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Original article

Long-term observational follow-up study of breast cancer diagnosed in women ≤40 years old

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ABSTRACT

The prognosis of young breast cancer patients has been considered to be much poorer than in older patients. Two hundred and sixty-eight premenopausal women with a median follow-up time of 74.0 months were included in the study. 33.5% had oestrogen receptor-negative and 34.6% progesterone receptor-negative tumours. 15.2% of the tumours were HER2-positive. Five-year breast cancer-specific survival (BCSS) was 81.1% and the corresponding 10-year figure was 72.3%. 91.8% of all relapses occurred within seven years of surgery. Among the ≤35-year-old women, only 2 of 38 (5.3%) relapsed beyond seven years of follow-up. Lymph node ratio was the most significant independent prognostic factor of poor disease-free survival and BCSS. This study revealed a high relapse rate in the youngest women as early as during the first few years after diagnosis, although their prognosis as a whole was surprisingly good.

Introduction

Breast cancer is a disease found mainly in older women, with 75% of cases occurring in women over 50 years of age.[1] Young women, i.e., those less than 40 years of age, make up less than 7.5 per cent of all women diagnosed with the disease each year. However, in Asian populations the incidence of breast cancer among young women may be over two-fold greater than in Western countries.[2,3] Although these are still relatively small proportions of all breast cancer cases, the absolute number of cases is on the rise as our population grows.

Young age (under 35 to 40 years old) of breast cancer patients has been proposed to be an independent prognostic factor of poor survival in occasional studies.[4,5] More frequently, however, young age has been a significant predictor only in univariate analysis[6–8] and there are also studies in which no such association has been found.[9] In addition, various authors have found a prognostic effect of age only in some subgroups, such as patients with lymph node-negative[10] or lymph node-positive disease,[2,11] with hormone receptor-unknown or hormone receptor-positive disease,[11] or those without cytotoxic treatment.[13] Most of these studies have severe limitations. The definition of "young patient" varies between studies. In addition, in most studies the follow-up times have been relatively restricted and the proportion of patients ≤35 years old is typically limited, which altogether complicates interpretation of the results.

In previously published reports, tumours in younger women have usually been of higher grade, with a higher proliferating fraction and more vascular invasion than those in older patients.[10,14–16] Most of the data on treatment effects are largely dependent upon older series collected. However, staging procedures, attention to small metastases in axillary lymph nodes and new prognostic markers and cancer types have resulted in substantial changes to a greater or lesser extent in recent years.

The aim of this study was to critically evaluate the mostly recently available details of biological characteristics in the youngest patient groups, to test whether women of >35 years but under 40 years have a prognosis different from that in women ≤35 years old and also to assess the effect of a given treatment on prognosis during a long follow-up period.

Patients and methods

The study material consisted of 269 consecutive Caucasian women with local or locally advanced invasive breast cancer whose primary operation was carried out in 1982–2008. Only 8 patients were operated upon during the 1980s. The clinical data was

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obtained from the archives of the Department of Oncology and Radiotherapy, Oulu University Hospital and the studied clinicopathological parameters were grade, TNM classification, the presence of either lymphatic vessel or vascular invasion, histology, HER2 (human epidermal growth factor receptor 2) status and Ki-67 immunostaining. The patients were ≤40 years old at the time of surgery (range 25–40 years, mean age 36.1 years) and all were premenopausal at the time of diagnosis. Ninety-four of the patients were ≤35 years old and 175 were ≥36 years old. The median follow-up time was 74.0 months (range 1–319 months).

Histopathology was evaluated after current WHO classification and patients were classed by means of TNM classification. Lymph node ratio (LNR) was defined as the number of positive nodes divided by the total number of examined nodes. For statistical analysis, LNR was studied as both a continuous variable (0–1.0) and a categorial variable (≤0.2 vs. >0.2–0.65 vs. >0.65). Steroid receptor status and Ki-67 expression were studied by immunohistochemistry as described previously.[17] Tumours expressing 0–9% of steroid receptors were considered to be negative. As regards Ki-67, the cut-off for negativity was <5%. The expression of HER2 was also studied by means of immunohistochemistry and when there was a HER2-positive result (either 2+ or 3+ on a scale from 0 to 3+), gene amplification status was determined using chromogenic *in situ* hybridization (CISH). Cancers with six or more gene copies were considered HER2-positive.[18]

We used SPSS 17.0 for Windows (Chicago, IL, USA) for statistical analysis. The significance of associations was determined by using Pearson's test, Fisher's exact probability test (both two-tailed), and Cox multivariate regression analysis. In survival analysis, Kaplan–Meier curves were used and significance was measured by means of log-rank, Breslow and Tarone–Ware tests. Probability values <0.05 were considered significant.

Results

Of the 269 women included in the study, 81 (30.1%) developed distant metastases during the follow-up time. The most common sites of distant metastases were bone ($n = 21$), liver ($n = 19$) and lung ($n = 12$). Eighteen patients had developed metastases at multiple sites when the distant metastases were diagnosed. Twenty-five (9.3%) women developed locoregional recurrence (LRR) during the follow-up period and contralateral cancer was diagnosed in 8 (3.0%) patients. Sixty-five (24.2%) patients died of breast cancer during follow-up.

The main clinical and pathological parameters of the study population are shown in Table 1. Nearly half (47.6%) of the patients were diagnosed with T1 disease and a corresponding portion also had node-negative disease. Many (88.8%) had ductal carcinoma, whereas lobular histology was diagnosed in 7.4% of the patients and other types (medullary, tubular, mucinous) covered 3.7% of the cases. HER2 status was positive in 15.2% of the patients. The figures for ER (oestrogen receptor)- and PR (progesterone receptor)-positive tumours were 58.0% and 57.2%, respectively. There were no statistically significant differences in clinicopathological parameters between patients of ≤35 and ≥36 years old, though nearly significant overexpression of PR was observed among the younger patients ($p = 0.06$).

Information about surgical and oncological treatment is presented in Table 2. To summarize, 29.0% of the women received hormone therapy – mostly tamoxifen (24.0% of all women). One hundred and ninety (70.6%) received adjuvant chemotherapy, typically cyclophosphamide-methotrexate-5-fluorouracil (CMF) (26.0%) or anthracyclin-based chemotherapy (26.8%). Seventy-two (26.8%) of the studied women received both hormone and cytotoxic therapy. There were no differences between patients of ≤35 and ≥36 years old in the ratio of use of neoadjuvant or adjuvant chemotherapy, the use of trastuzumab, or the proportion receiving hormone therapy. Sixteen women (5.9% of all patients) received trastuzumab in an adjuvant setting. Most of the patients (92.6%) were radiotherapy-treated, although those who were ≤35 years old more rarely received postoperative radiotherapy than those of ≥36 years old ($p = 0.02$). This may in part be due to the fact that more mastectomies were carried out in younger (78.7%) than in older (69.7%) patients.

Table 1
Main clinical and pathological parameters in the total study population and separately in age groups of ≤35 years and >35 years.

Parameter	All patients ($n = 269$)	Age ≤35 years ($n = 94$)	Age 36–40 years ($n = 175$)
Tumour size			
T_1	128 (47.6%)	45 (47.9%)	83 (47.4%)
T_2	109 (40.5%)	37 (39.4%)	72 (41.1%)
T_3	24 (8.9%)	8 (8.5%)	16 (9.1%)
T_4	8 (3.0%)	4 (4.3%)	4 (2.3%)
Nodal status			
N_0	128 (47.6%)	43 (45.7%)	85 (48.6%)
N_{1-3}	141 (52.4%)	51 (54.3%)	90 (51.4%)
Lymph node ratio			
≤0.2	184 (68.4%)	59 (62.8%)	125 (71.4%)
>0.2–0.6	48 (17.8%)	18 (19.1%)	30 (17.1%)
>0.6	30 (11.2%)	13 (13.8%)	17 (9.7%)
Unknown	7 (2.6%)	4 (4.3%)	3 (1.7%)
HER2 (CISH)			
Negative	136 (50.6%)	38 (40.4%)	98 (56.0%)
Positive	41 (15.2%)	14 (14.9%)	27 (15.4%)
Unknown	92 (34.2%)	42 (44.7%)	50 (28.6%)
Ki-67			
Negative	6 (2.2%)	0 (0.0%)	6 (3.4%)
Positive	128 (47.5%)	28 (40.4%)	90 (51.5%)
Unknown	134 (49.8%)	56 (59.6%)	79 (45.1%)
Histology			
Ductal	239 (88.8%)	80 (85.1%)	159 (90.9%)
Lobular	20 (7.4%)	8 (8.5%)	12 (6.9%)
Other	10 (3.7%)	6 (6.4%)	4 (2.2%)
Grade			
I	23 (8.6%)	6 (6.4%)	17 (9.7%)
II	95 (35.3%)	27 (28.7%)	68 (38.9%)
III	124 (46.1%)	44 (46.8%)	80 (45.7%)
Unknown	27 (10.0%)	17 (18.1%)	10 (5.7%)
Lymphatic vessel invasion			
Present	37 (13.8%)	13 (13.8%)	24 (13.7%)
Not present	211 (78.4%)	70 (74.5%)	141 (80.6%)
Unknown	21 (7.8%)	11 (11.7%)	10 (5.7%)
Vascular invasion			
Present	22 (8.2%)	4 (4.3%)	18 (10.3%)
Not present	226 (84.0%)	79 (84.0%)	147 (84.0%)
Unknown	21 (7.8%)	11 (11.7%)	10 (5.7%)
Extensive intraductal component			
Present	51 (19.0%)	17 (18.1%)	34 (19.4%)
Not present	218 (81.0%)	77 (81.9%)	141 (80.6%)
Oestrogen receptor			
Negative	90 (33.5%)	33 (35.1%)	57 (32.6%)
Positive	156 (58.0%)	50 (53.2%)	106 (60.6%)
Unknown	23 (8.6%)	11 (11.7%)	12 (6.9%)
Progesterone receptor			
Negative	93 (34.6%)	38 (40.4%)	55 (31.4%)
Positive	154 (57.2%)	45 (47.9%)	109 (62.3%)
Unknown	22 (8.2%)	11 (11.7%)	11 (6.3%)
Multifocal disease			
Yes	53 (19.7%)	21 (22.3%)	32 (18.3%)
No	216 (80.3%)	73 (77.7%)	143 (81.7%)
Age			
≤35 years	94 (34.9%)		
≥36 years	175 (65.1%)		

Table 2
Treatment. Regarding adjuvant chemotherapy, the taxane-based chemotherapy group included combined taxane-anthracyclin treatment. SNB = sentinel node biopsy; CMF = cyclophosphamide-methotrexate-5-fluorouracil.

Treatment	Number of patients (%)
Surgical treatment	
Mastectomy and axillary evacuation	187 (69.5%)
Excision and axillary evacuation	61 (22.7%)
Mastectomy, SNB and axillary evacuation	6 (2.2%)
Excision and SNB	6 (2.2%)
Excision, SNB and axillary evacuation	4 (1.5%)
Mastectomy and SNB	3 (1.1%)
Excision only	2 (0.7%)
Neoadjuvant chemotherapy	
No	261 (97.0%)
Yes	5 (1.9%)
Unknown	3 (1.1%)
Adjuvant chemotherapy	
No adjuvant chemotherapy	75 (27.9%)
Anthracyclin-based chemotherapy	72 (26.8%)
Taxane-based chemotherapy	47 (17.5%)
CMF	70 (26.0%)
Vinorelbine	1 (0.4%)
Unknown	4 (1.5%)
Postoperative radiotherapy	
No	18 (6.7%)
Yes	249 (92.6%)
Unknown	2 (1.1%)
Hormone therapy	
No	188 (69.9%)
Yes	78 (29.0%)
Unknown	3 (1.1%)

Survival analysis

Five-year breast cancer-specific survival (BCSS) in the whole study group was 81.1% and the 10-year figure was 72.3% (Fig. 1A). Corresponding figures for overall survival (OS) were essentially the same, 80.6% and 71.3% (Fig. 1)B. Disease-free survival (DFS) at 5 years was 65.2% and at 10 years 57.0%. Locoregional DFS at 5 years was 94.1% and at 10 years 90.9%. The 5-year distant metastases-free survival rate was 91.8% and the 10-year figure 89.2%. There were no locoregional or distant recurrences after 135 months of follow-up, and only 8 of 97 (8.2%) events occurred after 83 months.

In univariate analysis, large tumour size, lymph node metastases, high LNR, high grade, lymphatic vessel invasion and vascular invasion predicted poor survival (Table 3). Positive Ki-67 immunostaining ($p = 0.07$) and negative progesterone receptor (PR) status ($p = 0.06$) were not significantly associated with worse prognosis, although a trend was clear. Age of ≤35 years was associated with poor DFS according to the Breslow test ($p = 0.04$) (Fig. 2). However, according to log-rank and Tarone–Ware analysis the association was not significant. High LNR was the only studied parameter that predicted poor local control ($p = 0.02$).

In Cox multivariate regression analysis LNR was the only independent prognostic factor as regards worse BCSS when was evaluated as a continuous variable ($p < 0.001$). As a categorial variable (≤0.2 vs. >0.2–0.65 vs. >0.65) both LNR ($p < 0.001$) and the presence of lymphatic vessel invasion ($p = 0.02$) were independent prognostic factors of poor BCSS. Larger T-class ($p = 0.048$) and LNR as a continuous variable ($p < 0.001$) were independent prognostic factors of poor DFS. When LNR was considered as a categorical variable, increased primary tumour size ($p = 0.005$), lymph node-positive disease ($p = 0.04$) and LNR ($p = 0.001$) were independent predictors of unfavourable DFS.

We also tested the prognostic power of LNR when only the patients with at least 8 dissected lymph nodes were included in multivariate analysis. The results showed that in this population, LNR was an even more powerful predictor of BCSS and it was the only independent prognostic factor as either a continuous or a categorial variable (for both, $p < 0.001$). Regarding DFS in women with at least 8 dissected lymph nodes, LNR as a continuous variable was the only independent prognostic factor ($p < 0.001$). As categorial variables, both larger primary tumour ($p = 0.014$) and high LNR ($p < 0.001$) were independent predictors of poor DFS.

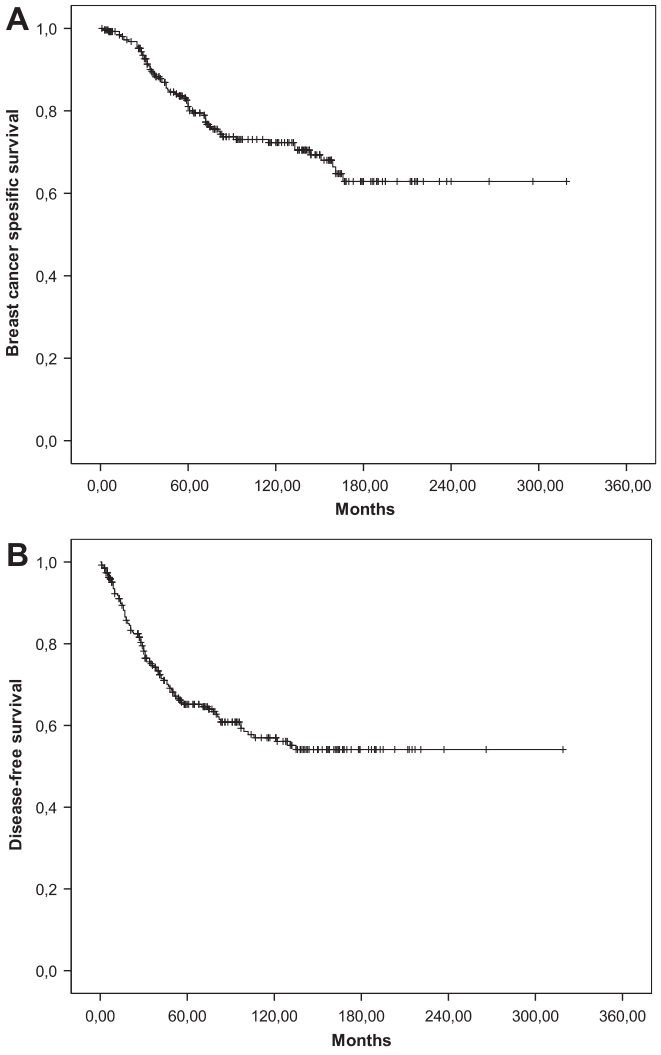

Fig. 1. A. Kaplan–Meier curve of breast cancer-specific survival. Crosses indicate censored cases. B. Kaplan–Meier curve of disease-free survival. Crosses indicate censored cases.

Discussion

Strengths of the current study were not only the large number of cases but in particular the long follow-up time, which allowed us to analyse survival data of young women with breast cancer in more depth than in most previous studies. On the other hand, the long follow-up time restricted the assessment of treatment methods (e.g., steroid receptor and HER2 assessments were not routinely carried out until the 1990s).

The 5- and 10-year BCSS rates were 81.1% and 72.3%, respectively, and the OS figures were essentially the same, as one could expect in this population. Previous studies on non-metastatic breast cancer in young women have yielded 5-year OS and BCSS rates ranging from 64 to 77 per cent.[9,19–21] The survival figures in

Table 3
Univariate Kaplan–Meier analysis of prognostic factors. Values of *p* are shown (log-rank test if not otherwise mentioned). Lymph node ratio is presented as a categorial variable (≤0.2 vs. >0.2–0.65 vs >0.65). NS = $p \geq 0.05$. *Breslow test; **Ductal vs. lobular vs. others; ***Node positive vs. negative.

	Overall survival	Breast cancer–specific survival	Disease-free survival	Local relapse-free survival	Distant metastases-free survival
Tumour size	<0.0001	<0.0001	<0.0001	NS	<0.0001
Nodal status***	<0.0001	<0.0001	<0.0001	NS	<0.0001
Lymph node ratio	<0.0001	<0.0001	<0.0001	<0.05	<0.0001
Ki-67	NS	NS	NS	NS	NS
Histology**	NS	NS	NS	NS	NS
HER2 (CISH)	NS	NS	<0.05	NS	NS
Grade	<0.05	<0.05	<0.01	NS	<0.01
Lymphatic vessel invasion	<0.0001	<0.0001	<0.0001	NS	<0.0001
Vascular invasion	<0.01	<0.05	<0.05	NS	<0.0001
Oestrogen receptor	NS	NS	NS	NS	NS
Progesterone receptor	NS	NS	NS	NS	NS
Multifocal disease	<0.05	0.022	NS	NS	NS
Age ≤35 or ≥36–40 years	NS	NS (0.062*)	0.040*	NS	NS (0.052*)

our material are therefore somewhat better than reported in previous series. However, in a more contemporary, large registry-based study by Ahn et al. a 5-year OS rate of 81.5% was found in patients <35 years old and the rate was 89.4% in patients 35 to 50 years old.[12] In the current study, the 5- and 10-year DFS rates were 65.2% and 57.0%, and these figures are also in keeping with, or slightly better than those previously reported.[19,21,22] One of the most interesting observations in the current study was the plateau in the DFS curve after ten years of follow-up (Fig. 1)B. More than 90 per cent (89 of 97) of the local or distant relapses occurred within seven years of surgery (80.6% of ER-positive and 93.1% of ER-negative patients). To the best of our knowledge, such a finding has not been reported previously and the novelty of this result may spring from the unusually long follow-up of our patients. This also tells about the aggressive nature of breast cancer in young women, especially those diagnosed at or below the age of 35 years, since in this group only 5.3% (2 of 38) of the patients developed a relapse later than after seven years of follow-up (Fig. 2).

Previously, large primary tumour size,[23] high stage,[24,25] positive nodal status[25] and lymphovascular invasion[26] have been reported as independent prognostic factors of OS in young breast cancer patients (upper limit of the definition varying between 35 and 45 years). Several investigators have suggested that LNR (the ratio of invaded/removed lymph nodes) could be an independent prognostic factor in stage I–III breast cancer, although the studies have involved women of all ages.[27–29] In the current material, high LNR as a continuous variable was alone a highly powerful prognostic factor of poor breast cancer-specific survival in multivariate analysis and in significance it clearly exceeded all traditional predictors of outcome. When LNR was divided into three risk-classes (≤0.2 vs. >0.2–0.65 vs. >0.65) (after the work of Vinh-Hung et al.[28]), lymphatic vessel invasion was a barely significant predictor of BCSS, whereas LNR had noticeably stronger prognostic power. Relatively large tumour size and high LNR (continuous variable) were independent predictors of short DFS. The current results suggest that LNR is a stronger prognostic factor of death from breast cancer than more traditional clinicopathological parameters, including pN classification, in young breast cancer patients. The prognostic power of LNR is highest when used as continuous variable and when there are a sufficient number of examined lymph nodes.

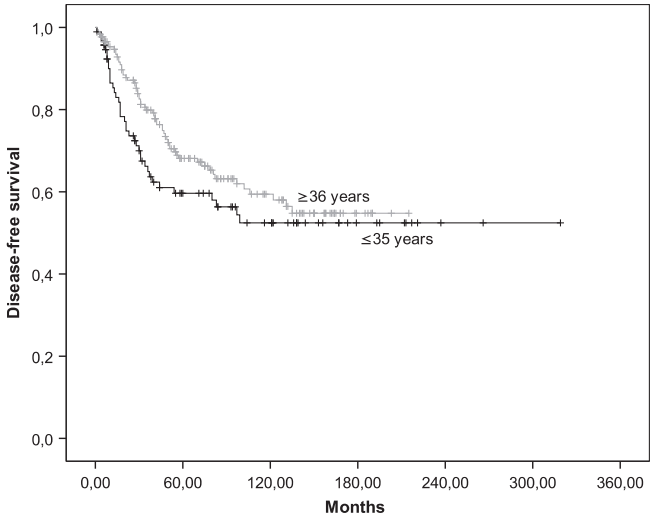

Fig. 2. Disease-free survival according to age (log-rank $p = 0.166$; Breslow $p = 0.040$; Tarone–Ware $p = 0.075$). Crosses indicate censored cases.

We observed decreased DFS and a trend towards decreased BCSS in ≤35-year-old patients compared with those of 36–40 years of age. The difference was statistically significant, however, only in the case of DFS and only during the first few years of follow-up (Breslow's test), when most of the relapses occurred in the youngest patients. Interestingly, this difference in DFS appeared to be a consequence of increased frequency of distant metastases in younger women, whereas the rate of LRR was the same in both age groups (9.3% in the whole study population). In several previous studies it has been proposed that age less than 35 years is an independent prognostic factor of LRR, the rate in this age group varying from 11% to 20.6%.[20–26,30] These studies, however, have involved comparison of women of less than 35 years of age versus all women of 35 or more. There is convincing data regarding the necessity of mastectomy (compared with breast-conserving surgery) in younger breast cancer patients (under 45 to 55 years old).[31–33] However, it seems that the difference in LRR does not become apparent until very young breast cancer patients are compared with mainly postmenopausal women.

Mutations in *BRCA* are over-represented among young women with breast cancer and these women are likely to have contralateral disease.[34,35] In our series only 3% of patients were diagnosed with cancer in the other breast. The low rate of contralateral cancer in our study may be associated with the high proportion of women receiving tamoxifen, since adjuvant tamoxifen therapy reduces the incidence of contralateral breast cancer by 90% in women <40 years of age.[36] The patients' *BRCA* status was not available and in theory a small proportion of women with *BRCA* mutations could explain the diminished incidence of contralateral cancers.

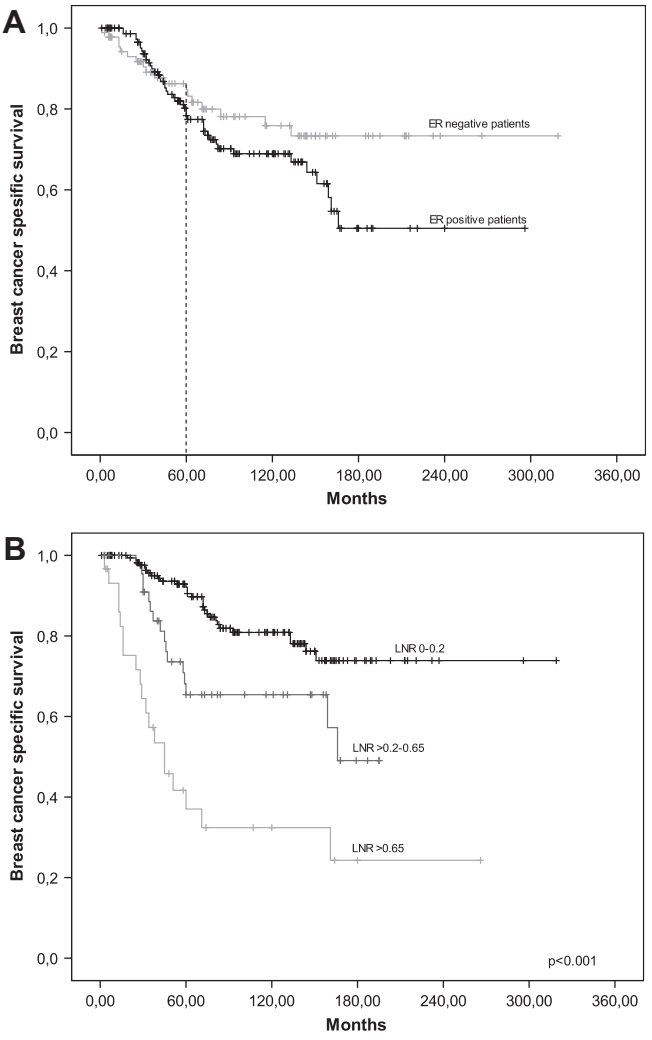

Fig. 3. A. Breast cancer-specific survival according to oestrogen receptor expression status. The 5-year point is marked with a dashed line (represents the end of anti-oestrogen therapy in the patients with hormone receptor-positive disease). Crosses indicate censored cases. ER = oestrogen receptor. B. Breast cancer-specific survival according to lymph node ratio (cut-offs used ≤0.2 vs. >0.2–0.65 vs. >0.65). Crosses indicate censored cases.

The results of several studies have indicated that there is a higher proportion of adverse prognostic factors in women of ≤35 years of age compared with older patients. Negative steroid receptor status, HER2 over-expression, high grade, lymphovascular invasion and high proliferation index have all been found to be over-represented in young patients.[10,11,15,16,24,37] However, the control groups in these studies have frequently been women with breast cancer diagnosed at ages up to 50 years, or even more. When we compared younger women with older ones in our material, there were no significant differences in the frequencies of clinicopathological parameters in the two groups. However, in contrast to most of the above-cited studies, our patient material consisted only of patients up to 40 years of age and all were premenopausal. Thus it seems that differences in the biology of breast cancer do not become sufficiently evident until young patients are compared with those near menopause.

There was a statistically non-significant trend ($p = 0.06$) towards more PR-negative tumours among the women ≤35 years old (40.4%) compared with those aged 36 to 40 (31.4%). In ER status the corresponding figures were 35.1% and 32.6%, respectively. Steroid receptor expression was somewhat lower compared with that in the large material described by Colleoni et al. with 1427 patients, where 49.1% of the patients under 35 year of age were PR-negative and 38.8% ER-negative, and also compared with the figures in a case-control study by Hartley et al. with PR-negative tumours in 50.0% and ER-negative tumours in 33.8% of women under the age of 40.[24,37] In other series the proportions of ER-negative patients have been around 50%.[9,12,21,25,38]

In contrast to older women, young breast cancer patients with ER-positive disease have poorer prognosis compared with those with ER-negative cancers.[39] The preferred choice of adjuvant hormone therapy in premenopausal women is five years of tamoxifen treatment. However, the optimal duration of tamoxifen therapy is still unknown and there are some recent observations suggesting that even longer treatment could be beneficial.[40] We observed an obvious increase in relapses and subsequently in breast cancer deaths after five years in patients with ER-positive disease, in contrast to ER-negative patients, where a similar trend was not evident (Fig. 3). One reason behind this observation may be that patients with ER-positive breast carcinomas tend to suffer relapse later than those with ER-negative cancers. On the other hand, five years represents the time-point when the ER-positive patients discontinued their anti-oestrogen therapy. It could be hypothesized that because of long endogenous oestrogen exposure in the youngest women, anti-oestrogen treatment probably should not be withdrawn after five years. This may apply especially to patients with ER-positive, but otherwise aggressive breast cancer and also to women with ER-positive tumours who do not develop amenorrhoea after adjuvant chemotherapy. Premenopausal women with cessation of menses after cytotoxic treatment are considered to have better prognoses compared with those without amenorrhoea.[41] Unfortunately, we did not have information on amenorrhoea status in our database.

Conclusions

We conclude that young women with breast cancer seem to have a high relapse rate during the first few years after diagnosis, although their prognosis in general is relatively good. This applies especially to cases with distant metastases, while the relapse rate as regards LRR is not different between women of ≤35 years of age and those who are 36 to 40 years old. Interestingly, nearly all relapses in women with ER-negative disease were discovered within seven years of diagnosis. Premenopausal women with ER-positive disease remain at an elevated risk of relapse even after this seven-year period, probably because of their endogenous exposure to oestrogen after the withdrawal of anti-hormone therapy. Finally, we report that the prognostic value of LNR seems very promising and it should be evaluated in future studies of young breast cancer patients to verify the current results.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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