RESEARCH ARTICLE

Breast Cancer Metastasis Associations with Clinicopathological Characteristics in Mexican Women Younger than 40 Years of Age

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Abstract

Background: In Mexico, breast cancer (BCa) is in first place regarding cancer mortality and has been established as a priority health issue. The incidence of metastasis from BCa is very high and presents as the principal mortality factor among women younger than 40 years of age. OBJECTIVE. To determine any associations between clinicopathological characteristics and metastasis in Mexican women under 40 years of age. **Methods:** During the 2010–2015 period, a total of 180 female BCa cases seen at the Navy General High Specialty Hospital, SEMAR, in Mexico City; we collected information on 20 patients with BCa younger than 40 years of age. Statistical analyses were conducted using the Kolmogorov–Smirnov, Students t, Fisher, Chi square, and Mantel–Haenszel tests. **Results:** The prevalence of women with BCa younger than the age of 40 years during the 2010–2015 period was 13.3%. We found a high frequency of obesity in of these cases (>75%); 100% of obese patients with a history of smoking presented with metastasis ($p < 0.05$). In addition, the hormone phenotype was important; HER2-positive cases were 12 times more likely tto exhibit metastasis ($p < 0.05$), while expression of estrogen and progesterone receptors appeared to be protective. Diabetes mellitus in combination with smoking was also a risk factor for development of metastasis ($p < 0.05$). **Conclusion:** In this study, we obtained essential data regarding risk of metastasis in young breast cancer cases which could be useful for predicting disease evolution and treatment response.

Keywords: Breast cancer- metastases- young women- Mexico

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Introduction

Breast Cancer (BCa) is a low-frequency neoplasm among young women; however, in the U.S., its prevalence has demonstrated an increase in women <40 years of age (Ribnikar et al., 2015). In Mexico, BCa has become the most ubiquitous malignancy among female population and it has been established as a priority health issue (González-Robledo et al., 2013). On the other hand, prognosis of the neoplasm has been associated with multiple factors, such as clinical stage at diagnosis (Robles-Castillo et al., 2011; Cárdenas-Sánchez et al., 2015), age (Robles-Castillo et al., 2011; Cárdenas-Sánchez et al., 2015), hormonal phenotype, alterations in molecular mechanism (O'Connor et al., 2016), and metastasis (Bandala et al., 2015). The incidence of metastasis in BCa has shown considerable increases among women <40 years of age, and it represents the main mortality factor in these women (Rodríguez-Cuevas et al., 2001; Ji et al., 2011). Some work has been conducted in order to find some methods that could predict the development of metastasis according to clinicopathological characteristics, but it has been limited (Anders et al., 2011; León-Hernández et al., 2014; Bandala et al., 2015; Swede et al., 2016). In this respect, the aim of the present work was to infer the clinicopathologic characteristics that could be related with the presence of metastasis in order to identify and control risk factors for BCa in younger Mexican women.

Materials and Methods

The files of patients with a diagnosis of BCa from 2010–2015 were 175, from which 20 cases involved women under the age of 40 years. The clinicopathologic data were analyzed according to ethic standards. The present work was approved by the local Ethical Research Committee, which granted approval with number 146.

Statistical analysis

We performed descriptive statistics of the clinicopathological variables, applying the Kolmogorov–Smirnov test, the Student t test, the Chi square test, the Fisher test, and the Mantel-Haenzel analysis. The Odds Ratio (OR) was calculated for each variable in order to determine the putative risk or

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protective factors. All analyses were performed by SPSS ver. 19.0 statistical software, with a significance value of $p < 0.05$.

Results

We found that highest prevalence of BCa occurred in 2010 in all ages, and interestingly, in 2012, the lowest global prevalence (all ages) and the lowest prevalence for women under the age of 40 years (Figure 1) were reported. The year 2015, presented the highest frequency of patients with BCa of <40 years of age (16.7%) related to all ages; their mean age was 36.4 ± 3.2 years, and minimal age was 30 years. According to risk factors, we found that this population presented a high frequency of obesity in >75% of cases. In a similar manner, these women showed a high incidence of contraceptive consumption. Mean Body Mass Index (BMI) was 30.1 ± 5.2 kg/m^2. According to the breast lesions, we could observe that there were no significance differences in terms of the affected breast (left or right): both breasts have the same probability of being affected. On the other hand and as expected the histological type with highest frequency, with 80% of the cases, was ductal carcinoma. The most frequent clinical stages were IIA and IV (Figure 2). Immunohistochemical markers revealed that Ki67 were found in 91% of cases and, according to expectations, HER2 were present in only 13.3%. On the other hand, Estrogen Receptors (ER) were found in 61.1%. Subtype ER+/Progesterone Receptor (PR)+ was the most frequent subtype found, with 56.0%, followed by the baseline-like subtype with 33.3% (Table 1). Treatment frequencies were as follows: 85.0% chemotherapy; 55.6% radiotherapy, and 73.7% mastectomy. At diagnosis, a positive lymph node could be found in 47.1% of cases and the presence of metastasis in 35.3%; interestingly, we found that women <40 years of age with smoking antecedents have a 5-times greater risk for metastasis and, more seriously, contraceptive consumption is associated with a 7-times greater risk for metastasis. On the other hand, there are apparently more probabilities for metastasis in ductal carcinoma when it appears in the right breast ($p = 0.05$) (Table 2). According to ImmunoHistoChemical (IHC) markers, we could observe that the absence of Progesterone Receptor (PR) is associated with high probabilities for metastasis. Interestingly, all patients (100.0%) with metastasis were negative for PR and, in addition, the absence of Estrogen Receptor (ER) confers a 12-times greater risk for metastasis; in the case of ER- and PR-, the risk for metastasis is 6-times higher, while, the presence of ER+, PR+, and absence of HER-2 is associated with a protective factor for developing metastasis (Table 3). Another important clue that we were able to observe was a significant association between metastasis and obesity ($p < 0.05$), this demonstrating that patients with obesity younger than the age of 40 years are most vulnerable to metastasis (Figure 3). It is noteworthy that all cases with obesity and smoking presented metastasis, although only 16.7% of patients with obesity but who were non-smokers suffered from metastasis. As expected, clinical stage at diagnosis is important for preventing metastasis; these could be observed because patients diagnosed at clinical stage III or IV were more susceptible to metastasis (71.4%; $p < 0.05$). In the same manner, patients with infiltrating ductal carcinoma with stage III or IV at diagnosis showed metastasis in 100% of cases, but not another histological type. Type 2 Diabetes Mellitus (DM2) exhibited a interesting significance: we found that patients with DM2 and smoking antecedent demonstrated an increased risk for metastasis ($p < 0.05$); in the same respect, patients with DM2 diagnosed with stage III or IV possess greater susceptibility for metastasis (a 2.4-times greater risk; $p < 0.05$).

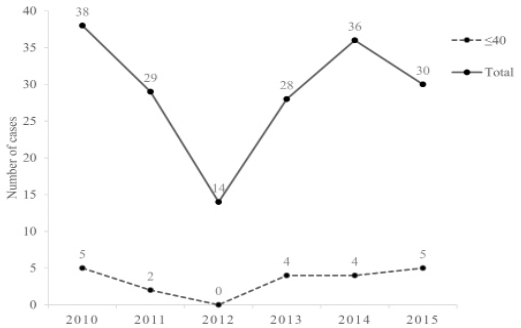

Figure 1. Global Prevalences of Women with BCa in All Ages and Younger Than 40 Years Related to Period of 2010-2015

Discussion

The incidence of BCa in young women is more frequent at the present time, and in Mexico, the incidence of these cases was reported as within a range of 10–15%. In

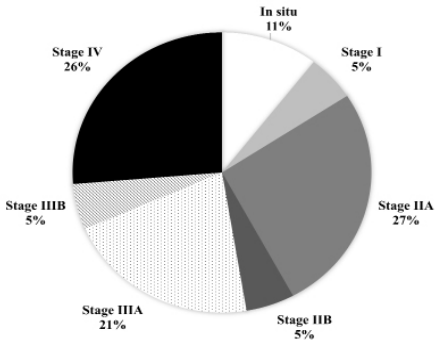

Figure 2. Frequency of Certain Clinical Stages of Women with BCa Younger Than 40 Years at the Moment of Diagnosis

Table 1. Frequencies of Histopathologic Markers Determined in Women with Breast Cancer (BCa) Younger Than 40 Years of Age

Markers	Frequency	Subtypes	Frequency
Her2	13.3%	(ER-/PR-)	31.3%
PR+	50.0%	(ER+/PR+)	56.3%
ER+	61.1%	(ER-/PR-/Her2-)	33.3%
Ki67	91.7%	(ER+/PR+/Her2+)	6.3%

BCa , Breast Cancer; +, Positive marker; -, Negative marker; PR , Progesterone Receptor; ER , Estrogen Receptor

Table 2. Metastasis Relationship to Lifestyle and Clinicopathological Risk Factors in Patients with Breast Cancer (BCa) Younger Than 40 Years of Age

	Metastasis			
	Yes (n = 6)	No (n = 13)	P	OR (95% CI)
Smoking	50% (3)	0	0.005*	5.3 (1.4-14.8)
BMI (kg/m^2)	31.2 ± 5.2	29.2 ± 5.4	0.61	-
DM2	16.7% (1)	7.7% (1)	0.54	2.4 (0.1-46.4)
Early menarche	50.0% (3)	23.0% (3)	0.39	2.3 (0.3-19.0)
Nulliparity	16.7% (1)	7.7% (1)	0.62	1.8 (0.1-35.4)
Non- breastfeeding	16.7% (1)	7.7% (1)	0.65	1.6 (0.3-12.4)
Oral contraceptive	83.3% (5)	30.8% (4)	0.04*	7.5 (0.01-1.6)
Age at first pregnancy	17.0 ± 1.6	21.3 + 1.5	0.04*	-
Right breast	83.3% (5)	38.5% (5)	0.0*	8.0 (0.7-90.0)
Infiltrating ductal carcinoma	83.3% (5)	76.9% (10)	0.62	1.5 (0.1-18.4)
Clinical stage III–IV	100.0% (6)	30.7% (4)	0.01*	-

*, Statistical significance; BCa , Breast Cancer; BMI , Body Mass Index; DM2 , Type 2 Diabetes Mellitus 2; OR , Odds Ratio; 95% CI , 95% Confidence Interval

Table 3. Metastasis Relationship to Histopathologic Markers in Patients with Breast Cancer (BCa) Younger Than 40 Years of Age

	Metastasis			
	Yes (n = 4)	No (n = 12)	p	OR (95% CI)
PR Negative	100.0% (4)	25.0% (3)	0.01*	-
ER Negative	75.0% (3)	25.0% (3)	0.03*	12 (0.006-1.09)
Her2+	0.0	25.0% (3)	0.33	-
Ki67+	100.0% (4)	50.0% (6)	0.42	-
(ER-/PR-/Her2-)	75%(3)	16.6% (2)	0.05*	12 (0.77-86.36)
(ER+/PR+/Her2+)	0.0	8.3% (1)	0.46	-
(ER-/PR-)	75.0% (3)	16.6% (2)	0.12	6 (0.56-63.98)
(ER+/PR+)	25.0% (1)	66.6% (8)	0.05*	PF 9.33 (0.008-1.40)
(ER+/PR+/Her2-)	25.0% (1)	50.0% (6)	0.42	PF 2.25 (0.05-3.97)

*, Statistical significance; PF, Protection Factor; +, Positive marker; -, Negative marker; PR , Progesterone Receptor; ER ,Estrogen Receptor

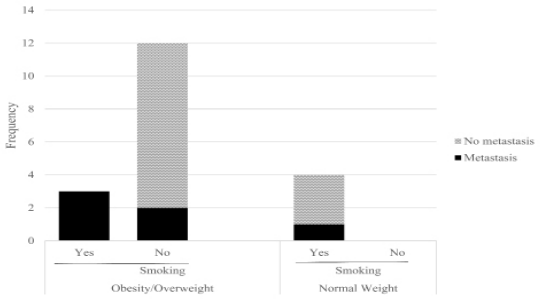

Figure 3. Metastasis Relationship of Obesity / Overweight and Smoking in BCa Women Younger Than 40 Years

our study, BCa global prevalence for women under the age of 40 years was 12%, similar to other studies performed in our country (Robles-Castillo et al., 2011; Villarreal-Garza et al., 2013), but were higher during 2015 (16.7%). It has been well reported that metastasis in young women is a frequent phenomenon, and in Mexico, it represents the 35–41% of these types of patients (Villarreal-Garza et al., 2013; León-Hernández et al., 2014). In this study, we reported obesity in nearly 66% of the cases analyzed, and previously, some reports revealed that obesity could be a protective factor in young women (Anders et al., 2009; Connor et al., 2013; Bandala et al., 2015). However, but in our case, we found a potential positive association between metastasis and obesity, similar to other reports (Chen et al., 2016). It is reported that the most frequent histological type in women younger than 40 years of age is ductal infiltrating carcinoma, representing in the U.S. 74.3%, in Europe 85%, and in Mexico, 88–96% (Kheirelseid et al., 2011; Robles-Castillo et al., 2011; Copson et al., 2013; Villarreal-Garza et al., 2013; Bandala et al., 2015). According to the literature, we found this histological type in 80% of cases and, similar to other reports, we observed that these lesions are associated with a high risk for metastasis (Johnson et al., 2013; Copson et al., 2013): however, we are not able to discard some variation related with geographical distribution or the patients' ethnic backgrounds (Smigal et al., 2006; Sachdev et al. 2010; Starlard et al., 2013). On the other hand, some studies reported that young women have high probabilities

of being diagnosed at advanced stages (Kheirelseid et al., 2011; Robles-Castillo et al., 2011; Bandala et al., 2012; Copson et al., 2013; Villarreal-Garza et al., 2013). In this case, we found a high percentage of women with stages III or IV (26.31 and 26.32%, respectively), representing one half of the analyzed patients; this could be explained as due to that the female population presented for breast medical examination after the age of 40 years or when they found an atypical breast formation, in other words, when the tumor was advanced (Rodríguez-Cuevas et al., 2000).

According to IHC markers, we found the presence of hormonal receptors (ER or PR) in one half of the samples, followed by baseline-like phenotype in approximately 30% of cases. In this regard, it is well known that the presence of both hormonal receptors with a negative expression of HER2 is a good prognosis marker (Puig-Vives et al., 2013), and in this study, we found a protective factor of 9.33 times in this phenotype, similar to others reports (Kheirelseid et al., 2011; Liukkonen et al., 2011; Copson et al., 2013). Meanwhile, subtype luminal-B HER2-positive, HER2-positive, and baseline-like phenotypes have been associated with poor prognosis, and in this study, we found similar data: in this case, these phenotypes confer a 12-times greater risk for developing metastasis, and this probably could be the reason for poor prognosis in these IHC markers (Johnson et al., 2013; Puig-Vives et al., 2013; Aktas et al., 2016). Many authors have studied smoking as a risk factor in BCa, showing that cigarette smoking is associated with a short survival time after treatment (Stefani et al., 2011; Park et al., 2012; Gou et al., 2013; Persson et al., 2016); in this study, we showed that the risk for metastasis is higher in patients with a history of smoking, and this could be explained in part by an adaptative mechanism of tumor cells produced by chromosomal imbalance or toxicity due to cigarette consumption (Hyndman 2016). On the other hand, in the present study, we found an association between DM2 and metastasis; these results are similar to those of other works, indicating that this has been associated with poor prognosis and perhaps with metastasis, due to that insulin resistance promotes tumor cell growth, and increases Reactive Oxygen Species (ROS) and the production of pro-angiogenic cytokines (Sciacca et al., 2013; Ferroni et al., 2015; O'Connor et al., 2016).

In this study, we provide some interesting data on the increase of the risk of metastasis according to some variables that could be useful in predicting disease evolution and treatment response; in this case, we could conclude that knowledge about risk factors or protective factors in BCa supply a very important clue, which could be applied in clinical practice in order to furnish a close vision of patient prognosis and to reduce institutional costs for failed or incorrect treatments.

References

Aktas B, Kasimir-Bauer S, Müller V, et al (2016). Comparison of the HER2, estrogen and progesterone receptor expression profile of primary tumor, metastases and circulating tumor cell in metastatic breast cancer patients. *BCM Cancer*, **16**, 522.

Anders CK, Johnson R, Litton J, Phillips M, Bleyer A (2009). Breast cancer before age 40 years. *Semin Oncol*, **36**, 237-49.

Anders CK, Deal AM, Miller CR, et al (2011). The prognostic contribution of clinical breast cancer subtype, age, and race among patients with breast cancer brain metastases. *Cancer*, **117**, 1602-11.

Bandala C, Floriano-Sánchez E, Cárdenas-Rodríguez N, López-Cruz J, Lara-Padilla E (2012). RNA expression of cytochrome P450 in Mexican women with breast cancer. *Asian Pac J Cancer Prev*, **13**, 2647-53.

Bandala C, De la Garza-Montaño P, Cortés-Algara A, et al (2015). Association of histopathological markers with clinio-pathological factors in Mexican women with breast cancer. *Asian Pac J Cancer Prev*, **16**, 8397-403.

Cárdenas-Sánchez J, Bargallo-Rocha E, Erazo-Valle A, et al (2015). Consenso Mexicano sobre diagnóstico y tratamiento del cáncer mamario. *Gaceta Mexicana de Oncología*, **14**, 2-55.

Chen L, Cook LS, Tang MT, et al (2016). Body mass index and risk of luminal, HER2-overxpressing, and triple negative breast cancer. *Breast Cancer Res Treat*, **157**, 545-54.

Connor AE, Baumgartner RN, Rinkston C, Baumgartner KB, (2013). Obesity and risk of breast cancer mortality in hispanic and non-hispanic white women: the New Mexico women's health study. *J Women´s Health*, **22**, 368-77.

Copson E, Eccles B, Maishman T, et al (2013). Prospective observational study of breast cancer treatment outcomes for UK women aged 18–40 years at diagnosis: the POSH study. *J Natl Cancer Inst*, **105**, 978-88.

Ferroni P, Riondino S, Buonomo O, et al (2015). Type 2 diabetes and breast cancer: the interplay between impaired glucose metabolism and oxidant stress. *Oxid Med Cell Longev*, **215**, 1-10.

González-Robledo MC, González-Robledo LM, Nigenda G, (2013). Public policy-making on breast cancer in Latin America. *Rev Panam Salud Publica*, **33**, 183-9.

Gou YJ, Xie DX, Yang KH, et al (2013). Alcohol consumption and breast cancer survival: A Meta-analysis of Cohort Studies. *Asian Pac J Cancer Prev*, **14**, 4785-90.

Hyndman K, Thomas R, Patterson S, et al (2016). Effectiveness of tobacco intervention education in health professional students' practice: a systematic review protocol. *JBI Database System Rev Implement Rep*, **14**, 78-90.

Ji XD, Li G, Feng YX, et al (2011). EphB3 is overexpressed in non-small-cell lung cancer and promotes tumor metastasis by enhancing cell survival and migration. *Cancer Res*, **71**, 156-66.

Johnson RH, Chien FL, Bleyer A, (2013). Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. *JAMA*, **309**, 800-5.

Kheirelseid EH, Boggs JM, Curran C, et al (2011). Younger age as a prognostic indicator in breast cancer a cohort study. *BMC Cancer*, **11**, 383.

León-Hernández SR, Padilla EL, Algara AC, et al (2014). Relation of alcohol/tobacco use with metastasis, hormonal (estrogen and progesterone) receptor status and c-erbB2 protein in mammary ductal carcinoma. *Asian Pac J Cancer Prev*, **15**, 5709-14.

Liukkonen S, Leidenius M, Saarto T, Sjöström-Mattson J, (2011). Breasts cancer in very young women. *Eur J Surg Oncol*, **37**, 1030-7.

O'Connor JP, Boult JK, Jamin Y, et al (2016). Oxygen-enhanced MRI accurately identifies, quantifies, and maps tumor hypoxia in preclinical cancer models. *Cancer Res*, **76**, 787-95.

Park SY, Kolonel LN, Henderson BE, Wilkens LR, (2012). Dietary fat and breast cancer in postmenopausal women

according to ethnicity and hormone receptor status: the multiethnic cohort study. *Cancer Prev Res (Phila)*, **5**, 216-28.
Persson M, Simonsson M, Markkula A, et al (2016). Impacts of smoking on endocrine treatment response in a prospective breast cancer cohort. *Br J Cancer*, **115**, 382-90.
Puig-Vives M, Sanchez MJ, Sanchez-Cantalejo J, et al (2013). Distribution and prognosis of molecular breast cancer subtypes defined by inmunohistochemical biomarkers in a spanish population-based study. *Gynecol Oncol*, **130**, 609-14.
Ribnikar D, Ribeiro JM, Pinto D, et al (2015). Breast cancer under age 40: a different approach. *Curr Treat Options in Oncol*, **16**, 16.
Robles-Castillo J, Ruvalcaba-Limón E, Maffuz A, Rodríguez-Cuevas S (2011). Breast cancer in Mexican women under 40. *Ginecol Obstet Mex*, **79**, 482-8.
Rodriguez-Cuevas S, Macías-Martínez CG, Labastida-Almendaro S (2000). Breast cancer in Mexico. Is it a young women disease?. *Ginecol Obstet Mex*, **68**, 185-90.
Rodríguez-Cuevas S, Macías CG, Franceschi D, Labastida S, (2001). Breast carcinoma presents a decade earlier in Mexican women than in women in the United States or European countries. *Cancer*, **91**, 863-8.
Sachdev JC, Ahmed S, Mirza MM, et al (2010). Does race affect outcomes in triple negative breast cancer?. *Breast Cancer (Auckl)*, **7**, 23-33.
Sciacca L, Vigneri R, Tumminia A, et al (2013). Clinical and molecular mechanisms favoring cancer initiation and progression in diabetic patients. *Nutr Metab Cardiovasc Dis*, **23**, 808-15.
Smigal C, Jemal A, Ward E, et al (2006). Trends in breast cancer by race and ethnicity: update 2006. *CA Cancer J Clinic*, **56**, 168-83.
Starlard-Davenport A, Glover-Collins K, Mahkoul I, et al (2013). Race is not a factor in overall survival in patients with triple negative breast cancer: a retrospective review. *Springerplus*, **2**, 516.
Stefani ED, Moore M, Aune D, et al (2011). Mate consumption and risk of cancer: a multi-site case-control study in Uruguay. *Asian Pac J Cancer Prev*, **12**, 1089-93.
Swede H, Sarwar A, Magge A, et al (2016). Mortality risk from comorbidities independent of triple-negative breast cancer status: NCI-SEER-based cohort analysis. *Cancer Causes Control*, **27**, 627-36.
Villarreal-Garza CM, Hoyos CM, Meza-Herrera V, et al (2013). Pathological characteristics and patterns of recurrence and mortality among young Mexican breast cancer patients. *Can Res*, **73**, 10-2.