Pergamon

European Journal of Cancer Vol. 33, No. 3, pp. 425–428, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00384-X

Original Paper

Effect of Age on the Survival of Breast Cancer Patients

K. Holli[1] and J. Isola[2]

[1]Department of Oncology, University Hospital of Tampere, B.O. Box 2000, FIN-33521 Tampere and School of Public Health, University of Tampere, B.O. Box 607, FIN-33101 Tampere; and [2]Department of Biomedical Sciences, University of Tampere, B.O. Box 607, FIN-33101 Tampere, Finland

Despite numerous studies, the effect of patient age on the prognosis of breast cancer is still uncertain. The aim of this study was to assess the influence of age on long-term relative survival, to control the results for the extent of disease at diagnosis and assess the association between biological markers and age of the patients. A population-based survival study was made to assess the 5- and 10-year relative survival. All 17 856 female breast cancer patients diagnosed in Finland and reported to the Finnish Cancer Registry in 1977–1986 were included. The results were controlled for the extent of the disease. The markers of biological aggressiveness of tumours and patients' age were correlated in a prospectively collected subset of 2107 patients from the Tampere University area. The relative 5-year and 10-year survival rates (RSRs) were highest in women 46–50 years of age, whereas there was no significant difference between younger and older age groups. No consistent survival trends were observed among the age groups in local, node-negative disease, whereas in node-positive disease the 10-year relative survival was best for women 41–45 years (49%) and poorest in women over 75 years (35%). The youngest age groups were significantly more often oestrogen receptor-negative, but only small differences were observed for S-phase fraction and progesterone receptor positivity. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: breast cancer, age, stage, biological aggressiveness, survival

Eur J Cancer, Vol. 33, No. 3, pp. 425–428, 1997

INTRODUCTION

NUMEROUS STUDIES have been performed on the effect of age on the prognosis of breast cancer patients. Some have indicated a shorter survival for young patients [1–6], whereas in others the prognosis has become poorer with increasing age [7–10]. Some reports have found perimenopausal women to have the best prognosis [11–15]. In some studies, no correlation has been found between age at diagnosis and prognosis [16–19]. Thus, the effect of age on prognosis seems still to be controversial. It is likely that survival differences between age groups can be reliably detected only in large population-based cancer registry databases.

The aim of the present study was to assess the influence of age on long-term relative survival. The results were controlled for the extent of disease at diagnosis, which is a major determinant of survival. In addition, the association between markers of biological aggressiveness (hormone receptors, ploidy, proliferative activity and c-erbB-2 oncoprotein overexpression) and age of patients was assessed in a further subset of 2107 breast cancer patients, in order to evaluate whether differences in biological properties of the tumour could explain the survival differences observed.

Correspondence to K. Holli.
Received 18 Mar. 1996; revised 29 Jul. 1996; accepted 3 Sep. 1996.

MATERIALS AND METHODS

All female breast cancer patients diagnosed in Finland and reported to the Finnish Cancer Registry from 1977 to 1986 were included except cases diagnosed at autopsy. The Finnish Cancer Registry is a nationwide and population-based registry, and its files are virtually complete [9]. Survival was calculated from the date of the first diagnosis of breast cancer until death or the closing date of the follow-up (31 December 1990). The age at diagnosis, stage of the disease and date and cause of death were also obtained from the Cancer Registry files. The follow-up of the breast cancer patients for death was done by regular linkage of the national population registry and the Cancer Registry. The

Table 1. Distribution of spread of disease by age at diagnosis in 16 045 breast cancer patients diagnosed in Finland from 1977 to 1986

Extent of disease	Age group											Total
	18–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70	71–75	76+	
Node-negative	50.3	54.6	53.9	57.1	58.8	55.0	50.9	54.0	56.7	56.2	59.3	8996 (56.1)
Node-positive	43.5	41.9	41.0	37.9	36.7	38.6	40.8	37.0	34.1	33.8	29.3	5798 (36.1)
Distant metastases	6.1	3.5	5.0	5.0	4.5	6.3	8.3	8.9	9.2	9.9	10.3	1251 (7.8)
Total (100%)	141	415	791	1212	1697	1612	1804	1827	1945	1848	2753	16045

Data of the extent of disease were available in 91.3% of cases.

Table 2. Distribution of extent of disease by age at diagnosis among breast cancer patients in the subset of patients (n = 2107) from whom prognostic factors were analysed

Extent of disease	Age group											Total
	18–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70	71–75	76+	
Node-negative	44.4	50.0	67.2	55.6	55.1	62.8	62.9	63.9	57.5	57.8	52.2	(1098) 58.0
Node-positive	55.6	50.0	32.8	43.0	44.0	35.7	35.7	35.6	41.6	40.1	43.2	(761) 40.2
Distant metastases	0.0	0.0	0.0	1.4	0.8	1.5	1.4	0.5	0.9	2.1	4.6	(34) 1.8
Total (100%)	9	22	64	142	243	199	210	216	226	192	370	1893

Data of the extent of disease were available in 89.9% of cases.

main study group consisted of 17 856 patients; their age distribution and the extent of disease is given in Table 1. The extent of the disease was recorded in 89.68% of the cases. The extent was divided into three categories: local (i.e. node-negative), node-positive and metastatic disease. Metastatic disease was not included in further analysis because of a small number of cases and short survival.

The effect of age was estimated in terms of relative risk of death from breast cancer, adjusted for extent of disease by Cox's regression method.

Survival rates were calculated using the life-table method. Relative survival was calculated as the ratio of observed to expected survival in an age-matched general population [9, 20]. The use of relative survival rates is based on the assumption that breast cancer patients have the same probability of dying from other causes as have people in the general population.

To explore the hypothesis that the biological aggressiveness of the tumour is associated with patient age, we analysed a separated subset of 2107 patients from 1990 to 1994, diagnosed in Tampere University area; their age and stage distribution are given in Table 2. Biological prognostic factors (oestrogen receptor, progesterone receptor, DNA-ploidy, S-phase fraction and c-erbB-2 oncoprotein) were prospectively analysed from these patients and analysis was successful for 92% of all cases. The methodology has been described in our previous contributions [21].

RESULTS

In all cases (n = 17 856) the relative 5- and 10-year survival rates were highest among women 46–50 years of age at diagnosis of primary breast cancer. The relative 10-year survival rate was 70% among women of 46–50 years, 60% among women less than 30 years of age, and 59% among women over 75 years of age (Figure 1).

For detailed survival analysis, the patient population was divided by the extent of disease at diagnosis. Extent of the disease differed significantly according to patient age (Table 1). The proportion of local, node-negative disease was lowest in the youngest age group (50.3%) and highest in the oldest age group (59.3%) (P = 0.0025; chi-square test for trend between age groups). The proportion of node-positive disease was highest in the youngest age group (43.5%) and lowest in the oldest age group (29.3%). This difference was significant (P < 0.0001; chi-square test for trend between age groups). Advanced disease at diagnosis i.e. distant metastasis, was most common in oldest women (10.3%) and decreased significantly with age (P < 0.0001) (Table 1).

No significant survival differences were observed in local, node-negative tumour disease by age (Figure 2). In node-positive disease, the best 10-year relative survival rates were observed among women between 41 and 45 years (49%), and the poorest 10-year relative survival rates were in the oldest age group i.e. women more than 75 years (35%) and

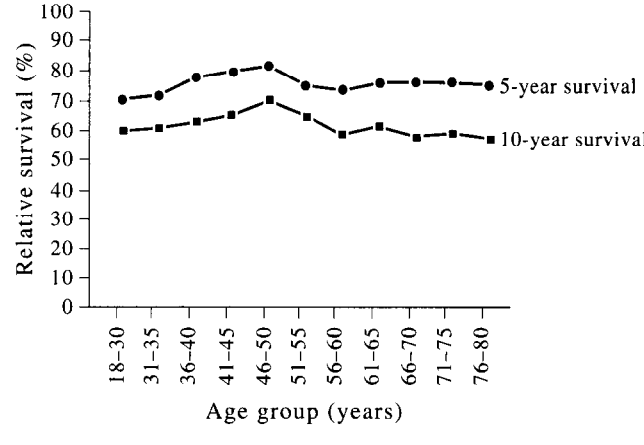

Figure 1. The relative 5- and 10-year survival rates by age for Finnish breast cancer patients diagnosed from 1977 to 1986.

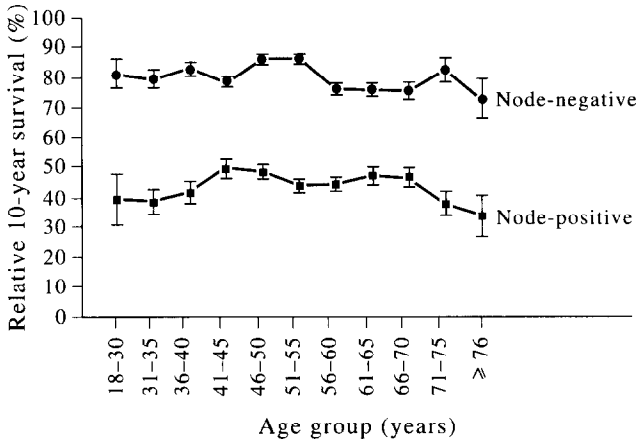

Figure 2. The relative 10-year survival rates by extent of the disease for the Finnish breast cancer patients diagnosed from 1977 to 1986.

the youngest group less than 35 years old (39%). The differences were significant ($P < 0.001$).

The relative risk of death (RR) was 0.59 (95% confidence interval (CI) 0.56–0.63) among women 46–50 years of age as compared with other age groups when the extent of disease was adjusted.

The proportions of oestrogen and progesterone receptor-positive tumours, c-erbB-2 oncoprotein overexpression, aneuploidy and high proliferation rate (S-phase fraction over the median, 8.5%) are shown in Figure 3. The proportion of oestrogen receptor-positive tumours increases and c-erbB-2 oncoprotein overexpression decreases significantly with age ($P < 0.0001$ and $P < 0.0011$ for linear trend, respectively.) No significant trends were seen for progesterone receptor, ploidy or S-phase fraction (Figure 3).

DISCUSSION

The discrepancies in previous results of the effect of patient age on survival in breast cancer have reasonable explanations. First, the age groupings have often been too crude, i.e. all premenopausal women being placed in the same category [7–9, 11]. Selection may have taken place in the series of patients referred to individual hospitals [2–6, 8]. Because the numbers of breast cancers are small at either ends of the age spectrum and because the survival differences between age groups are rather small, large patient series are needed [2, 8, 22]. In some studies, deaths due to causes other than breast cancer are not properly corrected [5, 23].

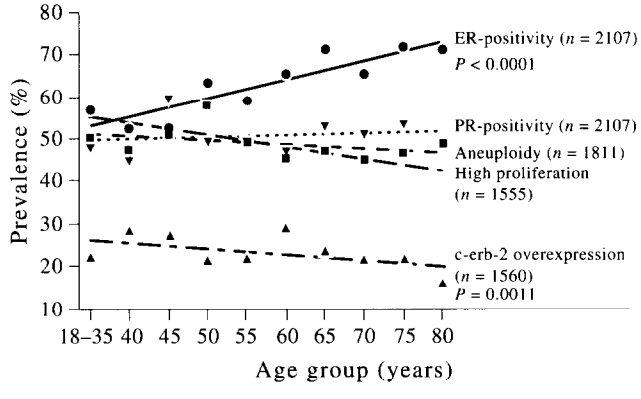

Figure 3. The proportion of oestrogen and progesterone receptor-positive tumours, c-erbB-2 oncoprotein overexpression, aneuploidy and high S-phase fraction for breast cancer patients diagnosed in Tampere University Hospital from 1990 to 1994.

The present study was based on data from a nationwide population-based cancer register. The vital status of the patients at the end of follow-up and causes of death were recorded from the national population registry. The median follow-up time was 10 years, and the series was large enough to permit analysis of survival of young women. We found an increase in the relative survival rates with age up to 50 years and a decrease thereafter. Thus, women 46–50 years of age had the most favourable prognosis, which is in contrast to previous results in which either young or old women have the best prognosis [1–10]. Our findings are concordant with those published by Adami and associates [12], Betta and associates [11] and Sant and associates [13], who also used nationwide cancer registry data.

The extent of disease at diagnosis is one confounding factor when the effect of age on survival is studied. The extent of disease at diagnosis is related to delay in diagnosis, which varies with age [24–26]. In our study, there was an increase of metastatic disease with age which supports this hypothesis, but there was a higher proportion of node-negative disease in older than younger women. The age at diagnosis seems to be an independent prognostic factor. When extent of disease was adjusted using Cox's regression method, the RR of death from breast cancer was 0.59 compared with other age groups.

We found that survival in local i.e. node-negative tumours was relatively stable in all age groups, whereas in node-positive disease the survival differences were more pronounced. This may reflect different treatment policies in node-positive disease in different ages, although in the period 1977–1986 postsurgical medical adjuvant therapy was not routinely used in Finland. Differences in primary surgical treatment are less likely. Conservative surgery started in Finland mainly after 1985 and lymphadenectomies are routinely done for all invasive breast cancer, independent of age. However, different treatment after recurrence [2, 27], and different response to hormonal therapy [4], may explain the observed differences in survival with age. In young patients, a recent pregnancy has been associated with a poor prognosis, suggesting that hormonal milieu may affect survival [5]. The observed decrease in survival after the age of 50 years has also been attributed to a change in hormonal balance [7, 8, 28, 29].

An alternative explanation for the effect of age on survival may be that, on average, tumours from age groups with favourable survival are biologically less aggressive than those tumours from age groups with lower survival [30]. This hypothesis was tested with another set of patients from whom a large panel of prognostic factors were analysed. This subset was comparable by age to the whole Finnish material, but taken from later years (1990–1994). The proportion of node-negative tumours were higher, mainly due to screening programmes which started in 1984 in Finland. Multivariate analysis was not possible from this set because of lack of follow-up time, which is why only the correlation of prognostic factors and age was possible. As also reported previously [31], the prevalence of oestrogen receptor-positive tumours

increased significantly with age and c-erbB-2 oncogene overexpression was more common in the youngest age group, but there was no significant differences in progesterone receptor status, ploidy, or tumour proliferation, which are known to be strong indicators of biological aggressiveness and patient survival [19]. The youngest patient group in this analysis was small so the conclusions from these data should be viewed with caution.

In this large population-based study, the best 10-year relative survival was in patients aged between 46 and 50 years. The prognostic significance of age seems to be independent of the extent of disease at diagnosis. However, in node-negative tumours, there was no significant difference in survival by age, whereas in node-positive disease the survival differences were significant and indicate that effect of age should be studied separately in different stage categories. Differences in some biological prognostic variables may, at most, only partly explain the age-related differences in survival.

1. Stoll BA. Does the malignancy of breast cancer vary with age? *J Clin Oncol* 1976, **2**, 73–80.
2. Falkson G, Gelman RS, Pretorius FJ. Age as a prognostic factor in recurrent breast cancer. *J Clin Oncol* 1986, **4**, 663–671.
3. Alberts AS, Falkson G, van der Merwe R. Metastatic breast cancer—age has a significant effect on survival. *SAMJ* 1991, **79**, 239–241.
4. Ribeiro GG, Swindell R. The prognosis of breast carcinoma in women aged less than 40 years. *Clin Radiol* 1981, **32**, 231–236.
5. Noyes RD, Spanos WJ, Montague ED. Breast cancer in women aged 30 and under. *Cancer* 1982, **49**, 1302–1304.
6. Marubini E, Mezzanotte G, Boracchi P, Veronesi U. Long term survival analysis: breast cancer and age at diagnosis. *Stat Med* 1990, **9**, 737–748.
7. Host H, Lund E. Age as a prognostic factor in breast cancer. *Cancer* 1986, **57**, 2217–2221.
8. Bergman L, Dekker G, van Kerkhoff E, Peterse H, van Dongan J, van Leeuwen F. Influence of age and comorbidity on treatment choice and survival in elderly patients with breast cancer: a population-based study. *Eur J Cancer* 1992, **28**, 1475–1480.
9. Hakulinen T, Pukkala E, Hakama M, Lehtonen M, Saxen E, Teppo L. Survival of cancer patients in Finland in 1953–1974. *Ann Clin Res* 1981, **13**, 48–50.
10. Mueller CB, Ames F, Anderson GD. Breast cancer in 3558 women: age as a significant determinant in the rate of dying and causes of death. *Surgery* 1978, **83**, 123–132.
11. Betta PG, Robutti F, Spinoglio G, Bottero G. A multivariate analysis of the prognostic significance of pathological features in breast cancer of perimenopausal age. *Pathologica* 1988, **80**, 287–292.
12. Adami HO, Malker B, Holmberg L, Persson I, Stone B. The relation between survival and age at diagnosis in breast cancer. *N Engl J Med* 1986, **315**, 559–563.
13. Sant M, Gatta G, Micheli A, Verdecchia A, Capocaccia R, Crosignani P, Berrino F. Survival and age at diagnosis of breast cancer in a population-based Cancer Registry. *Eur J Cancer* 1991, **27**, 981–984.
14. Chung M, Chang HR, Bland KI, Wanebo HJ. Younger women with breast carcinoma have a poorer prognosis than older women. *Cancer* 1996, **77**, 97–103.
15. Lees AW, Jenkins HJ, May CL, Cherian G, Lam EWH, Hanson J. Risk factors and 10-year breast cancer survival in northern Alberta. *Breast Cancer Res Treat* 1989, **13**, 143–151.
16. Boffetta P, Merletti F, Winkelmann R, Magnani C, Cappa A, Terracini B. Survival of breast cancer patients from Piedmont, Italy. *Cancer Causes and Control* 1993, **4**, 209–215.
17. Hibberd AD, Horwood LJ, Wells JE. Long term prognosis of women with breast cancer in New Zealand: study of survival to 30 years. *Br Med J* 1983, **286**, 1777–1779.
18. Wallgren A, Silferswärd C, Hultborn A. Carcinoma of the breast in women under 30 years of age: a clinical and histopathological study of all cases reported as carcinoma to the Swedish Cancer Registry. *Cancer* 1968, **40**, 916–923.
19. Clark GM, Sledge GW, Osborne CK, McGuire WL. Survival from first recurrence: relative importance of prognostic factors in 1015 breast cancer patients. *J Clin Oncol* 1987, **5**, 55–61.
20. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. *Comp Prog Biomed* 1985, **19**, 197–205.
21. Isola J, Visakorpi T, Holli K, Kallioniemi O-P. Association of overexpression of tumor suppressor protein p53 with rapid cell proliferation and poor prognosis in node negative breast cancer patients. *J Natl Cancer Inst* 1992, **84**, 1109–1114.
22. Langlands AO, Kerr GR. Prognosis in breast cancer: the effect of age and menstrual status. *J Clin Oncol* 1979, **5**, 123–133.
23. Rosen PP, Lesser ML, Kinne DW, Beattie EJ. Breast carcinoma in women 35 years of age or younger. *Ann Surg* 1984, **199**, 133–142.
24. Yancik R, Ries LG, Yates JW. Breast cancer in aging women. A population-based study of contrasts in stage, surgery and survival. *Cancer* 1989, **63**, 976–981.
25. Richardson Jl, Langholz B, Berstein L, Burciaga C, Danley K, Ross RK. Stage and delay in breast cancer diagnosis by race, socioeconomic status, age and year. *Br J Cancer* 1992, **65**, 922–926.
26. Holmberg L, Lindgren A, Norden T, Adami HO, Bergstrom R. Age as a determinant of axillary node involvement in invasive breast cancer. *Acta Oncol* 1992, **31**, 5.
27. Mehta RR, Hart G, Das Gupta TK. Steroid receptors in breast cancer patients. Influence of obesity and age at diagnosis. *Anticancer Res* 1992, **12**, 1311–1314.
28. Birks DM, Crawford GM, Ellison LG, Johnstone FRC. Carcinoma of breast in women 30 years of age or less. *Surg Gynecol Obstet* 1973, **137**, 21–52.
29. Bergman L, Dekker G, van Kerkhoff EHM, Peterse HL, van Dongan JA, van Leeuwen FE. The influence of age and comorbidity on treatment choice and its effect on survival in elderly patients with breast cancer. *Breast Cancer Res Treat* 1991, **18**, 189–198.
30. De la Rochefordiere A, Asselain B, Campana F, *et al.* Age as prognostic factor in premenopausal breast carcinoma. *Lancet* 1993, **341**, 1039–1043.
31. Bonnier P, Romain S, Charpin C, *et al.* Age as a prognostic factor in breast cancer: relationship to pathological and biological features. *Int J Cancer* 1995, **62**, 138–144.

Acknowledgements—We thank Lyly Teppo and Matti Hakama from the Finnish Cancer Registry for their cooperation and help.