Breast Cancers: Young Age the Significant Predictor

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Abstract

Background: The incidence of breast cancer in young women (age < 35) is low. The biology of the disease in this age group is poorly understood, and there are conflicting data regarding, the prognosis for these women compared to older patients.

Patients and methods: We retrospectively analyzed consecutive primary invasive breast cancer patients who underwent surgical procedures at our institution between 1990 and 2002. The younger age group was defined as patients aged <35 years at the time of diagnosis, the clinicopathological characteristics and treatment outcomes were compared between younger and older age groups.

Result: A total of 51 (12.5%) patients were aged <35. There was a significantly higher incidence of nuclear grade 3 and medullary histological-type tumors in younger patients compared to older patients. Axillary lymph node status, T stage, histological grade, and estrogen receptor status did not differ significantly between the two age groups. Younger patients had a greater probability of recurrence and death at all time periods, although there was no significant difference in disease-free survival between the two age groups.

In lymph node-negative patients, the younger group showed worse prognosis among lymph node-positive patients ($p<0.001$).

Conclusion: In multivariate analysis, young age remained a significant predictor of recurrence ($p=0.010$). Young age (<35) is an independent risk factor for relapse in operable breast cancer patients.

الخلاصة

المقدمة : نسبة حدوث سرطان الثدي لدى النساء الشابات (السن < 35)هي منخفضة. بيولوجيا هذا المرض في هذه الفئة العمرية غير مفهوم، و هناك بيانات متعارضة بشأن هذه الفئة العمرية مقارنة مع كبار السن.

طريقة البحث: تم خلال هذه الدراسة تحليل بأثر رجعي مريض سرطان الثدي الذي خضع لعملية جراحية في مؤسستنا في الفترة بين عامي 1990 و 2002. تعرف الفئة العمرية الأصغر سنا هي الفئة الأقل من 35 عام في وقت التشخيص .

النتائج: كانت نتائج العلاج مقارنة بين الشباب والفئات العمرية الأكبر سنا كالأتي:-

هناك زيادة كبيرة في معدل انتشار النووي (3) ، والصف النخاع النسجي من نوع الأورام في المرضى الأصغر سنا مقارنة مع المرضى من كبار السن. بالنسبة لحالة العقد اللمفية في البط ، المرحلة النسجية للورم ، والاستروجين المستقبلة لا تختلف بشكل كبير بين الفئات العمرية.

الاستنتاجات: احتمالية حدوث الوفاة و رجوع المرض أكبر عند الأصغر سنا في جميع الفترات الزمنية.

Introduction

Breast cancer is relatively rare in women less than 35 years of age, with this group accounting for less than 4% of the total number of breast cancer cases diagnosed in Western countries [1, 2]. Despite the disease being, relatively uncommon, it has a severe negative effect on the patients and their families. It remains controversial whether young age at diagnosis is an adverse prognostic factor in primary breast cancer. While some studies have found that younger patients have worse clinical outcomes than older patients [3, 4] others report younger patients have a more favorable prognosis or that there is no relationship between outcomes and age [5,6]. Various explanations have been given for these conflicting results, including small numbers of patients comprising the study population, differences in patient selection criteria and differences in the age groupings used in the analyses. Moreover,

It has long been debated whether breast cancer diagnosed at a young age is a clinically and etiologically distinct disease from breast cancer diagnosed later in life. Some researchers reported that tumors in younger women were of higher grade, higher proliferation fraction, had more vascular invasion, and expressed fewer estrogen and progesterone receptors compared to tumors in older women [7,8]. It is important for clinicians to clarify the existing controversy as to whether aggressive treatment for young women with breast cancer is justified.

Breast cancer is the most frequent cancer in Iraqi women and its incidence is increasing [9]. Breast cancer in young Iraqi women is a serious problem, with the proportion of young, age-onset breast cancer much higher than in western countries.

The aim of the present study: to retrospectively investigate clinicopathological characteristics and prognosis in a large group of young breast cancer patients (less than 35 years old) treated in the Hilla Surgical Hospitals, Department of Surgery, Medical College, and Babylon University, IRAQ.

Patients and Methods

The study was performed of all consecutive primary invasive breast cancer patients undergoing curative surgery in the Department of Surgery, Hilla Surgical Hospitals, Medical College, Babylon University between January 1990 and December 2002. Patients' records were reviewed for the following: age of onset, family history of breast cancer in 1st or 2nd degree relative, histological type of cancer, tumor size in pathology reviews, axillary lymph node status, histological grade (HG: Scarff-BloomRichardson classification), nuclear grade (NG: Black's nuclear grade), type of surgical procedure and adjuvant therapy administered. Disease was staged according to the American Joint Committee of Cancer (AJCC) system [10]. The 'younger' group was defined as patients less than 35 years old at the time of breast cancer diagnosis. Immunohistochemical expression of estrogen receptor (ER) and progesterone receptor (PR) were determined by the methods used before [11]. A cut-off value of 10% or more positively stained cells out of total cells in ten high-power fields was used in the classification of ER and PR expression levels.

The x2 test (Pearson statistic) was used to determine the differences in clinicopathological features between the two groups of patients. The follow-up duration was calculated from the date of diagnosis until the date of death or last contact. The disease-free survival was the time between diagnosis and confirmation of disease recurrence. The overall survival was the time between diagnosis and death as a result of any cause, regardless of recurrence events. Survival estimates were computed using, the Kaplan-Meier method [12] and the differences between survival times were assessed by means of the log., rank test [13]. Multivariate analyses were carried out using proportional hazards model [14].

Results

A total of 228 patients were eligible for this study, of which 51 (22.4%) were aged <35 at the time of diagnosis. The median follow-up was 60 months. Histology showed the incidence of medullary carcinoma was significantly higher than ductal carcinoma in the younger group (p=0.018). There was a significantly higher incidence of nuclear grade 3 in the younger group than in the older group (p=0.015). Axillary lymph node status, the most prominent prognostic factor in breast cancer, was not significantly different between the two age groups. Also, neither the family history of breast cancer in 1st or 2nd degree relatives, T stage, histological grade, nor ER or PR status (fig.1) were different between the two groups (Table 1). Frequencies of ER and PR positivity were low.

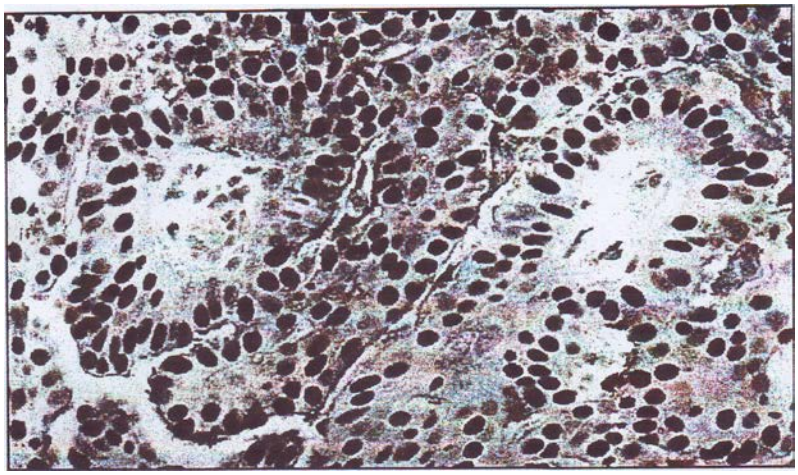

Fig 1. Representative Immunohistochemical staining for the expression of PR in breast carcinoma. Original magnification (× 400).

The proportion of breast-conserving surgery compared to mastectomy was similar in both groups. Axillary lymph node dissection, at least to the first Berg level was performed in younger and older patients. Adjuvant radiation therapy was administered to patients who underwent breast-conserving surgery and after mastectomy in patients who had four or more positive lymph nodes or a tumor >5 cm in diameter. Adjuvant chemotherapy was administered to 68.0% of younger and 58.7% of older patients. In terms of hormone therapy, tamoxifen was used for as long as 5 years after completion of surgery and adjuvant therapy. We classified a patient as tamoxifen treatment group if she got tamoxifen through more than a year before recurrence. The proportion of tamoxifen treated patients was significantly lower in young age group. Neither the type of surgery nor the postoperative adjuvant chemotherapy was significantly different between the two age groups (Table 2).

Younger patients had a worse disease free survival (greater probability of recurrence) at all time periods ($p<0.001$). At 5 years, the actuarial recurrence rate for patients <35 years old was 30.4% as compared with 18.7% for older patients. Overall survival among younger patients was significantly worse than for older patients ($p=0.002$). The 5-year survival rate was 80.0% for patients aged <35 years as compared with 88.5% for older patients. Stratified analysis according to axillary lymph node status was performed for disease-free survival. In lymph node-negative patients there was no significant difference in disease-free survival between the two age groups ($p=0.223$). However, in lymph node positive patients, disease-free survival was significantly worse in younger patients ($p<0.001$).

In multivariate analysis, young age (<35 years) remained a significant predictor of recurrence when entered into a model containing all potential demographic, patho-logic and immunohistochemical variables (Table 3). Hazard Ratio (HR), 1.7; 95% confidence interval, 1.1-2.6; $p=0.010$). However, young age was not a significant independent predictor of overall survival in the same Cox model (HR, 1.4; $p=0.242$). Because hormone therapy was done more frequently in older patients than g young age group (Table 2,3), we made another multivariate model involving hormone therapy in patients with ER positive and/or PR positive cancer to address the effect of hormone therapy on the prognostic signify-cance of young age. In this analysis, young age was still an independent significant prognostic factor while hormone therapy showed borderline significance (Table 4).

Discussion

Our results showed that operable young breast cancer patients (<35 years old) have a worse prognosis than older patients in terms of both

overall survival and recurrence. The difference in disease-free survival was clear in patients with Axillary lymph node metastasis, but was not observed in lymph node-negative patients. Even after controlling for differences in distribution of potential prognostic factors, young age remained a significant predictor of recurrence

The present findings support previous reports showing that women diagnosed with breast cancer at a younger age have a poorer prognosis compared with their older counterparts [3-7]. However, those reports suffered from limitations including a small younger patient sample size, a study period spanning too many years during which treatments changed, lack of information about pathological and protein markers, and a heterogeneous case population in terms of treatment strategy.

Table 1. Clinicopathological characteristics of younger and older age groups.

Characteristics	Age <35 (%) (n= 51)	Age>35 (n = 177)	*P* value
Age			
20-25	2 (3.5)		
26-30	11(22)		
31-35	38 (74.5)		
36-40)		31(17.8)	
41-50		79 (44.3)	
51-60		47 (26.6)	
60-70		16 (9.2)	
71-		4(2.0)	
Family history	4 (8.7)	13 (7.6)	0.511
Histology			
Ductal	47(93.0)	162(91.	
Lobular	1(0.3)	2(1.7)	
Medullary	2(3.9)	3(1.6)	0.018
Others histology	1(23)	10 (5.7)	
T .stage			
T 1	20 (38.7)	77 (43.2)	
T2	26 (51)	85 (47.9)	
T3-4	5(19)	15 (3.9)	0.126
lymph node metastasis			
Negative	27(53.9)	105 (59)	
Positive	24(46)	72 (41)	0.084
Histological grade			
1-2	25(58.6)	106 (60.0)	
3	11 (41.4)	71 (40.0)	0.767
Nuclear grade			
1-2	27(53)	100 (61.3)	
3	24(47)	77 (39)	0.015
ER			
Positive	23(47.1)	90 (51.3)	
Negative	28 (53)	34 (48.2)	0.198
PR			
Positive	25(36.7)	70 (43.5)	
Negative	26 (63.3)	92 (56.5)	0.068

Table 2. Treatment characteristics.

Characteristics	Age <35(%	Age>35 (%)	P value
Surgery			
Mastectomy	42 (82.4)	148 (83.1)	0.796
Conservation	9 (17.6)	29 (16.9)	
Chemotherapy			
Lymph node	13/27 (47.1)	42/106 (39.6)	0.281
Lymph node	20/22 (91.0)	62/72 (87.0)	0.674
Radiation Therapy	15 (28.5)	46 (25.9)	0.373
Hormone Therapy	14 (21.1)	49 (27.6)	0.028

Table 3. Multivariate analysis for predictors of recurrence based on the Cox proportional hazards regression model

Variables	HR	95% Confidence	p
Age <35 years	1.7	1.14-2.61	0.010
Tumor size >2 cm	2.0	1.30-3.07	0.002
Lymph node- positive	3.8	2.64-5.67	<0.001
Nuclear grade	3 1.4	0.90-2.39	0.124
Histological grade	3 0.9	0.54-1.49	0.675
ER	1.1	0.77-1.63	0.549
PR	2.1	1.41-3.19	0.001

Table 4. Multivariate analysis for predictors of recurrence involving hormone therapy in ER (+) and/or PR (+) patients.

Variables	HR	95% Confidence	*p*
Age <35 years	2.1	1.14-4.20	0.018
Tumor size≥2 cm	2.2	1.39-3.62	0.001
Lymph node-positive	3.3	1.81-6.14	<0.001
Nuclear grade 3	1.0	0.45-2.31	0.961
Histological grade 3	1.0	0.45-2.31	0.961
Hormone therapy (yes)	1.6	0.93-2.77	0.086

Table 5. Multivariate analysis for predictors of recurrence based on the Cox proportional hazards regression model after exclusion of patients >50 years old.

	HR	95%	P
Age <35	1.8	1.17-2.81	0.008
Tumor size ≥2cm	1.7	1.06-2.84	0.028
Lymph node-positive	4.2	2.64-6.82	<0.001
Nuclear Grade 3	1.0	0.60-1.91	0.810
Histological grade 3	1.0	0.60-1.91	0.883
ER	1.1	0.71-1.78	0.683
PR	2.0	1.27-3.37	0.004

The present study is aimed to directly compare the prognosis of younger (<35 years old) breast cancer patients with that of their older counterparts. The data in the present study were generated from patients undergoing treatment under the same contemporary strategy of surgery and adjuvant therapy over a relatively short time period (10 years). In addition, this study included a multivariate analysis of the difference in distribution of potential prognostic factors between the two age groups.

In this study, we found PR expression (Fig. 1) were significant independent predictors of disease recurrence. Currently, the role of PR status as a prognostic factor is not clear, with some evidence to suggest it is useful [15.16] and other evidence to the contrary [17]. The prognostic significance of PR in this data set can be investigated further as an independent analysis later.

Many studies concluded that age under 35 was a high risk factor for relapse in node-negative breast cancer patients [18, 19]. Kroman et al. [20] reported that young women with low-risk breast carcinoma who did not receive adjuvant treatment had a significantly increased risk of death from the disease. Furthermore, Fowble et al. [21] reported that young women with early stage breast cancer, especially those with lymph node-negative disease, had a relatively worse prognosis than older counterpart. In the present study, although no significant difference was observed between the two age groups in lymph node-negative patients, the pattern of survival curves implied younger patients may have a worse prognosis. It may be that a study with a larger case size and a longer follow-up duration would provide enough statistical power to show a significant difference in prognosis for node negative patients.

It has been suggested that younger women with breast cancer have a poorer prognosis because they present with later stage disease due to either physician or patient delay in diagnosis. However, in this study, no significant difference was found between the two age groups in terms of tumor size or lymph node status. Moreover, multivariate analysis indicated that young age is an independent negative prognostic factor. This issue of delayed diagnosis is not conclusive now and should be elucidated further in subsequent studies.

It is known that young breast cancer patients are more likely to have an inherited form of the disease [22]. However, the current study showed there was no significant difference in the family history of breast cancer between the two age groups. In the recent report by Choi et al. the prevalence of BRCA 1 and BRCA 2 mutations in women with breast cancer at a young age (<40) was as high as western population. However, most of the BRCA-associated patients had no family history of breast and/or ovarian cancer. That is, the penetrance appears to be low. They suggested that there may be different genetic and etiologic factors affecting transmission and penetrance of the BRCA genes in patients with breast cancer diagnosed at a young age [23].

Conclusions

Our results show that operable young breast cancer patients (<35 years old) have a worse prognosis than older patients in terms of both overall survival and recurrence. Even after controlling for differences in distribution of potential prognostic factors, young age is an independent predictor of recurrence. The underlying biology of young age breast cancer needs to be elucidated and development of tailored treatment for this patient population is crucial.

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