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Impact of Age on Survival of Patients with Operable Breast Cancer

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ABSTRACT

Background: Breast cancer arising in young patients (≤ 40 years) is being considered as a distinct clinical entity with more aggressive tumor features and poorer survival. Our aim was to assess the impact of age on survival among a large group of Iranian women diagnosed with breast cancer.

Methods: In a cross-sectional study, demographic and clinicopathological characteristics of patients with breast cancer who were treated in two referral centers in Tehran, Iran during the past 13 years were reviewed and extracted from an electronic database. Patients were divided into two groups based on the age at the time of diagnosis (≤40 and >40 years). The association of age with different clinicopathological features and its impact on disease-free survival were assessed.

Results: Study population comprised of 353(26.1%) patients who were 40 years old or younger and 1000(73.9%) who were older. Compared to older patients, younger participants had more commonly tumor size larger than 5 cm (P = 0.034), higher chance of lymph node metastasis (P = 0.036), and overexpression of HER-2 (P = 0.004). No significant differences were observed between the two groups regarding ER, PR, and LNR (lymph node ratio). Age was the only factor affecting patients' disease-free survival and younger patients had higher chance of local or distant metastases compared to older subjects (HR: 1.49, 95%CI: 1.02-2.17, P = 0.038).

Conclusions: Based on the results of current study, it can be suggested that younger patients who are diagnosed with breast cancer tend to have larger tumor size, higher chance of lymph node metastasis and overexpression of HER-2 compared to patients older than 40 years. Age was the only significant factor that was associated with shorter disease-free survival.

Introduction

The majority of patients who are diagnosed with breast cancer are more than 40 years old and only 7% of cases diagnosed between 2000 and 2005 were in younger patients (<40).[1] Due to the different tumor biology and poorer outcome observed in the latter group, breast tumor arising in younger patients is considered a rather distinct clinical entity.[2, 3] Breast tumors of young patients tend to have more unfavorable phenotypes such as being ER/PR negative and the presence of lymphovascular invasion.[3-5] Contrary to older women, young women do not undergo routine breast cancer screening unless they are at a high risk of developing breast cancer based on their family history or carrying BRCA1 and BRCA2 mutations.[6] Additionally, the

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higher density of breast parenchyma in these patients makes the mammographic assessment of the breast more difficult and leads to higher rate of false negative reports.[7,8]

The combination of all these factors (aggressive biological profile and delayed diagnosis) is associated with higher risk of local recurrence, distant metastasis and shorter survival in younger patients with breast cancer compared to older patients.[5,8] There were several discrepancies among the results of recent published articles on clinicopathological characteristics of breast tumor before 40 years of age (such as tumor size, HER-2 status and lymph node involvement).[3,5]

Our aim was to assess the association between age and breast tumor features and also patients' survival in a group of Iranian women who were treated in our institute during the past 13 years.

Methods

A cross-sectional study was designed to assess the association between the age at the time of diagnosis and breast cancer outcome. Electronic database of Kaviani Breast Disease Institute (KBDI) (Hakim software, PegahSoft Company, Tehran, Iran) was reviewed and the relevent information of women with operable breast cancer was extracted anonymously. Study protocol was in accordance with latest Declaration of Helsinki for investigation on human subjects. Most of the patients were treated by a single surgeon in two referral centers in Tehran, Iran during the past 13 years.

Definition of variables

Published reports suggest two different cut points (35 and 40 years) for assessing the effect of age on breast cancer survival. In this study, the cut-off of 40 years was chosen for categorizing patients into two groups. Primary outcome was disease-free survival (DFS), which was defined as the time between treatment initiation (surgery or neoadjuvant chemotherapy) and occurrence of local recurrence or distant metastasis.

Obtained data comprised both demographic and clinicopathological variables. Baseline characteristics included age at diagnosis, education, menstrual status, history of pregnancy, age at menarche, age at first pregnancy, history of lactation, and family history of breast cancer in first-degree relatives. Clinicopathological variables consisted of date of surgery, type of surgery, date of first round of neoadjuvant chemotherapy, tumor size, results of axillary lymph node dissection (ALND), immunohistochemistry (IHC) reports and patients' status at end of follow-up period. Number of positive lymph nodes was divided to total number of dissected nodes during ALND to measure lymph node ratio (LNR).

Statistical analysis

Statistical analyses were performed using SPSS software, version 20.0 (IBM Corp., NY, USA). Patients' characteristics were compared between the two age groups using independent t-test and Chi-square. Kaplan-Meier analysis was employed to assess the association of patients' demographic and clinicopathological characteristics and the interested outcome (DFS). All variables that showed significant association in univariate analyses were put in a multivariate Cox proportional model to identify the independent prognostic factors. P value of less than 0.05 was considered as statistically significant in all tests.

Results

A total of 1353 patients were included in the final analysis. Study population comprised of 353(26.1%) patients who were 40 years old or younger and

Table 1. Demographic characteristics of younger (≤ 40y) and older age groups

	≤ 40 (N = 353)	> 40 (N = 1000)	P-value
Mean age at menarche	13.36±1.38	13.41±1.65	0.623
Mean age at first pregnancy	20.20±8.75	21.53±6.17	0.024
Education			0.242
High school diploma	133(34.9%)	282(31.1%)	
University graduate – Non medical	193(59.6%)	586(64.6%)	
University graduate – Medical	18(5.6%)	39(4.3%)	
Menstrual cycles			<0.0001
Irregular	154(43.9%)	262(26.3%)	
Regular	197(56.1%)	734(73.7%)	
History pregnancy			0.613
Yes	293(83.0%)	842(84.2%)	
No	60(17.0%)	158(15.8%)	
History of lactation			0.063
Yes	277(78.5%)	832(83.2%)	
No	76(21.5%)	168(16.8%)	
Family history of breast Cancer			0.531
Yes	67(20.4%)	197(22.2%)	
No	262(79.6%)	689(77.8%)	

1000(73.9%) who were older. Mean age of patients in the former group was 34.59±4.22 years (ranging from 20 to 40 years), while the mean age of their counterparts in the latter group was 53.08±9.34 years (ranging from 41 to 89 years). Baseline characteristics of patients in both groups are presented in table 1.

The majority of patients in both groups had tumor size of 2 to 5 cm, the frequency of patients with tumor size larger than 5 cm was 10.8% in younger patients and 5.4% in older patients (P = 0.034). Among the available data for ALND pathologic results (846, 62.5%), women younger than 40 years were more commonly diagnosed with lymph node metastasis compared to older patients (58.8% vs. 50.5%, P = 0.036).

Although younger patients had higher LNR values the differences failed to reach statistical significance (median: 0.11 vs. 0.05, P = 0.052). HER-2 expression was considered negative if the reported scores in IHC reports were equal to 0 or +1, while patients with IHC scores of +2 and +3 were considered as HER-2 positive. Patients older than 40 years of age were more frequently categorized as HER-2 negative (65.0% vs. 45.5%, P = 0.004).

No significant differences were observed between the two groups regarding ER and PR status and lymphovascular invasion (Table 2).

Table 2. Comparing clinicopathological features of tumor between study groups

	≤ 40 (N = 353)	> 40 (N = 1000)	P-value
Tumor size			0.034
≤2cm	76 (37.5%)	217 (40.4%)	
2-5cm	106 (52%)	291 (54.2%)	
>5cm	22 (10.8%)	29 (5.4%)	
ALND results			0.036
Positive	134 (58.8%)	312 (50.5%)	
Negative	94 (41.2%)	306 (49.5%)	
Median LNR (IQR)	0.11 (0.0 – 0.44)	0.05 (0.0 – 0.33)	0.052
ER			0.198
Positive	172 (67.5%)	497 (71.9%)	
Negative	83 (23.5%)	194 (28.1%)	
PR			0.198
Positive	172 (67.5%)	497 (71.9%)	
Negative	83 (32.5%)	194 (28.1%)	
HER2			0.004
Positive	111 (45.5%)	230 (35.0%)	
Negative	133 (54.5%)	428 (65.0%)	
Lymphovascular Invasion			0.219
Positive	142 (41.9%)	411 (41.1%)	
Negative	197 (58.1%)	589 (58.9%)	

Follow-up data was available for 630 patients with median duration of 23.13 months (ranging from 0.13 to 159 months). Among those who received neoadjuvant chemotherapy (119 patients), the date of chemotherapy initiation was considered as the beginning of follow-up duration, while in the rest of patients date of surgery was used for this purpose. A total of 117 patients experienced local recurrence or distant metastasis. Patients below the age of 40 years had significant shorter DFS in comparison to older subjects (HR: 1.49, 95%CI: 1.02-2.17, P = 0.038) (Figure 1). In contrary, DFS was not significantly affected by tumor size (P = 0.599), lymph node metastasis (P = 0.063), or HER-2 expression (P = 0.160). Since age was the only prognostic factor for DFS, no multivariate analysis was performed.

A total 14 cancer-related deaths were recorded during the follow-up period. Due to the limited number of cancer-related deaths recorded in our database, we were unable to assess overall survival.

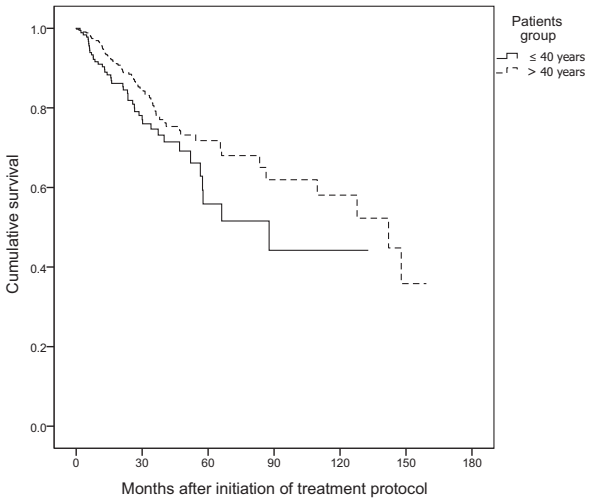

Figure 1. Comparing disease-free survival between patients aging ≤40 and >40 years

Discussion

Our results demonstrated that breast cancer arising in younger patients (≤40y) has distinctive clinicopathological profile compared to breast cancer detected in older patients. Patients who were younger at the time of diagnosis had lower DFS compared to their counterparts. Survival analyses showed that age was the only prognostic factor for higher risk of recurrence or death.

Characteristics of breast cancer before 40 years of age have been the subject of several studies during the past recent years.[5,9,10] Evidence suggests that younger women with breast cancer are diagnosed at later stages with more aggressive tumor biological features.[5] Most of the previous studies suffer from the limitation of heterogeneity in treatment strategy as they are multicenter or nationwide reports.[11] The current study is the report of patients who were mostly treated according to a same treatment protocol by a single surgeon.

Almost all studies published on this topic reported more aggressive tumor features among younger women with breast cancer; but, there is not a general consensus on the status of all clinicopathological characteristics. A study on 2040 Korean women with breast cancer revealed that younger patients had higher nuclear grade compared to older patients; however, there were no differences between the two groups regarding axillary lymph node involvement, histological grade, HER-2 expression and tumor size.[12] Colleoni *et al*. observed that younger patients are at increased risk of having ER/PR negative tumors, higher expression of Ki67, vascular and lymphatic invasion and higher nuclear grade compared to older patients.[5] They found no differences between two groups for pathological tumor size and the number of involved lymph nodes.[5] On the other hand, recent studies have consistently suggested that younger patients with breast cancer have poorer survival.[1,13-18]

It has been hypothesized that lower survival rate observed in younger patients might be due to higher stage at the time of diagnosis which might be the consequence of either patient or physician delay in diagnosis.[19,20] Han and colleagues reported that age was an important prognostic factor in patients with breast cancer independent of other clinicopathological features.[12] They suggested that higher stage at the time of diagnosis cannot be the only reason for observed differences. Our findings also showed that age at the time of diagnosis was the only factor related with patients' survival. Furthermore, a recent study on 585 young patients with breast cancer showed that most of them do not experience patient or physician delay in diagnosis.[21] It seems that more studies are needed to elucidate the association between these variables (age, delay in diagnosis, stage, survival). Moreover, Andres *et al*. conducted a comprehensive large-scale genomic analysis and reported that not only breast tumors in younger women have distinctive clinicopathological features but also the differences exist at the genomic levels.[3] They identified 367 gene sets that distinguished breast cancer detected in young women.[3] All these indicate that more research should be conducted to shed a light on the underlying reasons for observed poorer survival in younger patients.

The limitation of this study was our inability to assess the role of adjuvant treatments (chemotherapy or radiotherapy) on patients' survival due to high amount of missing data regarding these variables.

In conclusion, the results of the current study showed that younger patients (≤40y) who are diagnosed with breast cancer tend to have larger tumor size, higher rate of lymph node involvement, overexpression of HER-2 and shorter DFS compared to older patients.

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