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Prevalence of the Triple-Negative Phenotype in Mexican Patients with Breast Cancer Treated in Private Practice

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Abstract

Background: Identifying the biological profile of breast cancer is fundamental to predict the response to various treatments and for prognosis. The aim of this study was to determine the triple-negative breast cancer prevalence in patients treated in private practice in Mexico.

Methods: The study was performed using Mexican patients older than 18 years and had a histopathological diagnosis of breast adenocarcinoma and immunohistochemical studies for estrogen, progesterone, and HER2/Neu receptors, according to validated standards.

Results: A total of 1,989 patients with a mean age of 52.9 ± 13.4 (23–93) years and a tumor size of 2.72 ± 1.12 cm were evaluated. The TNBC biological subtype was observed in 17.3%, HER2/Neu overexpression in 22.6%, and the presence of positive hormonal receptors (estrogen and/or progesterone) in 60.1% of the cases. An association was found between the TNBC type and the degree of differentiation (P<0.01), p53 overexpression (P<0.01, OR=1.84, 95% CI 1.35–2.52), proliferation index (P<0.01, OR=1.83, 95% CI 1.44–2.34), and tumor size (P<0.01). TNBC patients were younger (P<0.01) and lymph node involvement was more common in these patients (P<0.01, OR=4.57, 95% CI 3.53–5.90).

Conclusions: TNBC is a highly aggressive tumor with a lower prevalence in women treated in private practice than in patients treated through the *Seguro Popular*, probably as a consequence of faster detection and opportune treatment.

Keywords: Breast cancer; Prevalence; Hormone receptors; Triple negative

Introduction

For decades, breast carcinomas were classified according to the histological type, grade of differentiation, clinical stage, and the expression of receptors for Estrogen (ER), Progesterone (PR), and the human epidermal growth factor receptor 2 (HER2) [1-5].

The absence of these three markers defines Triple-Negative Breast Cancer (TNBC), which represents 15–30% of invasive breast carcinomas [6-9]. More than 85% of the cases express high levels of genes related to proliferation, and the human epidermal growth factor is present in more than 60% of the cases [10,11]. The majority present p53 mutation and are highly proliferative because of the loss of function of the RB1 protein, which is a critical regulator of the cell cycle. TNBC is also associated with high levels of cyclin E, low levels of cyclin D1, and with breast cancer 1 (*BRCA1*; breast cancer 1, early onset) gene mutations [10].

Women who are young or of African-American descent are predominately affected by TNBC [12,13], and excessive weight and obesity are associated factors [10,14,15]. There usually are high histological grades, high proliferation indexes, and more advanced stages at diagnosis [10,12].

The biological behavior of TNBC tumors is aggressive, with higher levels of local and systemic recurrences. The relapse peak tends to be between the first and fifth year after the initial presentation, and the majority of deaths occur during the first five years [16]. Paradoxically, TNBC shows a strong clinical and pathological response to neoadjuvant chemotherapy [17,18].

The prevalence of TNBC has been determined as 23.1% in an open population residing in Central Mexico [19]. This group of patients only represents the part of the Mexican population that benefits from the National Health Insurance Program system named *Seguro Popular*, which covers people with low income and no other type of medical insurance. Conversely, a growing number of Mexican women, with a higher socioeconomic and cultural level than those covered by the *Seguro Popular*, have obtained private coverage with private insurance companies or direct payment, which is characterized by greater ease and speed when seeking medical services [20].

The objective of this study was to determine the prevalence and general characteristics of patients with TNBC, as well as the association between this phenotype and different markers of poor prognosis, among a group of women treated by private medical services in Western Mexico.

Materials and Methods

The women who participated in this study were Mexican, over 18

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years of age, residents of the state of Jalisco or of the nearby states that form Western Mexico, and diagnosed with breast adenocarcinoma between January 2006 and December 2011. Tissue samples fixed in paraffin had to be available for histopathological studies, histochemical assessment, and immunohistochemical studies that looked for ER, PR, and HER2/Neu. In the case of HER2/Neu++, Fluorescence In Situ Hybridization (FISH) was used.

The tumors were diagnosed by the same group of pathologists with expertise in breast cancer who used the classification of the World Health Organization and the Scarff–Bloom–Richardson grading system.

Material for the detection of the hormonal receptors was obtained from the tissue samples fixed in paraffin, and the receptors were determined using immunoperoxidase staining (Dako, Carpinteria, CA, USA). All cases were subjected to national quality controls (Reference Laboratory of the Pathology Department of the University Hospital of Nuevo León, Monterrey, Mexico) and external controls (United Kingdom Accreditation Service), with values > 10% considered as negative. The expression of HER2/Neu was determined using immunohistochemistry (Dako, Carpinteria, CA, USA). Tumors that were HER2/Neu++ based on HercepTest criteria were subjected to FISH.

Statistical analyses

Raw numbers were used for descriptive purposes, frequencies and proportions were used for the analysis of categorical variables, and means with standard deviation were used for the analysis of quantitative variables. The inferential analysis was performed using Pearson's chi-squared test via the determination of odds ratios (OR) and the 95% confidence intervals for the categorical variables. Student's *t* test was used for the analysis of quantitative variables. All tests were double-tailed and *P*-values < 0.05 were considered significant. The data were analyzed using the SPSS statistics package, version 20.0 for Windows (IBM, Chicago, IL, USA).

Ethical considerations

The study was conducted according to the principles of the Declaration of Helsinki and the Mexican Health Guidelines. The Ethical and Research Committees of the Integral Private Oncology Clinic, Guadalajara, Jalisco, Mexico approved all protocols. Full, written informed consent was obtained from all patients before their inclusion in the study. The authors declare non-financial competing interests.

Results

A total of 1,989 female patients were evaluated and their general characteristics are described in Table 1. The average age was 52.9 ± 13.4 (23–93) years. The size of the tumor (used as the sample) varied from 0.4 to 8 cm, with an average of 2.72 ± 1.12 cm. Of the tumors, 93.6% were ductal infiltrating carcinomas, 4.3% were lobular infiltrating carcinomas, and 2.1% were of other varieties. Only 9.2% of tumors were well differentiated, whereas moderately differentiated tumors accounted for 42% and poorly differentiated tumors accounted for 48.8% (P<0.01, OR=2.93, 95% CI 2.23–3.87) of the whole sample. Regarding the biological classification of the tumors, we found the TNBC subtype in 17.3% of the total studied population. Overexpression of the HER2/Neu protein (subtype HER2) was present in 22.6% of the patients, 5.6% of whom also had positive estrogen receptors (luminal HER) and 60.1% of whom corresponded to patients with positive hormonal receptors and negative HER2/Neu (luminal A and B).

Table 2 describes the results of the univariate analysis. An association was found between the TN subtype and the grade of cellular differentiation (P<0.01, OR=2.93, 95% CI 2.23–3.87), *p53* oncogene overexpression (P<0.01, OR=1.84, 95% CI 1.35–2.52), proliferation index (P<0.01, OR=1.83, 95% CI 1.44–2.34), and tumor size (P<0.01). An association was also found with age, as patients with TNBC were younger (P<0.01) and exhibited lymph node involvement more frequently (P<0.01, OR=4.57, 95% CI 3.53–5.90).

Discussion

In the first Mexican report on the epidemiological, clinical, and evolutive characteristics of patients with TNBC [19], the authors reported a prevalence of this specific tumor type that was similar to that observed in African-American women (23–30%) [14,15]. The prevalence found here was 17.3%, which was almost 6% less than the 23.1% found by Lara-Medina et al., [19] and was the sample closest to that observed in populations of Hispanic-American women (10–19.2%) [21,22].

According to other epidemiological studies, the prevalence of TNBC varies greatly with ethic differences, being as high as 82% in Danish women, 39% in Arabic women, 19.3% in Chinese women, and 15.9% in Taiwanese women [23-26]. The average age of onset in our TN patients was 50.8 years, which was slightly lower than that observed in patients with positivity for the hormonal receptors (53.15 years), similar to that reported by Lara-Medina [19] and Rodriguez-Cuevas [27], and 10 years younger than that reported for Caucasian women [11-13]. Amirikia et al. [14] reported an average age of onset of 54 years in Latino women compared with 64 years in the Caucasian population. This was similar to the 52 years of age reported by Ghosn in Lebanese patients [28], whereas Stead observed a general mean age of onset of 58 years in a population including African-American, Latino, and Caucasian women [15].

Lund et al. found significant age of onset differences between patients with TNBC (52 years) and a group of women with positive hormonal receptors (61 years) [13].

The distribution of tumor histology was similar in our patients with and without TNBC; 90% of our cases had the ductal type. Hormonal receptors were present in 60.1% and HER2/Neu overexpression was present in 22.6% of cases, which was similar to the results of previous studies and in agreement with previous results obtained in Mexico [9,11,17,19,29].

We found a marked difference in tumor size at first diagnosis, as tumors were larger in patients with TNBC (P<0.01). We also observed

Average age, years	52.9 ± 13.4 (23–93)
Tumor size, cm	2.72 ± 1.12 (0.4–8)
Histology	
Ductal infiltrating carcinoma	1862 (93.6%)
Lobular infiltrating carcinoma	86 (4.3%)
Other varieties: medullary, apocrine, mucinous, papillary, colloid, tubular, and cribriform	41 (2.1%)
Differentiation	
Well differentiated	184 (9.2%)
Moderately differentiated	835 (42%)
Poorly differentiated	970 (48.8%)
Positive estrogen and/or progesterone receptors	1195 (60.1%)
HER/Neu overexpression	449 (22.6%)
Triple-negative tumors	345 (17.3%)

Table 1: General characteristics of the patients with breast cancer.

	Non-triple-negative *n* = 1644	Triple-negative *n* = 345	*P*-value	OR (95% CI)
Age, years	53.15 ± 12.7	50.82 ± 12.5	< 0.01	
Size, cm	2.20 ± 1.29	3.21 ± 0.60	< 0.01	
Histology Ductal Lobular Others	 1544 (93.9%) 70 (4.3%) 30 (1.8%)	 318 (92.2%) 16 (4.6%) 11 (3.2%)	0.12	0.90 (0.50–1.64)
Scarff–Bloom–Richardson grading Well differentiated Moderately differentiated Poorly differentiated	 166 (10.1%) 750 (45.6%) 728 (44.3%)	 18 (5.2%) 85 (24.5%) 242 (71.3%)	< 0.01	2.93 (2.23–3.87)
Lymph nodes Positive Negative	 524 (32%) 1120 (68%)	 235 (68%) 110 (32%)	< 0.01	4.57 (3.53–5.90)
P53 Positive Negative	 1198 (72.9%) 446 (27.1%)	 287 (83.3%) 58 (16.7%)	< 0.01	1.84 (1.35–2.52)
Ki67 index Absent Present	 904 (55%) 740 (45%)	 138 (40%) 207 (60%)	< 0.01	1.83 (1.44–2.34)
OR: odds ratio; *CI*: confidence interval.				

Table 2: Univariate analysis of breast tumor characteristics.

less cellular differentiation in this group ($P<0.01$), together with the expression of the p53 oncogene ($P<0.01$), a higher Ki67 cellular proliferation index, and lymph node involvement ($P<0.01$), all of which represent defined characteristics of this type of neoplasm [30-32].

Our study did not assess risk factors, such as family history of breast cancer, obesity, number of pregnancies and breastfeeding, use of contraceptives, associated illnesses (such as diabetes mellitus and arterial hypertension), and hormonal status (pre- and postmenopause), all of which have been associated with the presence of TNBC [33-37]. Lara-Medina et al. [19] did not demonstrate a significant association between the presence of obesity and TNBC in their general population; however, those authors observed an association between these parameters when using a multivariate analysis, as they found significant differences when comparing the postmenopausal hormonal state with a body mass index < 30 kg/m^2, which was probably a consequence of a high prevalence of obesity. According to the latest 2012 National Health Survey in Mexico, a high proportion of adult women are obese, representing a real public health problem [38]. The survey reported that only 29.4% of adult women had a normal weight, 35.4% were overweight, and obesity was present in 35.2% of women.

The most significant finding in our series was the lower prevalence of TNBC compared with other studies. We attribute this difference to the fact that the patients were treated in private medical practice. In Mexico, the majority of the population has access to public medical services, such as those provided by the Secretariat of Health, the Mexican Social Security Institute, the Institute for Social Security and Services for State Workers, the Army and Navy Medical Services, and, since 2003, the National Health Insurance Program named *Seguro Popular* [38]. Despite the fact that more than 90% of Mexicans have access to these services, the opportunity to receive early detection and medical attention is still much lower than the levels reported in developed countries. About 60% of breast carcinomas are detected at a locally invasive stage, and less than 10% of the neoplasms are detected in the early stages [19,27,39].

Those people who can cover the cost of private medical services with a direct payment or through an insurance company have faster access to an opportune diagnosis. Moreover, they have a higher awareness than does the general population of prevention, which helps identify carcinomas in the earlier stages [20]. This probably helps to explain the lower prevalence of TNBC observed in our patients compared with that reported by Lara-Medina *et al* from the National Cancer Institute of Mexico [19].

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