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Research Article

Young Age: The Most Significant Factor Contributing to Poorer Prognosis in Mexican Women with Breast Cancer

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Abstract

Background: Breast cancer is the main cause of death by cancer in Mexican women of age 25 or older. This disease has steadily increased amongst young women. They usually present an aggressive and advanced breast cancer.

Methods: Data on women diagnosed with breast cancer between 2005 and 2011 was collected by retrospectively reviewing in FUCAM. The five-year disease-free survival (DFS) and overall survival (OS) were compared between patients younger than and older than 40. Clinical, pathological and immunohistochemical characteristics were assessed, and the variables with statistical significance were analyzed in a multivariate analysis.

Results: From 2291 patients treated, a total of 276 patients (12.0%) of ages 23-40 were diagnosed with breast cancer in this institution. Over half of these patients were diagnosed with an advanced clinical stage (III or IV) and the triple-negative subtype was the most frequently found. Both young age and absence of estrogen receptors were highly correlated with poorer outcome. A mean follow-up of 38.25 months showed significantly lower rates of both disease-free survival and overall survival in women under 40 years old. **Conclusion:** This study shows that 12% of Mexican women with breast cancer are 40 years old or younger, significantly higher compared with other countries. Young women present an unfavorable outcome. Regardless the adverse clinical and histopathologic characteristics, young age is the most important independent factor contributing to poor prognosis.

ABBREVIATIONS

FUCAM: Breast Disease Institute FUCAM, ER: Estrogen Receptors; PR Progesterone Receptors, DFS: Disease Free Survival; OS: Overall Survival; HER-2 Human Epidermal Growth Factor 2 Receptor Protein

INTRODUCTION

Since 2006, breast cancer has been the leading cause of cancer death among women older than 25 in Mexico [1], and the frequency of breast cancer in pre-menopausal women has been steadily rising [2]. While many studies report an incidence of breast cancer of less than 6% in women younger than 40 [2,3], we found an incidence of 12.0% at Breast Disease Institute (FUCAM) in Mexico City.

It has been described previously that young women are more likely to present more aggressive and advanced breast cancer [4]. Despite these findings, controversies still exist regarding the optimal treatment because the benefits of more aggressive therapies are not well established [2].

The purpose of this study is to describe the clinical and pathologic characteristics and the factors associated with a poorer prognosis in Mexican young women (40 or younger) with breast cancer compared with older women (40 or older) with breast cancer.

MATERIALS AND METHODS

Institutional review board approval was obtained before starting this study. A retrospective study was conducted in which all women aged 40 or younger who were diagnosed with

breast cancer in our institution between 2005 and 2011 were compared with those older than 40. TNM/AJCC stage (Tumor, Node, Metastases / American Joint Committee on Cancer), tumor grade, nodal status, lymphovascular invasion and treatments were all evaluated. Immunohistochemical panel was performed according to the American Society of Clinical Oncology and the College of American Pathologists and Molecular phenotypes were determined according to the St. Gallen International Breast Cancer Conference [5-7]. Luminal A tumors were defined as having high expression of the estrogen receptors (ER) and progesterone receptors (PR), no over expression of the human epidermal growth factor 2 receptor protein (Her-2), and low Ki-67 (<14%). Luminal B tumors were subdivided into those with high Ki-67 (≥14%), low expression of PR (<20%) or over expression of Her-2. The triple-negative subtype was defined as completely lacking both ER and PR, and having normal expression of the Her-2 [8]. Finally, the Her-2 phenotype was defined as having over expression of the human epidermal growth factor 2 receptor protein (Her-2), completely lacking both ER and PR.

The data are presented as the mean values with standard deviation. The differences between groups were assessed using a univariate analysis. Statistical tests including the X^2 test, Student's t-test, U Mann-Whitney test or an ANOVA test were used as needed. Five-year disease-free survival (DFS) and overall survival (OS) were evaluated using a Kaplan Meyer curve; differences between groups were calculated using a log-rank test. The variables that were statistically significant between groups were introduced in a multivariate analysis. Statistical significance was defined as $p < 0.05$. The statistical analyses were performed with SPSS Statistics 17.0, Chicago IL.

RESULTS

From 2005 to 2011, a total of 2291 patients were diagnosed with breast cancer in our institution, 276 of them were 40 or younger at the time of diagnosis, accounting for 12.0% of all patients. Thirty-three patients, who represented 1.44% of the total, were between 23 and 30 years old. Of the 276 diagnosed patients, 225 were treated at our institution, and the other 51 patients were treated elsewhere. The median age of the patients with ages from 23 - 40 was 37 years. Six patients were diagnosed with bilateral breast cancer, and one of them developed contra lateral breast cancer when she was 42 years old. Three patients in the group of young women were lost during the follow-up.

Clinical Staging

Patient staging were analyzed according to the TNM/AJCC Breast Cancer staging system [9]. More than half of the patients who were 40 or younger at the time of diagnosis presented a tumor that was classified as a clinical stage III or IV (51.2%), whereas only 31.3% of women over 40 years of age were diagnosed with a tumor classified in these stages ($p<0.001$). Early-stage breast cancer diagnosis (IIB or lower) was established in 42.3% of the young women and in 64.7% of the older women ($p<0.001$). A non-statistical difference was found between groups in metastatic breast cancer at the time of diagnosis ($p<0.9$). Clinical stage could not be defined in 6.4% and 4.0% of the groups of young women and old women, respectively, because they received initial treatment outside the institution ($p<0.001$) (Table 1).

Nodal status

Metastatic lymph nodes were found in 40.9% of the patients of the young group. Although no significant differences were found between the groups regarding axillary lymph node metastasis ($p = 0.594$), women younger than 40 were more likely to have more than three metastatic axillary lymph nodes. In contrast, patients over 40 years frequently had metastasis only in one to three (pN1) axillary lymph nodes ($p = 0.011$) (Table 2). More than 10 axillary lymph node metastasis were found in nineteen patients in the younger group. Because 68 patients did not receive surgical treatment at FUCAM, the pathological nodal status could not be assessed. In addition, no statistical differences were found between age groups regarding extra capsular invasion in axillary lymph nodes ($p = 0.449$) (Table 1).

Tumor grade

Tumor grade was established in 213 cases of women of the young group, according to the modified Scarff Bloom Richardson grading system [10]. Intermediate-grade tumors were the most prevalent in both groups, but it is worth noting that poorly

Table 1: Clinico pathological tumor characteristics between groups.

	≤ 40 years old n (%)	>40 years old n (%)	TOTAL
Clinical Stage At Diagnosis *			
0	12 (4.3)	157 (7.8)	<0.001
I	17 (6.0)	342 (17.1)	
II A	42 (14.9)	461 (23)	
II B	48 (17.1)	336 (16.8)	
IIIA	56 (19.9)	215 (10.7)	<0.001
III B	60 (21.4)	254 (12.7)	
III C	5 (1.8)	56 (2.8)	
IV	23 (8.2)	103 (5.1)	0.90
Non-clinical-stage	18 (6.4)	81 (4.0)	<0.001
Axillary Lymph Nodes Status *			
Negative nodes	98 (34.9)	1291 (56.4)	0.594
Positive nodes	115 (40.9)	998 (43.6)	
1 to 3	56 (48.7)	798 (80.0)	0.011
4 to 9	59 (51.3)	200 (20.0)	
Capsular rupture	63 (54.7)	397 (39.7)	0.449
Scarff Bloom Richardson Grading System *			
Grade 1	4 (1.4)	136 (13.1)	<0.001
Grade 2	119 (55.9)	666 (64.3)	
Grade 3	90 (42.3)	233 (22.5)	
Not assessed	68	143	
Immunohistochemical Panel *			
ER positivity	113 (40.2)	1148 (70.5)	<0.001
PR positivity	107 (38.0)	940 (57.7)	0.005
Triple-negative	83 (34.7)	226 (13.9)	<0.001
Her-2 expression	47 (19.7)	336 (20.9)	0.638

*Includes the clinical stages of patients under 40 years old diagnosed with bilateral breast cancer

Table 2: Molecular phenotypes in women under 40 years old according to the St Gallen International Breast Cancer Conference (2013) [5]. The triple negative breast cancer was the most common subtype.

	≤ 40 years old n (%)	>40 years old n (%)
Luminal A	52 (21.8)	526 (32.3)
Luminal B (High Ki-67 or low PR)	48 (20.1)	469 (28.8)
Luminal B (Her-2)	16 (6.7)	116 (7.1)
Her-2 subtype	31 (13.0)	226 (13.8)
Triple-negative	83 (34.7)	227 (13.9)
Luminal Ki-67 not assessed	9 (3.8)	67 (4.1)

differentiated tumors were significantly more frequent among young women (p<0.001) (Table 1).

Lymphovascular invasion

Both groups were compared with respect to lymphovascular tumoral invasion. While 40.9% of women less than 40 years old presented this adverse prognostic factor, it was found in only 33.5% of women over 40 years old (p = 0.05).

Molecular subtypes

Immunohistochemical subtypes (Luminal, triple-negative and Her-2) were assessed in 239 of the 276 young patients according to the 13th St. Gallen International Breast Cancer Conference (2013) Expert Panel [7] and compared with patients in the older age group. ER and PR were more frequently expressed in tumors among older women, whereas a triple-negative subtype was more frequently present in tumors among younger women. No statistical differences were found regarding the over-expression of the Her-2 receptor (Table 1). The molecular subtypes of the young women group are shown in Table 2.

Treatment

Treatments were determined during tumor board sessions in 225 of the young patients. For initial treatment, surgery was performed in 106 patients (47.1%), and neoadjuvant chemotherapy was administered to 125 patients (55.6%). As a second treatment, surgery was performed in 102 patients and chemotherapy was administered to in 78 patients. Radiotherapy was given according to the NCCN (National Comprehensive Cancer Network) Breast Cancer Clinical Practice Guidelines [11] and given to 122 patients (54.2%). Nine patients of the young group received radiotherapy before surgery due to a lack of response to neoadjuvant chemotherapy. Hormonal therapy, mainly with tamoxifen, was administered to all patients with ER/PR positivity as standard of care treatment. Aromatase inhibitors were administered only if oophorectomy or ovarian suppression was performed.

In the older group, initial treatment consisted of surgery in 1077 (53.7%) patients and chemotherapy in 522 (26%) patients. Radiotherapy was given as needed to 849 patients (42.2%). Hormonal therapy was also administered if expression of ER or PR was found. Most patients in both groups received anthracycline/taxane-based chemotherapy regimens and trastuzumab was added to standard treatments when over expression of Her-2 was present.

Disease-free and overall survival

Five-year disease-free survival and overall survival were assessed after a mean follow-up of 38.25 months (5 – 129 months), and statistically significant differences were found between age groups (p<0.001) (Figure 1). Young women had significantly lower rates of both disease-free survival and overall survival compared with older women (Figure 2). No differences in the pattern of recurrence (local, regional or distant) were found between groups (p = *0.950).*

The variables with a statistical difference between groups were compared in a multivariate analysis. The triple-negative subtype, high grade tumors, absence of the expression of both ER and PR, young age, lymphovascular invasion and advanced stage were included. Young a*ge* was the most important independent factor that contributed to mortality (p=0.007); in addition, lymphovascular invasion and absence of the expression of ER were correlated with poorer outcome (Table 3).

DISCUSSION

Breast cancer is the leading cause of cancer death among women in Mexico [1]. Breast cancer in young women is commonly associated with adverse clinico pathological characteristics and prognosis [12]. It has been reported that between 5 and 6% of all breast cancers are found in young women [2-4]. In this study, 12.0% (n=276) of the patients diagnosed with breast cancer were 40 or younger, and of these, 33 (11.95%) were 30 or younger at

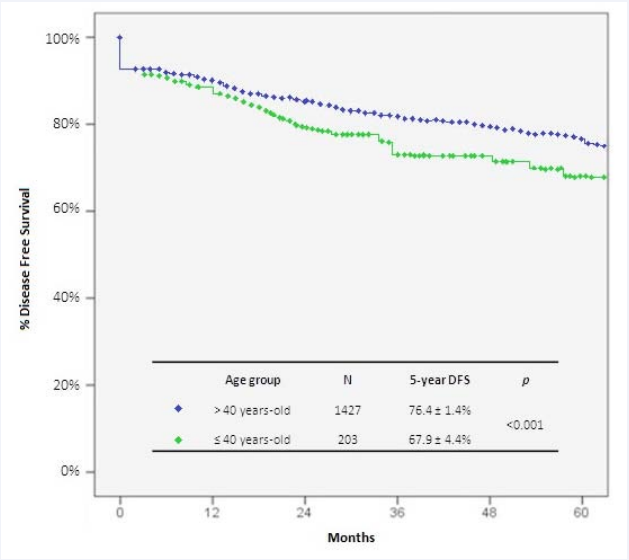

Figure 1 5-year Disease Free Survival (DFS).

Table 3: Multivariate analysis: Young age was by far the most important factor for poorer prognosis in young women.

Multivariate analysis		
Variables with statistical significance	**β Value**	***p***
Young age	7.173	0.007
Lymphovascular invasion	3.449	0.063
Lack of ER expression	3.159	0.075

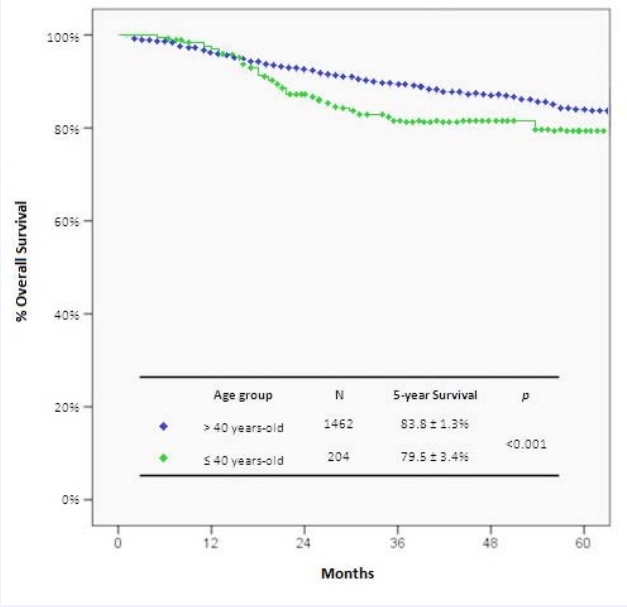

Figure 2 5-year Overall Survival.

the time of diagnosis. A similar high incidence of breast cancer in young women was reported in China [13].

Breast cancer develops a decade earlier in Mexican women compared with women in the U.S. or European countries [14]. Although, this could be explained by the age distribution of the population in Mexico, where women under 40 years old represent 71% of all women in the country [15]

Many features have been associated with worst prognosis in young women with breast cancer. In accordance with other studies, we demonstrate that young age is the most important independent factor that is correlated with poor prognosis [16,17]. In addition, a large study from Korea revealed that the risk of death increased by 5% for every 1-year reduction in the age of patients who were less than 35 years old at the time of diagnosis [18].

According to the Mexican Health Guidelines, mammographic screening should be performed biannually in women who are over 40 years old, but not in women under 40 years old. Most of the younger patients ask for medical care when a palpable mass is present [19]. Similar to other studies, our study found that tumors in young women were usually diagnosed at a more advanced stage [3,19]. In our institution, 51.2% of the women who were 40 or younger at the time of diagnosis presented with breast cancer in clinical stage III or IV, while 31.3% of the patients over 40 years old presented the disease within this range of stages. This could be due to the lack of mammographic screening in young women, a more aggressive biology or a delay in the diagnosis due to breast density or medical compliance [3,20,21].

Although we determined that there was no statistical difference in lymph node metastasis between both age groups, a higher proportion of young women had more than three lymph nodes with metastasis (51.3 vs. 20%). In addition to being a more advanced stage, a high nodal involvement (more than three lymph node with metastasis) has been correlated with a greater probability for local recurrence with a risk ratio (RR) of 4.3 [16].

Consistent with other published data, the tumors of young patients usually had unfavorable biological characteristics [12,16,21,22]. We provide evidence that the lack of expression of ER is highly correlated with poor outcome [17], and high-grade tumors were more frequently found in women under 40 years old [12,16].Although intermediate-grade tumors were the predominant type in both age groups in this study, poorly differentiated tumors were found almost twice as frequently in young women (42.3% vs. 22.5%). In addition, lymphovascular invasion was more frequently found in tumors of young women.

According to the biological characteristics of different tumors, Copson et al. reported that triple-negative tumors were found in 34% of patients younger than 40 [18]; we found a similar incidence of triple-negative tumors (34.7%). This was the most prevalent phenotype in our study, which differed from other studies where the Luminal B subtype was the most frequent phenotype in young women with breast cancer [23]. It should be noted that only 13.5% of the patients over 40 years of age presented triple-negative tumors; similar rates are reported in other studies performed in Mexico, Puerto Rico and Tampa, Florida [24-26] The triple-negative phenotype is considered to be more aggressive and is associated with shorter survival [12,27]. It is important to mention that luminal type tumors were identified in 70% of women over 40 years old, however, this subtype was present in less than 50% of women under 40 years old. Finally, Her-2 overexpression found in this study (19.7%) was similar to other studies; no significant difference was found in women less than 40 years old compared with women over 40 yearsold [21].

Cancello et al. found that women younger than 35 years old with triple-negative, luminal B or Her-2 positive breast cancer had a less favorable prognosis when compared with older women with same subtypes [28].

As reported previously, almost 90% of young women received chemotherapy as part of their treatment. Neoadjuvant chemotherapy was administered to the 55.6% of the young patients, mainly due to the locally advanced stage at the time of diagnosis. It is important to remember that up to 40% of women younger than 40 will develop premature menopause, and counseling regarding this topic is recommended [29].

Anderson et al. showed that regardless of less extensive surgical resections, the introduction of new chemotherapeutic agents has improved the survival of young women with breast cancer in the last decades [30]. Despite this, we still found significant differences in 5-year disease-free survival and overall survival rates between women younger than 40 and women older than 40. Yildirim et al. reported that age is the most important factor in relapse [12], and young age remains a predictor for mortality [4,31]. Bharat et al. reports that women under 40 years old have a 1.5-fold higher probability of dying by breast cancer [16].

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