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Prognostic Factors Associated with Survival in Women with Breast Cancer from Veracruz, Mexico

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Abstract

Objective: The present study analyzed the geographical location and prognostic, clinical, physiological, and biochemical factors associated with breast cancer (BC) in women based on their treatment.

Methods: We conducted a retrospective cohort study encompassing a 5-year follow-up period of 114 women from rural and urban areas who were diagnosed with BC in 2009 at the State Cancer Center (CECAN) in Xalapa, Veracruz, Mexico. The probability of survival was calculated using the Kaplan-Meier estimator and Log Rank test with a confidence interval of 95%. We determined the prognostic factors in a multivariate analysis using the Cox proportional hazards model. The point estimate was the hazard ratio (HR) and 95% confidence interval (CI).

Results: The overall survival ratio for the study participants was 68% and 63% after 52 and 60 months, respectively. The lowest survival ratio corresponded to clinical stages IIIB (38%) and IV (10%) and patients showing tumor cell metastasis (24%). There were significant differences between groups ($p<0.001$), including women under 40 years of age (36%, $p<0.003$) and those with positive HR (83%, $p=0.006$). Women who received adjuvant treatment and had a tumor size less than 2 cm lived longer (75%, $p<0.001$). The multivariate analysis identified a number of prognostic factors that are unfavorable for women with BC, including a diagnosis of clinical stage IV (Hazard ratio=11.88; 95% CI=2.88-44.88) and the presence of metastasis (Hazard ratio=4.95; 95% CI=1.78-13.76).

Conclusion: General tumor characteristics, such as metastasis, disease stage and family history, are important for survival and can serve as prognostic factors for BC patients. Moreover, the lower survival of women less than 40 years of age should be considered as a decision-making factor when selecting from treatment options.

Keywords: Breast cancer; Survival; Metastasis; Axillary nodes; Hormone receptors; Clinical stage

Introduction

Breast cancer (BC) has become a critical health concern worldwide. Despite an increased global incidence in developed countries, the number of deaths due to BC is higher in developing countries [1]. In Mexico, the mortality rate for BC patients diagnosed at advanced clinical stages has increased 30% in the last 20 years [2]. Earlier diagnoses are often not possible due to the difficulty accessing care and treatment [3]. Breast cancer is a heterogeneous disease comprising several subgroups characterized by clinical symptoms and the pathological, molecular and biological characteristics of the tumor. The general characteristics of the primary tumor significantly impact the prognosis and survival of BC patients [4].

The risk of metastasis and death shows a positive correlation with tumor size and the number of axillary lymph nodes involved. The axillary status is undoubtedly the most valuable criterion for survival. Patients with axillary metastases have a 50% chance of recurrence within 5 years [5]. Early cancer detection can improve survival rates by reducing the risk of metastasis. Latin American countries must overcome major challenges to increase early detection rates and reduce the number of advanced-stage diagnoses [6].

Breast cancer (BC) is the most prevalent cause of morbidity (21.2%) and mortality (17.71%) in women from Veracruz, Mexico [7]. Epidemiological evidence indicates that hormonal, dietetic, genetic, socioeconomic, ethnic and especially environmental factors can influence BC rates. In the rural area of Veracruz, Mexico, exposure to toxic substances, such as pesticides (Organochlorides) with high persistence in the environment, is a significant problem. These pesticides can act as hormonal disruptors and bio-accumulate in humans [8]. With the exception of clinical stage, tumor characteristics and treatment type, there are a limited number of independent and prognostic factors for BC. However, geographic location may be an important factor. Survival and recurrence rates for BC patients vary widely and are influenced by a number of factors, including demographic variables related to tumor size, and the status of hormone receptors and human epidermal growth factor receptor 2 (HER2) [9]. HER2 is strongly associated with an increased disease recurrence and poor prognosis [10,11]. The recent evolution of new chemotherapeutic agents, third-generation aromatase inhibitors and targeted therapies has increased the survival of BC patients [12]. However, these improvements are not enough to cure metastatic cancer.

In Mexico, there is an increasing incidence of BC, a higher

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frequency in the occurrence of advanced disease stages, increasing costs and high mortality rates [13]. Prognostic factors must be identified to improve the survival of women with BC. Furthermore, advances in medical treatments and screening programs in Veracruz, Mexico are urgently needed.

Materials and Methods

A retrospective cohort analysis of a five-year follow-up of women treated at Centro Estatal de Cancerología (State Cancer Center, CECAN) in Veracruz, Mexico was completed in accordance with patient consent and authorized by the hospital. We analyzed the medical records of women who were diagnosed with BC in 2009. Histopathology was used to confirm the diagnoses.

A total of 114 women with similar demographic characteristics were selected out of a single cohort of 133 patients. Women with recurrent BC or living in another State of the Mexican Republic were excluded. Data were obtained from the patient's medical records. The Department of Social Work and health authorities assisted with the location of women who stopped visiting their physicians.

Information regarding the histological type and clinical stage of the tumor was classified according to the criteria of the American joint commission on cancer (AJCC) [14]. This information was obtained through a review of multiple sections of medical records, including socio-demographic data, ob-gyn history and comorbidities, and morphological characteristics, diagnosis and treatment. The analysis was conducted by the research team. This study was evaluated and approved by the Ethics Committee of the CECAN.

The response variable (survival) was calculated based on the time elapsed between the time of BC diagnosis and patient death. The time of diagnosis was determined using data from histological tissue tests, imaging studies and medical records. The date and cause of death was obtained from the death certificate. Next, the survival times were statistically analyzed.

Statistical Analysis

Survival

The Kaplan-Meier estimator is one of the best options to measure the survival rates of subjects after treatment. In clinical and community trials, the effect of an intervention was assessed by measuring the number of surviving patients over a defined period of time after treatment [15].

The Kaplan-Meier estimator was used to calculate the survival rates during the 5-year follow-up period after BC diagnosis [16]. The following factors were considered: a) survivors of the study to date, b) participants who left the cohort to receive treatment at another health institution or did not complete their treatment and c) death by a cause other than BC. The chances of survival for each potential prognostic factor were compared using the Log Rank Test [16]. Subsequently, the Cox's regression model was used for a multivariate survival analysis to adjust the prognostic factors for potential confounders [14]. The hazard ratios and their respective 95% confidence intervals were calculated. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0..

Results

Of the 133 available patients, 4 were excluded because they lived in another State of the Mexican Republic, 13 were excluded due to recurrent BC, and 2 were excluded due to diagnosis with a cancer other than BC. Thus, the total number of BC patients included in the final analysis was 114.

The patient characteristics according to the disease stage at diagnosis are shown in Table 1. There were 66 (63.45%) women living in urban areas of the State of Veracruz. Seventy-two women (69.23%) had a basic level of education consisting of elementary and secondary school. The majority of participants were housewives. There was not a significant difference between the ages, in women at the early stage of cancer when compared with the age of women at advanced stages of the disease.

Tumor characteristics

The most common histological type, which occurred in 96 (84.2 %) patients, was invasive ductal carcinoma, followed by mixed carcinomas (Table 2). According to the Scarff-Bloom-Richardson, Nottingham system, 2 (2.2%) patients had highly differentiated carcinomas, 45 (50.0%) patients had moderately differentiated carcinomas, and 43 (47.7%) patients had poorly differentiated carcinomas. Lymphovascular invasion was found in 25 (21.9%) patients.

Hormone receptors (HR) were found in 72% of tumors, including 47 (52.2%) tumors that were positive for estrogen receptors. The receptor type was not determined in 28.0% of the HR-positive tumors.

Expression of the membrane protein HER2/neu was found in 73.7% of tumors. Of these 84 cases, the HER2/neu status was considered negative in 60 cases (71.4%). In the remaining 24 cases (28.6%), 27 tumors (34.6%) were Luminal A (HR+/HER2-), 8 tumors (10.3%) were Luminal B (HR+/HER2+), and 22 cases (28.2%) were triple negative (RH-/HER2-) (Figure 1).

Survival

The overall survival rate for women during a 5-year (60-month) follow-up was 63%. After 52 months, the survival rate was 68% with a 95% CI of 47.44-55.71 (Table 2). Young age (<40 years) was positively associated with metastatic breast cancer during the follow-up period. Young patients showed a statistically significant decrease in survival

	Clinical stage[a]		p value
	Early n=52	Advanced n=52	
Age (years), n (%)			
19-40	4 (7.7)	16 (30.7)	0.42
41-59	35 (67.3)	26 (50.1)	
≥60	13 (25.0)	10 (19.2)	
Place of residence, n (%)			
Urban	35 (67.3)	31 (59.6)	0.54
Rural	17 (32.7)	21 (40.4)	
Schooling, n (%)			
Null	9 (17.3)	9 (17.3)	
Basic	33 (63.5)	39 (75.0)	0.35
Upper middle	6 (11.5)	3 (5.8)	
Top	4 (7.70)	1 (1.90)	
Occupation, n (%)			
Housewife	47 (90.4)	50 (96.2)	
Worker	4 (7.70)	1 (1.9)	0.39
Student	1 (1.9)	1 (1.9)	

[a]There were 10 patients unsorted, according to the clinical record. [b]AJJC: American Joint Commission on Cancer. Comparison of proportions by the Chi-square test.

Table 1: Comparison of subjects of study according to AJJC[a] stage at the time of diagnosis of the breast Cancer.

Variable	n	Survival 5-year Follow-up (%)	p value[a]
Age			
≤40	22	36	0.003
40	92	70	
Pregnancy			
Yes	104	64	0.808
No	10	60	
Abortion			
Yes	15	80	0.149
No	99	60	
Menopause			
Yes	73	69	0.158
No	41	54	
Comorbidities			
Type 2 diabetes mellitus	9	65	0.914
Hypertension	22	74	
Both	4	75	
Distant metastases			
Present	25	24	< 0.001
Absent	89	74	
Treatment			
Adjuvant	64	75	
Neoadjuvant	19	31	< 0.001
Both	27	67	
[a]Test Log- Rank			

Table 2: Survival of women according to age and other clinical variables.

Variable	n	Survival 5-year follow-up (%)	p value[c]
Histologic grade[a]			
Grade 1	2	100	0.242
Grade 2	45	73	
Grade 3	43	60	
Histologic type			
Ductal carcinoma	96	65	
Lobular carcinoma	7	42	
Others	8	75	0.119
Unknown	3	33	
Tumor size, cm			
<2	14	92	
2-5	51	74	<0.001
>5	29	38	
Metastatic lymph node			
Positivo	67	61	
Negative	29	82	0.042
Homone receptor status			
Estrogen receptor[b]			
Positive	47	83	0.006
Negative	35	60	
Progesterone receptor [b]			
Positive	32	81	0.053
Negative	43	65	
HER2 status[b]			
Positive	24	54	0.029
Negative	60	75	
[a]1: Well-differentiated, 2: Moderately differentiated 3: Poorly differentiated. [b]Biochemical factors. [c]Test Log- Rank			

Table 3: Survival women according to tumor characteristic and biochemical factors.

rate when compared with the 70% survival rate in middle-aged and old-aged patients (p=0.003). At the end of the follow-up period, 42 women died from BC (36.8%). Cancer metastasis was observed in women at advanced disease stages, and this group showed the lowest survival rate (40.0%) when compared with patients at earlier stages (p<0.001). The difference in survival rates between cancer stages was statistically significant (p<0.001) (Figure 1).

Comorbidities included the presence of other diseases in 30% of patients, hypertension in 58.3% of patients, diabetes mellitus in 22.2% of patients, hypertension and diabetes in 11.3% of patients, and other chronic disease in 8% of patients. However, differences in the survival rates of these groups were not statistically significant. Thus, comorbidities were ineffective as prognostic factors (Table 2).

Women with breast-conserving surgery and 17 patients who received both chemotherapy and radiation therapy showed an improved survival rate (73.3%, p=0.04). Of the patients who received hormonal treatment, 47 (49%) received tamoxifen therapy and showed a higher survival rate (78.3%, p=0.05) (Figure 1). In contrast, women who received neoadjuvant therapy showed a decreased survival rate (54.5%, p=0.005). Histology and nuclear screenings showed no significant differences between the groups (Table 3).

Prognostic factors for survival (Multivariate analysis)

Table 4 shows a multivariate analysis using the Cox regression model to identify prognostic factors. Node and distance metastasis was observed (Hazard ratio=5.08, 95% CI=2.60-9.94). In patients with a family history of cancer, the survival rate showed a two-fold reduction when compared with women who had no family history of cancer. A decreased survival rate was associated with advanced clinical stages IIIB (Hazard ratio=5.08, 95% CI=1.78-14.2) and IV (Hazard ratio=20.92, 95% CI=6.59-66.39). In Model 2, an estrogen receptor-positive tumor was identified as a protective factor (HR=0.195, 95% CI=0.043-0.895). Within the stratified results over the follow-up period, young age (<40 years), tumor size, and treatment type were associated with a poor prognosis. However, these results were not statistically significant. Comorbidities were also found to be ineffective as prognostic factors.

Discussion

Our results showed that cancer metastasis was an important predictor for recurrence and poor survival. In fact, metastasis was the leading cause of death in BC patients. A significant number of patients experienced early metastasis to the bone, lung and viscera. BC of the bone is reported to be the most common location for metastasis [17]. Due to the small number of patients with late recurrence, we cannot draw definitive conclusions between patients with early versus late recurrence. Molecular subtypes (luminal) are associated with preferential sites of recurrence [18].

During the 5-year follow-up, HR-positive tumors corresponded to a significant increase of approximately 35% in the overall survival rate when compared with HR-negative tumors. The association of HR status with survival was independent of the main clinical and pathological variables. Similar data were observed in a large cohort study of patients with stage I to III HER2-positive breast cancer. Specifically, the authors found significant associations between HR status and the cancer presenting features, patterns of recurrence and survival outcomes [19].

Breast cancer diagnoses based on immunohistochemical (IHC) parameters result in a more informed prognosis. Our study confirms the adverse characteristics of certain breast cancers, including HR+/HER2+,

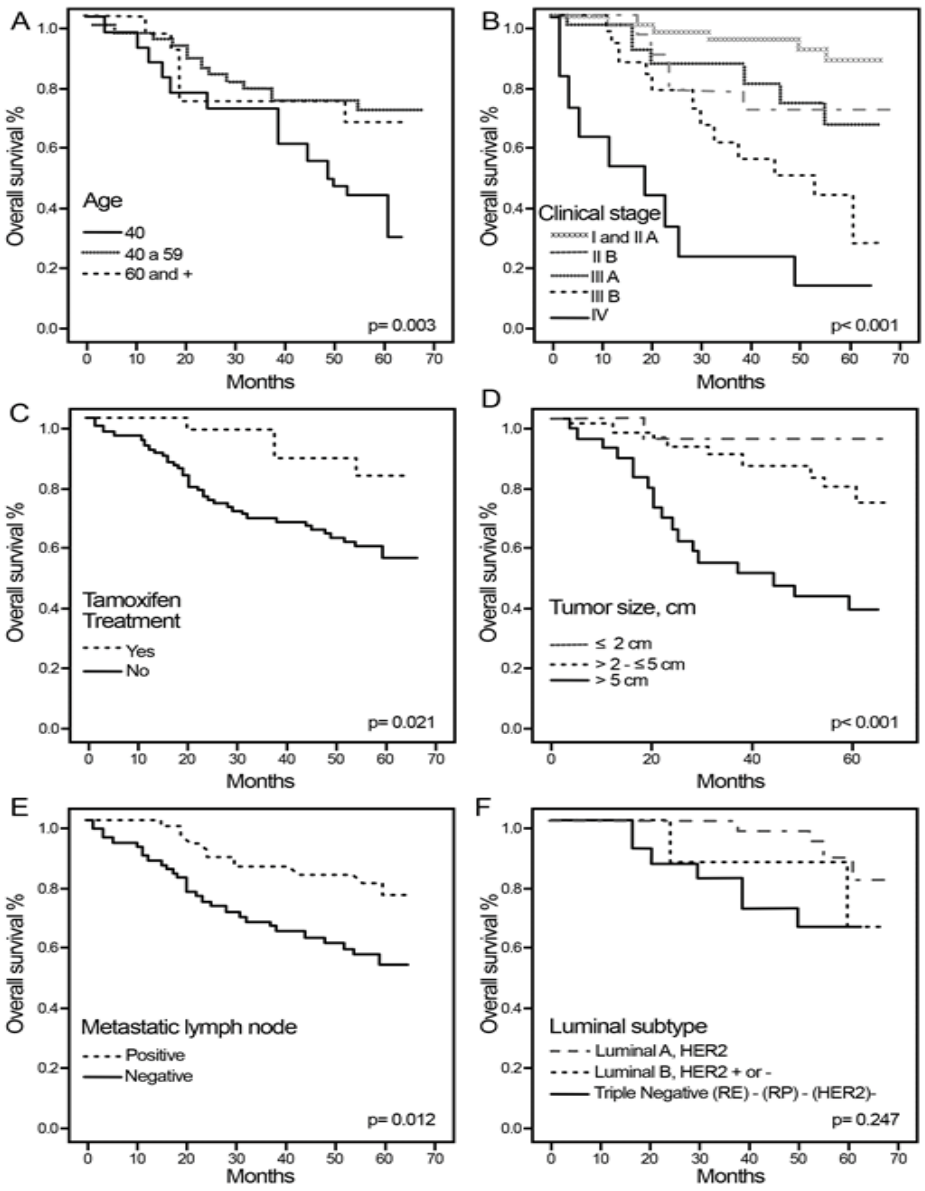

Figure 1: Kaplan-Meier curves of overall survival breast cancer A: age; B: clinical stage; C: treatment adjuvant endocrine; D: Tumor size; E: Metastatic lymph node; F: Subtypes BC (Luminal A, Luminal B and triple-negative).

HR−/HER2+, and triple negative subtypes, significantly increased the risk of death. Indeed, the risk of death from triple negative breast cancer is substantial. Both US- and foreign-born Hispanic women diagnosed with this subtype had an approximately 4-fold greater risk of death than those with HR+/HER2-breast cancer [20-22].

Tumor size and spread to the axillary lymph nodes (LN) are two classic prognostic indicators used to determine the appropriate treatment [23,24]. In our study, an increase in tumor size and up to four positive LN corresponded to a progressive decline. A lower 5-year survival rate (38%, $p \leq 0.001$) was observed in patients with tumors greater than or equal to 5 cm when compared with patients with a tumor size <2 cm. Although we could not identify a prognostic cut-off value for tumor size or the number of LN involved, a decreased survival rate in patients with these characteristics was clearly observed.

Currently, clinical stage is an important factor for prognosis and determining the appropriate cancer treatment [25]. Patients with locally advanced tumors (clinical stage III) showed a larger tumor load and lower survival expectancy; in addition, the most common surgery in these patients was a mastectomy (67.5%). Similarly, we found that 43.9% of patients were at advanced stages (stage III-IV), and patients in stage IV had a worse prognosis (Hazard ratio 2.88, 95% CI=11.36 to 44.8). Survival rates vary in Latin American countries (30-40%) [26]. However, these rates might seem excessive when compared with European countries [27].

Our study determined that BC patients <40 years of age had a lower survival rate when compared with patients older than 40 years of age (36%, p=0.003). Young women tended to have large, aggressive tumors with a larger nuclear grade. Previous research has linked tumor behavior with its biological characteristics [28,29]. Despite the extensive treatment in these previous studies, the rates for local and

Factor	Hazard ratio (95%CI)[a]	P
Clinical stage		
I (0 I, IIa)	1	
IIB	2.07 (0.55-7.74)	0.281
IIIA	3.29 (1.08-9.99)	0.036
IIIB	5.08 (1.78-14.52)	0.002
IV	20.92 (6.59-66.39)	0.001
Distant metastases		
Present	5.08 (2.60-9.94)	<0.001
Absent	1	
Family history breast cancer		
Yes	2.10 (1.02-4.31)	0.045
No	1	
Model 2		
Clinical stage		
I (0 I, IIA)	1	
IIB	4.26 (0.36-50.57)	0.251
IIIA	18.39 (1.67-202.4)	0.17
IIIB	16.55 (1.72-159.4)	0.015
IV	21.48 (1.42-324.96)	0.027
Distant metastases		
Present	17.18 (2.99-74.01)	<0.001
Absent	1	
Estrogen receptor		
Positive	0.195 (0.043-0.895)	0.035
Negative	1	
Her2 receptor positive	--	0.522
Metastatic lymph node	--	0.385
Tumor size >2cm	--	0.58
Age ≤40	--	0.054
Treatment Adjuvant	--	0.269

[a]Reference group: Hazard ratio=1. Her2 receptor positive, Metastatic lymph node, Tumor size >2cm, Age ≤ 40 and treatment adjuvant.

Table 4: Multivariate analysis of risk of death in breast cancer.

distant failure were higher; however, the mortality rate was lower when compared with other reports [30].

The influence of age on BC prognosis is controversial, and the literature contains many conflicting reports. As a patient reaches old age, there is a progressive decrease in survival [31]. Surprisingly, the multivariate analysis of our study cohort did not find this correlation to be a predictor of survival.

While family history is a well-established etiological risk factor for BC, its relationship with survival remains unclear. In our study population, 27.3% of patients with at least one family member with a history of breast cancer had a worse prognosis. Previous studies observed an improvement in the survival rates of women with a positive family history; in addition, the increased rate became more evident as the number of affected relatives increased [32]. However, other studies found no difference in mortality rates between patients with or without a family history of BC [33].

A high mortality rate (36.8%) corresponded to a poor overall survival after 5 years (63.3%) and a recurrence of 5.3%. The poor survival rate was partly due to diagnoses at advanced stages and poor access to treatment. The latency between initial cancer suspicions and a definitive diagnosis can affect clinical outcomes [3,34]. Moreover, patients who discontinued treatment and regular follow-up visits showed a decreased survival rate (41.9%, p=0.001).

Adjuvant treatments after surgery are the main factor for improved survival rates in BC patients [35]. Adjuvant chemotherapy is beneficial in high-risk cases of resected, invasive BC. Patients undergoing neoadjuvant chemotherapy before mastectomy did not show the same improvement in survival rates. One explanation for this difference is the use of a combined analysis of several prospective trials in which all BC subgroups did not respond to neoadjuvant chemotherapy; however, other studies maintain that adjuvant treatment is a good predictor of survival [15,36].

Additional hormone therapy improved the survival of patients with HR-positive tumors (78.3%, p=0.05). A large series study of women at high risk for late recurrence benefited from an intense, long-term endocrine therapy (over 5 years) [37,38].

In our study, trastuzumab was effective for metastatic HER2-positive tumors; however, there was not a significant change in the survival rate of these patients. Notably, the incidence of cardiotoxicity in women treated with trastuzumab in HER2-positive metastatic breast cancer was higher in the elderly. Despite this toxicity, the median survival time was longer [39-43].

Given the lack of regional data, our study offers a valuable contribution to the field, despite its limitations. A weakness of the study was the lack of Ki-67 data. The retrospective nature of this observation and the sources of our database prevented us from obtaining a centralized assessment of HER2 status. However, the quality of determining HER2 status does not differ between the two groups. Thus, this potential limitation does not negate the effectiveness of the overall survival analysis.

The recognition of this growing problem in Mexico and the generation of consistent results will optimize the monitoring (pre- and post-surgical), survival and recurrence of BC and improve the management and control of risk factors. Recurring breast cancer screenings can provide better post-surgical follow-up schedules and treatment regimens that can increase the survival rate of patients.

In Mexico, knowledge on BC remains limited; however, efforts have been made to overcome this problem. Increased access to effective methods of early detection intensified education programs and improved information resources are critically needed to achieve a sufficient societal response.

Conclusions

We determined that a high proportion of BC patients lived in urban areas. The majority of women had a basic level of education; however, a percentage of participants had no prior schooling. A poor survival rate in women at advanced cancer stages was observed. In addition, women under 40 years of age showed a relatively lower survival rate. According to treatment type, women undergoing adjuvant therapy showed an improved survival rate. The survival predictors of this cohort included the presence of metastasis, an advanced disease stage and a family history of cancer. Our data suggest that age is an important decision-making factor for adjuvant therapy. Further research is required to determine the applicability of these findings to other BC patient cohorts in Mexico.

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