

Breast Cancer Characteristics and Survival in a Hispanic Population of Costa Rica

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ABSTRACT

BACKGROUND: Breast cancer characteristics may vary according to the patient's ethnic group. The goal of this cohort study was to evaluate the characteristics of a group of Costa Rican breast cancer patients and their relationship with survival.

METHODS: Age, stage, tumor grade, immunohistochemistry, lymphovascular invasion, recurrence, and survival data on 199 Hispanic patients with breast cancer diagnosis, treated between January 2009 and May 2010, were collected from a single institution in San Jose, Costa Rica. The data were statistically analyzed for significance.

RESULTS: Median age at diagnosis was 53 years. With a median follow-up of 46.5 months, there was an 88% overall survival rate. Thirty-seven percent of the patients ($p < 0.001$) were at stages III and IV during diagnosis. The hormone receptor human epidermal receptor negative phenotype (*HR-HER2-*) ($p < 0.001$) was present in 17% of the cases. In a multivariate analysis, local (risk ratio, RR: 7.2; confidence interval, CI 95%: 3.8–7.6; $p = 0.06$) and distant recurrence (RR: 14.9; CI 95%: 7.7–28.9; $p = 0.01$) showed the strongest association with the probability of death from the disease. Patients with *HR-HER2-* phenotype tumors reported more local recurrences ($p = 0.04$), a higher tumor grade ($p < 0.01$), and lower overall survival than patients with other breast cancer phenotypes ($p = 0.01$).

CONCLUSIONS: Although this study analyzes a modest number of cases, it is an initial insight into factors that may contribute to differences in breast cancer outcomes among Hispanic women in Costa Rica. The higher proportion of triple negative tumors, advanced stage, and younger median age at diagnosis could contribute to the inferior prognostic described among Hispanic women. There may be a different distribution of tumor subtypes compared to non-Hispanic white women. Further studies are necessary to confirm such findings.

KEYWORDS: breast, cancer, Hispanic, Costa Rica, immunohistochemistry

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Introduction

The population in Costa Rica recently diagnosed with breast cancer is increasing. According to statistics from Costa Rica's National Cancer Registry, the adjusted incidence rate has increased from 37.66 to 44.09 per 100,000 women in 10 years, and breast cancer is the leading cause of cancer-related death in women.¹

Characteristics of the disease appear to be different according to the patient's ethnic group. Hispanic women seem to have an increased mortality risk after being diagnosed with breast cancer, are diagnosed at a later stage,^{2–4} report a lower median age at diagnosis,^{5–7} and feature a different immunohistochemical tumor subtype distribution, compared to non-Hispanic white women.^{6–8}



Hormone receptors (HR) are proteins expressed in breast epithelium and stroma that bind to circulating hormones to trigger cellular changes. The HRs more extensively studied in breast cancer are estrogen receptors (ER) and progesterone receptors (PR).⁹ Patients diagnosed with HR+ tumors are usually older, more responsive to hormone therapy, and tend to have better disease-free and overall survival.

HER2 is a transmembrane tyrosine kinase receptor that belongs to the epidermal growth factor group, encoded by the *ERBB2-HER2* oncogene. Its overexpression is associated with a more aggressive cancer behavior and worse prognosis.⁹ Therapy with the humanized monoclonal antibody Trastuzumab directed to the HER2 receptor has shown an inhibitory effect on tumor growth.

Tumors lacking HR and HER2 expression are associated with younger age at diagnosis, a more aggressive clinical course and worse results than other breast cancer subtypes. The *HR-HER2-* subtype has been found in higher proportion in African-American and Hispanic, than in Caucasian and Asian breast cancer patients.^{5,8,10}

This cohort study aims to evaluate the traits of a Hispanic group of breast cancer patients, such as mean age at diagnosis, stage of disease, tumor grade, immunohistochemistry (IHC), and their relationship with survival. The purpose is to contribute to improve health programs and adapt them to the patient's requirements.

Methodology

We requested the statistics department at San Juan de Dios Hospital of the Costa Rican Social Security System (*Caja Costarricense del Seguro Social*), a reference cancer treatment center for Costa Rica's South Central Region, to provide a list of patients with "breast cancer" diagnosis discharged from the Hospital from January 2009 to May 2010. The study procedures were approved by the hospital's institutional review board.

The analysis included all Hispanic women newly diagnosed with in situ or invasive breast cancer. A group of 199 patients was continuously selected from the list by the medical records department and clinical-pathological data were collected for each patient. The data analyzed in each medical record, if any, were patient's age in years, ethnicity, cancer stage, subsequent hospitalizations, operative note, pathology report, and follow-up visits to the Hospital until June 1, 2013.

Information on stage and lymph node status was collected according to the American Joint Committee on Cancer's (AJCC, 7th edition) staging criteria. The histopathological type was classified as ductal, lobular, both, or other. Histologic grading was classified according to the modified Bloom and Richardson method by Elston and Ellis (Nottingham's grading system). Lymph vessel invasion was assessed using hematoxylin-eosin stained glass slides. Vascular channels lined by thin endothelial cells, especially close to the small

arteries and veins, were considered as lymph vessels, and tumor emboli were floating in the lumen in lymph vessel invasion-positive cases.

Immunohistochemical subtypes such as ER, PR, and *HER2* status were determined by IHC. Antigen retrieval was performed in a decloaking steam chamber. Manual antibody incubation, DAKO "in vision" detection system, DAB Chromogen System, and bluish Gill H&E staining using lithium carbonate were used. For HR receptor staining, primary antibodies were applied at a 1:30 dilution for 1 hour. After 30-minute incubation with a secondary antibody, DAKO detection solution was applied. The last step was the addition of a substrate-chromogen solution. The cutoff for receptor positivity was 1%.

For HER2 staining, primary HER2 antibodies were applied for 30 minutes. After 30-minute incubation with a secondary antibody, a substrate-chromogen solution was added. It was scored on a qualitative scale based on staining intensity: 0 and 1+ were negative; 3+ was considered positive; and 2+ was considered borderline, and sent to an external laboratory for fluorescence in situ hybridization (FISH) evaluation. FISH was scored on a quantitative scale: less than 2 copies of the *HER2* gene was negative, and 2 or more copies was *HER2*-positive.

Follow-up visits until June 1, 2013 were analyzed for distal or local recurrence. Patients with initial metastatic disease were separated from patients who experienced distant recurrence a period of time after initial diagnosis. The survival status and date of death were confirmed at the Civil Registry of Costa Rica on a case-by-case basis. Survival time was defined in days from the time of diagnosis at the hospital to the date of death, or survival confirmation on June 1, 2013. Seven variables were selected and identified by their significance for mortality statistical analysis.

Statistical Analysis

Sample size. In 2009 and 2010, there were a total of 957 and 997 newly diagnosed breast cancer cases in Costa Rica. The sample size was calculated based on 87% expected survival, which in statistical terms is a proportion, for which the formula $N = Z^2 \times P \times (1 - P) / D^2$ was used, where $Z = CI$ chosen (if $\alpha = 95\%$, $Z = 1.96$); $P =$ expected ratio, 0.87; $D =$ maximum error, 0.05; and $n =$ sample size, 173. Although the recommended sample size is 173 cases, information for more cases was collected due to the probability of finding records with incomplete information. Since the information was obtained retrospectively from medical records, selection bias was avoided because the sample was selected randomly.

For descriptive purposes, continuous variables were summarized as arithmetic means with standard deviations and medians with ranges, and categorical variables were summarized as relative frequencies, ratios, and 95% CIs. Inferential comparisons were performed using the Student's *t*-test or the



Mann–Whitney U test according to distribution (normal or not normal) determined by the Kolmogorov–Smirnov test.

Pearson chi-square tests and relative risk ratios (RRs) were used to compare the clinical and pathological variables. For the multivariate analysis, the variables included were those bearing clinical significance and those that were significant or nearly statistically significant ($p < 0.05$) in the univariate analysis.

All variables were dichotomized for survival analysis. Adjustment of potential confounders was carried out with Cox proportional hazards regression analysis. All tests were two-sided, and significance was set at $p > 0.05$. SPSS software (version 20.0; SPSS, Chicago, IL) was used for data analysis purposes.

Differences between breast cancer subtypes with regards to clinical-pathological characteristics were examined using analysis of variance, χ^2 tests, or Fisher's exact test. The log-rank test was used to compare mean survival across IHC subtypes. StatView statistical software (version 3.0; Abacus, Baltimore, MD) was used to manage and analyze data. Statistical differences were considered significant at $p \leq 0.05$.

Results

Clinical-pathological and non-cancer specific survival data on 199 Hispanic patients with breast cancer diagnosis were collected from a single institution in San Jose, Costa Rica.

Table 1 displays the population's general characteristics. Median age at breast cancer diagnosis was 53 years. The histopathological type was 80% ductal carcinoma. Stage was distributed as follows: Stage 0, 3%; stages I and II, 59.3%; and stages III and IV, 37.1%. Survival for a median follow-up of 46.5 months was 88%. The immunohistochemical subtypes were HR+HER2–, 62.3%; HR+HER2+, 9%; HR–HER2+, 9.5%; and HR–HER2–, 17.1%. The proportion of HR– and/or HER2+ tumors was higher for patients under 50 years than for older patients, this relation is not statistically significant ($p = 0.32$). There were 7 (3.5%) local and 11 (5.52%) distant recurrences.

Using the univariate analysis, there were differences in age ($p = 0.003$), stage ($p < 0.001$), immunohistochemical subtype ($p = 0.02$), lymphovascular invasion ($p = 0.015$), local recurrence ($p < 0.001$), distant recurrence ($p < 0.001$), and survival. No statistically significant difference was found for histologic grade ($p = 0.33$) and survival.

Dichotomized variables and their analysis are included in Table 2. In the univariate analysis, age >50 years ($p < 0.001$, RR: 4.1), stages III and IV ($p < 0.001$, RR: 5.8), presence of lymphovascular invasion ($p < 0.02$), HR–HER2– IHC ($p < 0.001$, RR: 2.7), local recurrence ($p < 0.001$, RR: 7.2), and distant recurrence ($p < 0.001$, RR: 14.9) were statistically significant differences in patients who died after diagnosis. Grade III tumor ($p = 0.18$, RR: 1.8) was not significantly associated with survival. In the multivariate analysis, local ($p = 0.06$) and systemic recurrence ($p = 0.01$) showed the

strongest association with the probability of dying from the disease.

Table 3 shows the characteristics of 195 patients according to the immunohistochemical subtype. Differences in histological grade ($p < 0.01$) were observed: grade III was less frequent in the HR+HER2– subtype (21.8%) and more frequent in the HR–HER2– subtype (64.7%). Local recurrence showed an uneven distribution in the study groups ($p = 0.04$), the event being most frequent in HR–HER2– patients (11.8%). With a median follow-up of 45.6 months, breast cancer subtypes significantly differed in survival rate ($p = 0.01$): HR+HER2–, 91.9%; HR+HER2+, 94.4%; HR–HER2+, 89.5%; and HR–HER2–, 73.5%.

Patients with HR– and/or HER2+ overexpression tumors were more likely to present with an advanced stage than patients with HR+HER2– tumors; however, this was not statistically significant ($p = 0.18$). No significant differences were found in age ($p = 0.44$), lymphovascular invasion ($p = 0.86$), and distant recurrence ($p = 0.42$) between subgroups.

Discussion

The median age at diagnosis of this group of patients was 53 years. Different to the mean age at breast cancer diagnosis of 61–63 years among Australian and European women,¹¹ a younger median age at cancer diagnosis has been described for Hispanic women.^{4–8,12} In some studies, the median age is 10 years younger than the average age reported in the United States, and there is a higher proportion of non-Hispanic whites (57%) diagnosed with breast cancer younger than 60-years old, when compared to their white counterparts (47%).^{2–4}

The distribution of breast cancer subtypes among young patients has been found to be different from that observed in older women, and has further variations with race/ethnicity. Young women are also more likely to be diagnosed with stages III/IV disease and high-grade tumors than older women.¹³ Hispanics are described as the ethnic group with the highest percentage of women under 41 years diagnosed with breast cancer.⁸

Thirty-seven percent of the patients in the group had stages III and IV cancer at diagnosis. This is much higher than the number described in other studies for Central and South American women with stages III and IV cancer at diagnosis (14.3%).² Social and cultural barriers, like “fear to be left by her partner, poor awareness of the population and primary health providers, as well as deficient mammographic screening programs,” could lead to an advanced stage at diagnosis.⁴ Hispanic women have been found to have a 1.7- to 2.5-fold elevation in the risk of stages III and IV tumors, compared to non-Hispanic whites.^{2–6,14} Warner et al³ found Hispanic and other minority women were more likely to show up with cancer symptoms versus a problem detected through screening mammography, and experienced longer times from initial signs of cancer to final diagnosis.



Table 1. General characteristics of patients with breast cancer in Costa Rica.

	NO. OF PATIENTS, (%)	P VALUE*	
Age, years-old			
<50 years	74 (37.2)		
50–70 years	103 (51.8)	.03	
>70 years	22 (11.1)		
AJCC stage			
0	6 (3)		
I	35 (17.6)		
IA	31 (15.6)		
IB	4 (2)		
II	83 (41.7)		
IIA	50 (25.1)		
IIB	33 (16.6)	<.001	
III	67 (33.6)		
IIIA	38 (19.1)		
IIIB	15 (7.5)		
IIIC	14 (7)		
IV	7 (3.5)		
Missing	1 (0.05)		
Immunohistochemical (IHC) subtype			
HR+/HER2–	124 (62.3)		
<50 years	41 (20.6)		
>50 years	83 (41.7)		
HR+/HER2+	18 (9)		
<50 years	8 (4.02)		
>50 years	10 (5.02)		
HR–/HER2+	19 (9.5)	.02	.32*
<50 years	10 (5.02)		
>50 years	9 (4.52)		
HR–/HER2–	34 (17.1)		
<50 years	14 (7.03)		
>50 years	20 (10.05)		
Missing	4 (2.01)		
Histologic grade			
Grade I	27 (13.6)		
Grade II	74 (37.2)	.33	
Grade III	62 (31.1)		
Missing	36 (18.1)		
Lymphovascular			
Invasion present	34 (17.08)		
Absent	66 (33.16)	.015	
Missing	99 (49.74)		
Local recurrence			
Present	7 (3.58)	<.001	
Absent	192 (98.46)		
Distal			
Recurrence	11 (5.53)		
Present	182 (91.46)	<.001	
Absent	6 (3.02)		
Stage IV			

Notes: *Univariate analysis. **IHC subtype and age.

The group of patients diagnosed with stage I disease was small (17.6%). In previous publications, only a small percentage of Hispanic women are diagnosed with stage I breast cancer,^{2–6,14} Walters et al reported that stage I at diagnosis ranged from 30% to 45%, and stages III and IV from 8% to 22%, depending on the screening program implemented by the country, in a European, Canadian, and Australian population study.¹¹ Sassi et al described that Hispanic women who developed breast cancer had somewhat lower probability of early stage diagnosis than non-Hispanic white women, but with more steeply increasing screening rates, there was a similar increase in the number of cases diagnosed at an early stage.¹⁵ Rodriguez-Cuevas et al described results of a first mammography screening program in Mexico. Even though it was a case study of 208 patients, one-third of diagnosis were stage 0 or I, 42%, stage II and 26.7%, stage III. These results were different from other published data of Mexican breast cancer series, in which 25–40% were stages I and II and 57% were stages III and IV.⁵

In our study, the percentage for the HR–HER2– phenotype is higher (17.1%) than in non-Hispanic whites (11.7–12.5%).^{7,8} This proportion (17.2–17.3%) has been reported for Hispanics in previous studies,^{16,10} which is higher than the one reported for Japanese patients (8%),¹⁷ but lower than for African-Americans (24.6–27.9%).^{8,10} A higher proportion of HR–HER2– (23%) has also been described by Lara-Medina et al in Hispanic patients.⁶

Patients with HR–HER2– phenotype tumors experienced more local recurrences, had higher tumor grades, and lower overall survival than patients with other breast cancer phenotypes. Hispanics have been found more likely to present high-grade tumors than non-Hispanic whites.⁷ HR–HER2– tumors exhibit in average a high-grade tumor: over 80% of HR–HER2– tumors have high histologic grade, compared to less than 20% of the HR+HER2– tumors.^{8,18} Local recurrence has been described as three times higher in patients with the HR–HER2– phenotype than with the HR+HER2– phenotype.¹⁸

Three-year survival for HR–HER2– patients was lower than for patients with other immunohistochemical subtypes (73.5%). In California studies, survival among women with HR–HER2– breast cancer was lower: they reported a 76–77% 5-year survival rate, compared to 93–96% 5-year survival rate for women with other types of breast cancer.^{10,19,20} In Japanese women, there was also a lower overall survival (86.2%) for basal-like cancer than for the luminal A phenotype (96.9%).¹⁷

With a median follow-up of 46.5 months, there was an 88% survival rate for patients in this group. There was a 3-year overall survival rate of 91% to 94% in other two European countries, Canada, and Australia, compared to 87% and 89% in UK and Denmark, related to screening implementation and differences in treatment.¹¹ Hispanics have been described to have a 1.3- to 2-fold increase in mortality risk compared to non-Hispanic whites.^{2,21}



Table 2. Dichotomized clinico pathologic characteristics of patients with breast cancer in Costa Rica.

CHARACTERISTIC	NO. OF PATIENTS, (%)				UNIVARIATE ANALYSIS		MULTIVARIATE LOGISTIC REGRESSION ANALYSIS P
	ALIVE		DEAD		P	RR (95% CI)	
Age							
<50 years	71	95.9%	3	4.1%			
>50 years	104	86.0%	17	14.0%	<.01	4.1 (1.2–13.4)	.95
AJCC stage							
I and II	113	95.8%	5	4.2%			
III and IV	55	75.3%	18	24.7%	<.001	5.8 (2.25–414.9)	.59
Histologic grade							
1 and 2	93	92.1%	8	7.9%			
3	53	85.5%	9	14.5%	.18	1.8 (0.74–4.5)	NA
Lymphovascular invasion							
Absent	34	100%	0	0%			
Present	52	78.8%	14	21.2%	.015	NA	.94
Distant recurrence							
No	172	94.5%	10	5.5%			
Yes	2	18.2%	9	81.8%	<.001	14.9 (7.7–28.9)	.01
Local recurrence							
No	173	90.1%	19	9.9%			
Yes	2	28.6%	5	71.4%	<.001	7.2 (3.8–13.6)	.06
Immunohistochemical subtype							
HR+HER2–, HR+HER2+, and HR–HER2+	148	91.9%	13	8.1%			
HR–HER2–	25	73.5%	9	26.5%	<.001	2.7 (1.2–5.8)	.93

Abbreviations: RR, relative risk; CI, confidence interval.

Table 3. Prevalence of immunohistochemical subtypes and clinico-pathologic characteristics of patients in Costa Rica.

	ALL CASES	HR+HER2–	HR+HER2+	HR–HER2+	HR–HER2–	P VALUE*
Number of cases	195	124	18	19	34	
Age, median (range), years-old	53 (24–88)	54 (24–86)	50.5 (29–71)	49 (26–72)	52 (27–88)	.44
AJCC stage						
I and II	114 58.5%	81 65.9%	8 53.3%	7 41.2%	18 54.5%	.18
III and IV	74 37.9%	42 34.1%	7 46.7%	10 58.8%	15 45.5%	
0	6 3.1%					
Missing	1 0.5%					
Histologic grade						
I and II	99 50.8%	79 63.7%	9 50.0%	8 42.1%	3 8.8%	<.01
III	61 31.3%	27 21.8%	5 27.8%	7 36.8%	22 64.7%	
Missing	35 17.9%	18 14.5%	4 22.2%	4 21.1%	9 26.5%	
Lymphovascular invasion						
Present	34 17.4%	24 19.4%	3 16.7%	2 10.5%	5 14.7%	.86
Absent	66 33.8%	43 34.7%	5 27.8%	7 36.8%	11 32.4%	
Missing	95 4.7%	57 46.0%	10 55.6%	10 52.6%	18 52.9%	
Local recurrence						
Present	7 3.6%	3 2.4%	0 0%	0 0%	4 11.8%	.04
Absent	188 96.4%	121 97.6%	18 100.0%	19 100.0%	30 88.2%	
Distant recurrence						
Present	11 5.6%	6 4.9%	0 0%	2 10.5%	3 9.7%	.42
Absent	178 91.3%	116 95.1%	17 100%	17 89.5%	28 90.3%	
Initial stage IV	6 3.1%					
Follow-up, median (range), months	45.6 (2–55.4)					
Overall survival	88.7%	91.9%	94.4%	89.5%	73.5%	.01**

Notes: *Compares four subtypes using Fisher's exact text. **Log rank test.



Hines et al⁷ found tumor single marker staining for HER2+ was 31.9% in Hispanics, compared to 14.3% in non-Hispanic whites. In our study, 18.5% of the tumors displayed single marker staining for HER2+, or were FISH+. The slightly higher survival in this study for the HR+HER2+ subtype compared to the HR+HER2- may be explained in part by public access to treatment and systemic therapies, as well as sample size and short follow-up period.

Information from patient records was not found for tumor grade in 18.1% of the cases and for lymphatic invasion in 50% of the cases. No standardized synoptic report for breast cancer was used by pathologists at the time; therefore, information was omitted in some pathology reports. Future changes in reporting are expected with the recent implementation of the standardized synoptic report for breast pathology, and the assignment of a specialized group of pathologists to work on breast diseases.

The study's weakness is that the patient cohort is from a single institution, which is a reference cancer treatment center for Costa Rica's South Central Region; hence, the data may not reflect the true epidemiology of the entire Hispanic population in Costa Rica.

This is the first published study of breast cancer clinical-pathological characteristics and survival of Costa Rican breast cancer patients, according to Medline search terms: breast cancer, Costa Rica.

Conclusions

These findings may provide an initial insight to factors that contribute to differences in breast cancer outcomes among Hispanic women in Costa Rica. The higher proportion of triple negative tumors, advanced stage, and younger median age at diagnosis could lead to a worse cancer prognosis in this group.

The higher proportion of stages III and IV tumors at diagnosis demands a review of the region's breast cancer screening program. It is important to make emphasis on breast cancer awareness programs for the population and primary care physicians, and to investigate social and cultural barriers that make earlier cancer detection a difficult task.

Since patients are diagnosed at a younger age, it is desirable to organize programs for fertility preservation and genetic testing, among others, to improve patient care.

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Author Contributions

Conceived and designed the experiments: NSR. Analyzed the data: NSR, MCB. Wrote the first draft of the manuscript: NSR.

Contributed to the writing of the manuscript: NSR, MCB. Agree with manuscript results and conclusions: NSR, MCB. Jointly developed the structure and arguments for the paper: NSR, MCB. Made critical revisions and approved final version: NSR, MCB. All authors reviewed and approved of the final manuscript.

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