cancer Registry	1975–1981			70	
Italy, Varese RTL	1976–1981	92	78	69	58
The Netherlands (SOOZ)‡	1980–1985	93	82	73	

*Surveillance, Epidemiology and End Results Program.
†Enquête Permanente sur le Cancer.
‡"Incidence, Survival, Mortality and Patterns of Care for Cancer" programme.

reason for a better overall survival. Therefore, although calendar period of diagnosis may probably explain a great part of the variability in breast cancer survival, a standardised collection of cancer registries' data and follow-up procedures would be useful in order to obtain reliable survival comparisons among countries.

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