

Characteristics and prognosis of breast cancer in younger women

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Summary

Purpose: Women under 40 years of age comprise a small proportion of patients with breast cancer. Clinical and pathological features of the disease in these patients are different from those in older patients with this type of cancer. In the present study we investigated the clinicopathological characteristics and prognostic factors in young patients with breast cancer.

Methods: We retrospectively reviewed the medical records of 249 consecutive breast cancer patients who were admitted to our department between August 2001 and December 2005. Clinicopathological features were determined both in patients under and over 40 years of age.

Results: 106 (42.5%) patients were under and 143 (57.5%) were over 40 years. The mean age was 35.2 years for those under 40 years and 54 for those older than 40 years.

At diagnosis, 10.4% of the patients in the younger age group and 7.0% in the older age group had metastasis ($p=0.500$). Patients in the younger age group exhibited higher estrogen receptor (ER) negativity (48.1 vs. 37.1%) ($p=0.425$) and a higher percentage of family history of breast cancer (4.7 vs. 2.8%) ($p=0.651$). Breast cancer in younger women was more frequently associated with other poor prognostic factors such as perineural and/or lymphovascular invasion. The 5-year overall survival was 6.3% for the younger patients and 22.2% for the older ones ($p=0.004$).

Conclusion: This study demonstrates that breast cancer in younger patients has significantly more poor prognostic features compared to older ones.

Key words: breast cancer, prognosis, risk factors, young women

Introduction

Breast cancer is the most common type of cancer among women. However, it is infrequent at young age. Some authors have accepted patients under 35 years as young, while some others have considered patients under 40 years as young patients. The incidence of breast cancer in women under 35 years is between 4-12.5% in different series [1,2]. The incidence is also low among those under 40 years old. The highest incidence reported in the literature is 28% [2].

The clinical and pathological profile of breast cancer in young women is significantly different than in older patients, with a predominance of unfavorable prognostic parameters. These patients usually have a poorer prognosis. It has been reported that younger pa-

tients have more metastatic axillary lymph nodes and higher incidence of local recurrences than older patients [3]. Some authors reported that breast cancer in younger women was of higher grade, higher proliferation fraction, had more vascular invasion, and expressed less ER and progesterone receptor (PR) positivity compared to tumors of older women [4,5]. Moreover, women under 40 had a higher overall rate of recurrence and a lower 5-year overall survival [6]. Additionally, family history of breast cancer is more common in patients under 40 years compared to older ones [7].

We have observed a higher breast cancer rate in young patients in our hospital compared to the literature. For this reason, we investigated the clinicopathological characteristics and prognostic factors in young patients with breast cancer admitted to our hospital.

Methods

Study participants

We retrospectively reviewed the medical records of 249 patients with invasive breast cancer, including male patients who were admitted to the departments of medical oncology and radiation oncology of the Dicle University Hospital between August 2001 and December 2005. Patients with metastasis at the time of diagnosis were also included in the study. Age, histological type, size of primary tumor, axillary lymph node status, histological and nuclear grade, ER, PR, c-erbB2 status and family history of breast cancer were reviewed. Both female and male patients under 40 years of age at the time of breast cancer diagnosis were considered as young.

Statistical analysis

SPSS (version 13.0) was used for statistical analyses. The χ^2 (Pearson statistics) test was used to determine differences in clinical and pathological features between the two age groups. A p-value of <0.05 was considered as significant. Progression-free survival and overall survival were computed using Kaplan-Meier method and the differences between survival times were assessed by log-rank test. Moreover, univariate and multivariate analysis were carried out using Cox proportional hazard model.

Results

A total of 249 patients were reviewed in this study. Among them, 106 (42.5%) patients were less than 40 years of age at the time of diagnosis. The remaining 143 (57.5%) patients were over 40 years. Among those under 40 years, 2 were males. There were also 6 male patients among the patients aged over 40 years. The median age was 36 years (range 23-40) in the younger age group and 55 years (range 41-86) in the older age group. The median follow-up time was 60 months for both groups.

Histology and stage

Histological breast cancer types were similar in both groups. The most common histological type in both groups was invasive ductal carcinoma (Table 1). The proportion of patients with T4 disease was higher in the younger group (14.2 vs. 8.4%), but the difference was not statistically significant ($p=0.26$). The distribution of other T stages was similar in both groups. Initially, 11 patients (10.4%) in the younger age group, and 10 patients

Table 1. Clinicopathological characteristics

Characteristic	Age <40 years n (%)	Age \geq 40 years n (%)	p-value
Number of patients			
Female	104 (98.2)	137 (95.9)	
Male	2 (1.8)	6 (4.1)	
Total	106 (42.5)	143 (57.5)	
Histological type			
Ductal	87 (82.1)	115 (80.4)	0.9332
Lobular	9 (8.5)	14 (9.8)	0.9461
Mixed	5 (4.7)	4 (2.8)	0.6519
Others	5 (4.7)	10 (7.0)	
T stage			
T1	7 (6.6)	14 (9.8)	0.5725
T2	46 (43.4)	63 (44.0)	0.9116
T3	38 (35.8)	54 (37.8)	0.9756
T4	15 (14.2)	12 (8.4)	0.2616
Stage 4 at onset	11 (10.4)	10 (7.0)	0.5009
Lymph node status			
Negative	19 (20.0)	32 (24.1)	
Positive	76 (80.0)	103 (75.9)	0.7075
ER			
Positive	55 (51.9)	90 (62.9)	
Negative	51 (48.1)	53 (37.1)	0.4254
PR			
Positive	58 (54.8)	70 (48.9)	
Negative	48 (45.2)	73 (51.1)	0.69
c-erbB-2			
Positive	41 (45.5)	42 (34.7)	
Negative	49 (54.5)	79 (65.3)	0.3592
Histological grade			
1-2	40 (47.1)	65 (57.0)	
3	45 (52.9)	49 (43.0)	
Nuclear grade			
1-2	37 (43.6)	67 (58.8)	
3	48 (56.4)	67 (41.2)	
Family history*	5 (4.7)	4 (2.8)	0.6519

*Patients who had at least one 1st or 2nd degree relatives with breast cancer

(7.0%) in the older age group had stage 4 disease. Patients in both groups underwent similar surgical procedures. Sentinel lymph node procedure was performed to 3 patients. Axillary lymph node dissection was performed in 95 (89.6%) patients in the younger and 133 (93.0%) patients in the older age group. Among these 95 patients in the younger age group undergoing axillary lymph node dissection, 76 (80.0%) had lymph node metastasis. One hundred and thirty-three patients in the older age group underwent axillary lymph node dissection. The proportion of patients with 0 and 1-3 positive lymph nodes was higher in the older age group, while there were more patients with 4-9 and >10 positive lymph nodes in the younger age group, although the difference between the two age groups was not statistically significant (Table 2). The rate of ER negativity was higher in the younger

Table 2. Lymph node status

Number of lymph nodes	Age <40 years n (%)	Age ≥40 years n (%)	p-value
0	19 (20.0)	32 (24.1)	0.7492
1-3	14 (17.9)	27 (20.3)	0.5237
4-9	31 (32.6)	38 (28.6)	0.6488
>10	28 (29.5)	36 (27.1)	0.7902

age group and PR negativity was higher in the older age group of patients, although the differences between the two groups were not statistically significant for both hormone receptors. c-erbB2 was positive in 45.5% of the younger and in 34.7% of the older patients. This difference was also not statistically significant (Table 1). The number of patients with histological and nuclear grade 3 disease was higher in the younger age group, but this difference too, did not reach statistical significance. Similarly, the rate of a positive family history did not differ significantly among the two groups.

Therapies administered

Adjuvant radiation therapy (RT) was administered after mastectomy to patients who had ≥4 positive lymph nodes or T3 disease and patients who had undergone breast-conserving surgery. Fifty-eight (57%) patients in the younger and 93 (65%) patients in the older age group received adjuvant RT. Among younger patients, 98.9% who had undergone surgery were administered adjuvant chemotherapy (CT). In this group, only one of the patients undergoing surgery did not receive adjuvant CT. In the older age group, 93.9% of the patients were administered adjuvant CT. The most common chemotherapy regimens were 4 cycles of cyclophosphamide + doxorubicin (AC; 25 patients) or 6 cycles of cyclophosphamide + methotrexate + 5-fluorouracil (CMF; 37 patients). After completion of the adjuvant treatments, hormone therapy with tamoxifen was administered for up to 5 years in steroid receptor-positive patients.

Recurrence and survival

During follow-up of all of the cases, tumor recurrence was observed in 40 patients from the younger and in 52 patients from the older age group, with the former showing a trend towards distant metastasis and the latter a trend for local recurrence. Bone was the most common site for distant metastasis in both groups. Metastatic sites and incidence were similar in both groups (Table 3).

Kaplan-Meier survival curves were compared by the log-rank test. Younger patients had a worse progression-free survival, which was 10 and 18 months

Table 3. Sites of metastases

Site	Age <40 years n (%)	Age ≥40 years n (%)	p-value
Bone	18 (45.0)	21 (40.3)	0.6111
Brain	7 (17.5)	6 (11.5)	0.9688
Lung	5 (12.5)	8 (15.3)	0.8885
Liver	2 (5.0)	1 (1.9)	0.5469
Locoregional	8 (20.0)	16 (30.7)	0.8139

for younger and older patients, respectively (Figure 1; $p=0.04$). Overall survival of younger patients was significantly worse compared with older patients (Figure 2; $p=0.004$). Median survival was 20 months for patients under 40 years and 24 months for patients over 40 years ($p=0.04$) and 5-year survival was 6.3 and 22.2%, respectively ($p=0.004$). Multivariate analysis identified age as independent prognostic factor, while estrogen receptors status was a dependent variable (Table 4).

Discussion

The incidence of breast cancer in women aged under 40 years is lower. However, there is a rise in the inci-

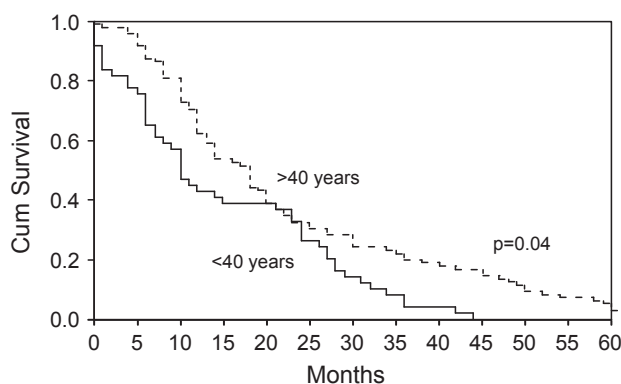
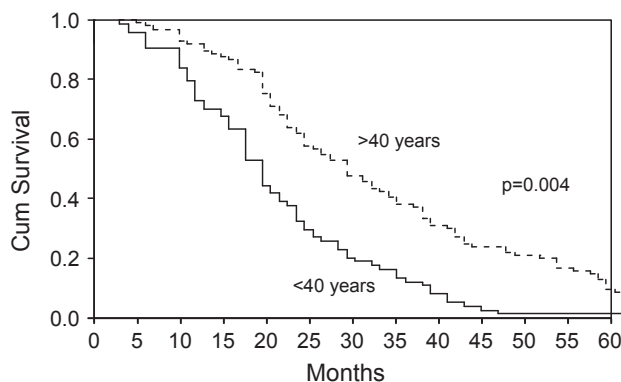
**Figure 1.** Progression-free survival in younger and older patients.**Figure 2.** Overall survival in younger and older patients.

Table 4. Multivariate analysis

	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>df</i>	<i>Sig</i>	<i>Exp (B)</i>
Age (<40 vs. ≥40 years)	0.526	0.456	1.326	1	0.250	1.691
ER (pos vs. neg)	0.919	0.439	4.372	1	0.037	2.506
PR (pos vs. neg)	-0.781	0.418	3.486	1	0.062	0.458
T stage (early vs. late)	-0.490	0.403	1.479	1	0.224	0.612
Lymph node (pos vs. neg)	-0.629	0.490	1.648	1	0.199	0.533

dence of breast cancer in young females through the years worldwide. In the United States, figures from the National Cancer Institute (NCI) Surveillance, Epidemiology and End-Results (SEER) database show that approximately 2.7% of breast cancer patients are younger than 35 years [8]. According to Kothari et al. [9], women under the age of 35 years comprise only 5% of breast cancer cases. El Saghir et al. reported a breast cancer incidence of 8.1% in women under the age of 35 years [10]. According to Han et al., the percentage of breast cancer patients under 40 years is 28% [2]. In our group of patients the incidence of breast cancer under the age of 40 was 42.5%. This is the highest incidence in the literature.

It is widely believed that breast carcinoma in young women is characterized by a relatively unfavorable prognosis and unusual pathological features. Young patients have larger tumor sizes, more positive lymph nodes, more negative hormone receptors and higher tumor grades than older patients [10-12]. In our study, when T stages were taken into account, the number of patients with T4 tumors was greater in the younger age group, although, similar to other studies, the difference between the younger and older age groups was not statistically significant [10]. In our younger group of patients, there were more patients in stage 4 at presentation, however, this difference was not statistically significant, either. The delay in seeking medical help and consequently delayed diagnosis may be a result of the generally shy, withdrawn social nature of younger patients and this may account for or contribute to the higher incidence of initially metastatic tumors at presentation in this patient population. Additionally, we did not find in the literature any data on male breast cancer patients under 40 years old. Two of the patients in our younger age group were males. However, this number is not enough to make any comments over male patients.

Similar to other reports, we did not find a significant difference among the two age groups in terms of the number of positive lymph nodes [2,10]. Fowble et al. reported a poorer prognosis in lymph node-negative stage I and II young patients [13]. On the contrary, Han et al. reported that lymph node negativity did not affect the prognosis in a negative way [2]. We also noticed that

lymph node status did not affect prognosis. Although the proportion of young patients with breast cancer was high, the missing information in their medical records might have brought us to this conclusion. Chow and Ho [14] reported ER positivity in 53% of premenopausal and in 61.6% of postmenopausal women with breast cancer. In the same study PR positivity was 51.5% and 46.2% in pre- and postmenopausal patients, respectively [14]. We found an ER positivity of 51.9% in our younger patients and 62.9% in the older patients with breast cancer. We calculated the PR positivity as 54.8% and 48.9% in younger and older groups, respectively. c-erbB-2 positivity differs widely in different reports. In a study by Colleoni et al. [4], c-erbB-2 positivity in women under 40 years was 38.5%, while in the same age group Tsutsui et al. also reported c-erbB-2 positivity in only 17.2% of their patients [15]. In addition, Choi et al. reported c-erbB-2 positivity in 47.5% of their Korean patients and in 15.8% of Caucasian patients [16]. In the present study, c-erbB-2 was found positive in 45.5% of patients under 40 and in 34.7% of patients over 40 years of age. These figures suggest that c-erbB-2 expression may show variations among patients from different racial origins.

In conclusion, in our patient group the percentage of young patients with breast cancer was higher than the figures given in the literature. This might be a result of a younger population pyramid of the country. However, since a review of the current literature reveals a rise in the number of young breast cancer patients through the years worldwide, the underlying causes of this shift must be investigated in large population-based studies. We have not found any single clinicopathological factor playing a statistically significant role in the prognosis of the younger patients when compared to older patients, however all these factors sum up to cause a worse survival in patients under the age of 40.

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