RESEARCH ARTICLE

Metastasis Risk Reduction Related with Beta-Blocker Treatment in Mexican Women with Breast Cancer

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Abstract

Background: Breast Cancer (BCa) is the most common malignant tumour in Mexican women. In BCa, several studies have linked β2-adrenergic receptor activation with increased tumour growth and progression as related with Epinephrine-NorEpinephrine (E-NE) stimulation. The aim of this study was to describe Beta-Blocker (BB) treatment related with reduction of the risk of metastasis in Mexican patients with BCa. Materials and Methods: We collected data of 120 patients seen at the High-Specialty Naval General Hospital in Mexico City (HOSGENAES), all of these with a histopathological diagnosis of BCa. Four groups of patients were divided as follows: without Systemic Arterial Hypertension (SAH); with SAH treatment with non-selective BB; with SAH treatment with selective BB, and with SAH treatment with other antihypertensive drugs. Chi-square, Mantel-Haenszel, Student t, and ANOVA tests were performed for data analysis. Results: On average, patients were 54.8±11.8 years of age. Risk factors such as smoking and consuming alcohol exhibited a frequency of 33 and 36.5% respectively. Clinical stages III- IV were found in 50% of patients, while, 30% of patients had arterial hypertension (n=29 and N=96, respectively) and 17.5% used BB. One hundred percent of patients with arterial hypertension treated with BB for β1 - and β2 -adrenergic-receptors did not present metastasis globally, but patients treated with β1 BB presented 30% of metastasis while patients treated with no BB or without SAH had around 70% of metastasis. Conclusions: In Mexican patients with BCa and SAH treated with non-selective (β1- and β2-adrenergic receptors) BB, a decrease in the risk for metastasis was observed at the time of diagnosis.

Keywords: Breast cancer - beta-blocker - arterial hypertension - metastasis

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Introduction

Breast Cancer (BCa) is one of the most common tumors among women (Dimitrakopoulos et al., 2015). There were an estimated 494,000 new cases of breast cancer diagnosed in Europe and about 1.6 million worldwide in 2012 (Lyon and France, 2013). The contribution of genetic factors in BCa is estimated to be about 5% of all cases but approximately 25% of cases are diagnosed with early disease onset prior to the age of 30 years (Alanazi and Khan, 2016). BCa incidence has increased in the last few years in Mexico (DGIS/SINAIS, 2010; Bandala et al., 2012; Anaya-Ruiz et al., 2014). Most importantly, BCa could be treated opportunely at early moments in the disease, in order to reduce mortality (Dey, 2014). BCa is a highly survivable disease with 5-year survival rates of approximately 90%, but not in our country (ACS/BCFF, 2011).

Several reports have demonstrated that risk factors for BCa are related with demography, socioeconomic status, genetics, lifestyle, and reproductive behavior, among other factors (Tirona et al., 2010; Justo et al., 2013). Recent studies showed that β-adrenergic signaling exerted an influence on the biological processes involved in the development of the carcinoma by influencing tumor cells and their microenvironment (Wang et al., 2016). The β-adrenergic system comprises catecholamines (Tang et al., 2013). β-Adrenergic signaling has been found to regulate multiple cellular processes that contribute to the initiation and progression of cancer, including inflammation, angiogenesis, apoptosis/anoikis, cell motility and trafficking, and cellular immune response. Epidemiologic studies have linked the use of Beta-Blockers (BB) to reduced rates of progression for several solid tumors. The three subtypes of β-adrenergic receptor subtypes, that is, β1-, β2-, and β3-, are present at many sites of tumor growth and metastasis (Cole and Sood, 2012). Stress hormones such as Epinephrine (E) and NorEpinephrine (NE) promote the migration and invasion of tumor cells in multiple ways throught β2- adrenergic

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receptor (Barron et al., 2012). This fact was reported in ovarian cancer cells, in patients treated with Propranolol exhibiting decreased disease aggressiveness (Sood et al., 2006). Similar biological effects have been reported in several other tumor types, including colon and head and neck cancers (Yang et al., 2002; Drell et al., 2003). BB (Propanolol, Nadolol; β1-/β2–adrenergic receptor- non-selective) inhibited prometastatic effects by between 50 and 100% (Barron et al., 2012). Despite the great amount of information related with BB and BCa, this is, to our knowledge, the first study In Mexican patients with BCa related with the indirect study of catecholamines and metastasis.

Materials and Methods

Procedures

We included 120 patients with a diagnosis of BCa who were seen at the High-Specialty, Naval General Hospital (HOSGENAES) in Mexico City. We reviewed the clinical and pathological data, taking into account ethical standards for consultation.

Statistical analysis

We calculated medians and Standard Deviation (SD), frequencies and percentages, and Odds Ratios (OR), and the Kolmogorov-Smirnov, chi-square, Mantel-Haenszel, and ANOVA tests were applied. Data analysis was performed using the SPSS ver.19 statistical software program. A 95% Confidence Interval (95% CI) was considered.

Results

We studied 120 female Mexican patients diagnosed with BCa who were treated at HOSGENAES. The average age of these patients was 54.8±11.8 years, with a range of 32-91 years. We observed that the majority of patients were >50 years of age (67.5%). BCa frequencies by age group are depicted in Figure 1. Regarding risk factors consumption of tobacco and alcohol were positive at frequencies of 33 and 36.5% respectively. In relation to the clinical stage at diagnosis, 11% were stage I (I: 8%, IA: 3%), 39% were stage II (II: 1%, IIA: 22%, IIB 16%), 30% were in stage III (III: 1%, IIIA 20%, IIIB: 3%, IIIC: 6%) and 20% were in stage IV. Regarding frequency of histological type, 71.7% (86 cases) was canalicular carcinoma, with invasive ductal carcinoma most common in 40.8% of cases, followed by infiltrating ductal carcinoma in 27.5% of cases; 14.2% was not specified, the 6.7% was lobular carcinoma, and others comprised 2.5% (and included mixed carcinoma, secondary tumor, and chondroid type), and adenocarcinoma, and mucinous metaplastic carcinoma, with 1.7% respectively. With respect to histopathologic marker frequency, 55.5% were positive for Progesterone Receptor (PR), the 63.6% were

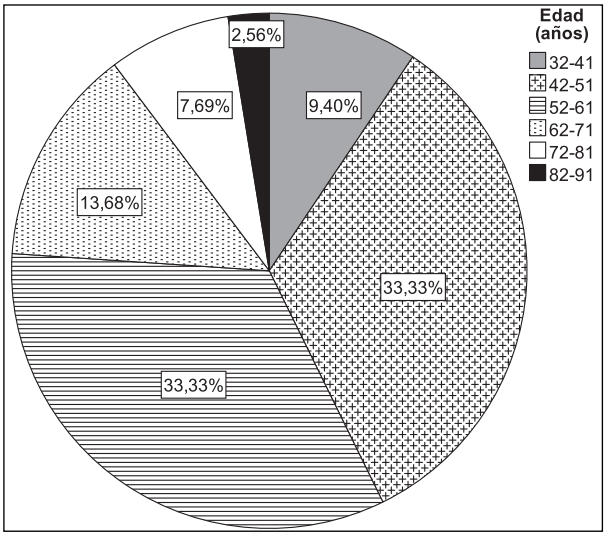

Figure 1. Prevalence of Age of Diagnosis of BCa (Years)

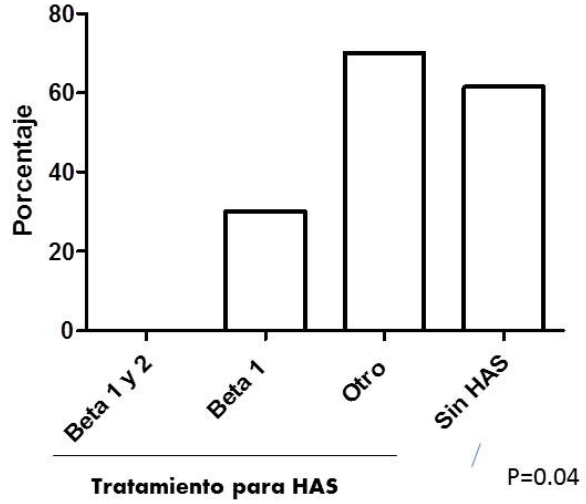

Figure 2. Metastasis in the Different Study Groups

Table 1. Metastasis Relationship with Age of BCa Diagnoses

P=0.04*	Metastasis		Total
	Yes	No	
Age intervals (years)			
32-41	30% (3)	70%(7)	100% (10)
42-51	25.6% (10)	74.4% (29)	100% (39)
52-61	43.2% (16)	56.8% (21)	100% (37)
62-71	0	100% (15)	100% (15)
72-81	11.1% (1)	88.9% (8)	100% (9)
82-91	33.3% (1)	66.7% (2)	100% (3)
Total	27.4% (31)	72.6% (82)	100% (113)

Table 2. Metastasis, Blood Hypertension and Treatment with non Slective (β1 y β2) β-blockers Relation

p=0.05* 62% Statistical Power				Metastasis		Total
				Yes	No	
Blood Hypertension	YES	Treatment with non selective β-blockers	YES	0	5 (26.3%)	5 (17.2%)
			NO	100% (10)	14 (73.7%)	24 (82.8%)
		Total		100% (10)	100% (19)	100% (29)
	NO	Total		16 (100%)	51 (100%)	67 (100%)

Table 3. Metastasis Relation to Different Study Groups and Factor Risk in BCa

	Hypertension + BB (β1 y β2)	Hypertension + BB (β1)	Hypertension + Others	Non Hypertension
Age (years)	58±1.3	54±4.5	47±6.8	56.38±13.9
Smoking	50%	50%	25%	30.8%
Alcoholism	50%	50%	25%	38.5%
Tumor Stage III-IV	0	33.3%	66.7%	60%
HER2+	0	66.7%	12.5%	30.8%
PR+	50%	33.3%	50%	76.9%
ER+	50%	66.7%	62.5%	84.6%
Triple +	0	33.3 %	12.5%	15.4%
Triple -	50%	33.3%	37.5%	7.7%

positive for Estrogen Receptor (ER), and 26.8% were positive for Human Epidermal growth factor Receptor 2 (HER2); the triple positive result (PR+, ER+, HER2+) was found in 13.1%, while the triple negative result (PR-, ER-, HER2-) was found in 22.2%.

The finding of metastasis at diagnosis was 27.8% (n= 115; N= 32). Metastasis was related with age ($p<0.05$), and was observed in 43.2% of patients in the age group comprising 52 to 61 years, followed by the age group corresponding to 32 to 41 years, with 30% of cases. Frequencies are presented in Table 1. In patients aged> 50 years, tumor metastasis was associated with stages III-IV (86.7%; p=0.0001); patients classified in these stages, were at a 23.56 times greater risk for metastasis (95% Confidence Interval 4.3-126.6). This is also associated with Progesterone Receptor positive (PR+) (29.4%: p=0.01), Estrogen Receptor positive (ER+) (35.3%; p= 0.001), and triple subtype negative (35.3%; p=0.04; OR =3.8; 95% CI, 1.0-14.1). It is not associated with the HER2+ marker, the triple positive subtype, smoking, or alcoholism, but these frequencies were 47.1, 17.6, 37.5, and 38%, respectively. It is noteworthy that in this stratum of patients, the finding of metastasis was related with the infiltrating ductal carcinoma histological type in 47.1% of cases. In patients <50 years of age, the discovery of metastasis associated with stages III and IV in 100% of cases (p=0.01) was not significantly related with the HER2+ marker, PR+, ER+, Triple+, Triple-, smoking, and alcoholism ($p>0.05$), but these frequencies were 20, 40, 40, 0, 30, 0 and 10%, respectively. Another finding was that 50% of patients with metastasis were associated with the infiltrating ductal carcinoma histological type. On the other hand, 30.2% of patients had hypertension (n=29; N=96) and only 17.2% (n=5) was treated with BB for β1- and β2-adrenergic receptors, 34% with BB for selective β1- receptors, and 48.7% with other treatments. To perform the analysis, the records of 24 patients were eliminated because these were not complete regarding metastasis, SAH, and treatment. One hundred percent of patients with SAH treated with BB for β1- and β2-adrenergic receptor did not develop metastasis, from a global point of view, while 30% of patients with SAH treated with BB for selective β1-receptors if they presented metastasis and 70% of patients with SAH were treated with other drugs, while 61.5% of patients without SAH were positive for metastasis ($p<0.05$). (Figure 2). Table 2 illustrates the frequencies of the relationship between patients with and without SAH, treatment with and without BB for β1- and β2- adrenergic receptors, and the discovery of metastasis. Table 3 demonstrates the relationship of patients with metastasis with the groups portrayed: SAH + BBβ1 and β2, + BBβ1 SAH, SAH-Others, and No SAH and risk factors for BCa. On average, the patients observed here were older, and highest percentage of smoking and alcohol consumption was observed in the SAH+ BBβ1 and BBβ2 groups, while in comparison with the higher frequency of stages III and IV was localized in the SAH-Others group, while increased frequency of HER2+ receptors was in the SAH+ BBβ1 group, and increased frequency of ER+ was in the group without SAH.

Discussion

Several studies have linked the use of βeta-Blockers (BB) with the reduction of metastasis in different types of solid tumors (Cole and Sood, 2012). In our results, the average age of patients in whom BCa was diagnosed (around 50 years) is similar to that of reports of other studies performed in Mexico and in Latin American countries (Rummel et al., 2012; Keyhani et al., 2013; Justo et al., 2013; Villarreal-Garza et al., 2013; Floriano-Sanchez et al., 2014; Ji et al., 2014; Doval et al., 2015). For these patients, the frequency of smoking and alcohol consumption were 33 and 36.5%, respectively. Several studies indicate that in smoking- stimulated autonomic activation of the nervous system with the release of catecholamines for nerve terminals (Zhang et al., 2011), ductal carcinoma was the most frequent histological type and stage II was the most common diagnosis. These findings were similar to those of other reports (Rummel et al., 2012; Cardenas-Rodriguez et al., 2012; Keyhani et al., 2013; Justo et al., 2013; Petric et al., 2014; Ji et al., 2014). The frequency of ER+ in the current sample of patients with BCa was higher than the frequency reported in other studies as follows: 12.9% lower *vs*. Keyhani et al. (2013) ; 19.7% *vs*. Rummel et al. (2012); 4.7% *vs*. Maschio et al. (2014); 3.9% *vs*. Doval et al. (2015), and 13.7% *vs*. Ji et al. (2014). Meanwhile, the frequency of PR+ presently detected was higher than that reported by several authors (55.5% *vs*. Gates et al., 2012; 8.5% *vs*. Keyhani et al., 2013; and 16.9% *vs*. Ji et al., 2014). Pervaiz et al. (2015) found an association between ER+ and histological grade, while PR+ was associated with this factor and tumor size. Floriano-Sanchez et al. (2014) found a significant relation of ER+ with alcoholism and PR+. HER2/neu was positive in 26.8% of cases studied herein, very similar to that reported by various authors (24.7% higher *vs*. Gates et al., 2012; 21.2% *vs*. Keyhani

et al., 2013; 20.7% *vs*. Doval et al., 2015, and 9.1% *vs*. Ji et al., 2014, which was identified by Fluorescence In Situ Hybridization [FISH]). In Mexico, about 10% of patients with BCa will have metastatic disease; however, depending on the clinical stage at diagnosis, up to 75% of patients have systemic recurrence, according to the findings in this study. Therefore, it is possible that there is a close correlation between clinical stage and the risk for metastasis, in which the percentage reported in other studies is similar to the results obtained in this study, in which stages III-IV are more likely to develop metastasis in patients aged >50 years (Cabrero et al., 2010). Our findings indicate that BB could provide a clinical benefit in breast cancer through inhibition of the prometastatic effects of beta-Adrenergic Receptor (β-AR) signaling on tumor immune responses and the tumor microenvironment. BB have previously been shown to improve Overall Survival (OS) with their cardioprotective effects, and the improvement in cancer suggests a cancer-specific effect (Melhem-Bertrandt, 2011). Several studies in other countries have demonstrated that β2-adrenergic receptor inhibition could significantly suppress the malignant transformation of different cancer types, and this could play a role in the prevention and treatment of metastasis (Quoc Luong, 2012; Wang et al., 2016). We showed that the non-selective β1-/β2-adrenergic receptor BB was related with not finding of metastasis in the moment of diagnosis in Mexican patients with BCa; these results were similar to those reported by General Medical Services Ireland, linked with National Cancer Registry of Ireland patient records, where the study population consisted of all women age 40 years or older with a diagnosis of invasive BCa in stages I-IV, where women who took Propranolol (a non-selective BB) were less prone to tumor stage IV compared with patients not treated with BB. This study concluded that this type of drug inhibited prometastatic effects within a range of 50-100% (Barron et al., 2012). The study of this mechanism is important, because the adrenergic signal is related with the following different biological-biochemical processes in carcinogenesis: metastasis; angiogenesis; immunological response, anoikis inhibition; etc. (Lutgendorf and Sood., 2011). Despite these molecular evidences, clinical studies are scarce, mainly in Mexico.

Our findings are intended to arouse the interest of health personnel who have contact with patients with cancer, in order to assess the possible coadjuvant prescription of these drugs to reduce tumor aggressiveness and metastasis, not only in breast cancer, because these drugs could be effective in all types of tumors.

References

Alanazi I, Khan Z (2016). Understanding EGFR signaling in breast cancer and breast cancer stem cells: overexpression and therapeutic implications. *Asian Pac J Cancer Prev*, **17**, 445-53.

Anaya-Ruiz M, Vallejo-Ruiz V, Flores-Mendoza L, et al (2014). Female breast cancer incidence and mortality in Mexico, 2000-2010. *Asian Pac J Cancer Prev*, **15**, 1477-9.

American Cancer Society. Breast Cancer Facts & Figures 2011 Y 2012. Atlanta: American Cancer Society, Inc; 2013.

Bandala C, Floriano-Sanchez E, Cardenas-Rodriguez N, et al (2012). RNA expression of cytochrome P450 in Mexican women with breast cancer. *Asian Pac J Cancer Prev*, **13**, 2647-53.

Barron TI, Sharp L, Visvanathan K (2012). Beta-adrenergic blocking drugs in breast cancer: a perspective review. *Therapeutic Advances Med Oncol*, **4**, 113-25.

Cabrero A, Picón G, Gisela K, et al (2010). Cancer de mama metastasico: estudio clinico-patológico de 300 casos. *Patologia*, **48**, 18-22.

Cardenas-Rodriguez N, Lara-Padilla E, Bandala C, et al (2012). CYP2W1, CYP4F11 and CYP8A1 polymorphisms and interaction of CYP2W1 genotypes with risk factors in Mexican women with breast cancer. *Asian Pac J Cancer Prev*, **13**, 837-46.

Cole SW, Sood AK (2012). Molecular pathways: beta-adrenergic signaling in cancer. *Clinical Cancer Res*, **18**, 1201-6.

Dey S (2014). Preventing breast cancer in LMICs via screening and/or early detection: The real and the surreal. *World J Clin Oncol*, **5**, 509-19.

Dimitrakopoulos FI, Kottorou A, Antonacopoulou AG, et al (2015). Early-stage breast cancer in the elderly: confronting an old clinical problem. *J Breast Cancer*, **18**, 207-17.

Dirección General de Información en Salud (DGIS). Base de datos de defunciones 1979-2009. Sistema Nacional de Información en Salud (SINAIS).

Doval DC, Sharma A, Sinha R, et al (2015). Immunohistochemical profile of breast cancer patients at a tertiary care hospital in New Delhi, India. *Asian Pac J Cancer Prev*, **16**, 4959-64.

Drell TL, Joseph J, Lang K, et al (2003). Effects of neurotransmitters on the chemokinesis and chemotaxis of MDA-MB-468 human breast carcinoma cells. *Breast Cancer Res Treat*, **80**, 63–70.

Floriano-Sanchez E, Rodriguez NC, Bandala C, et al (2014). CYP3A4 expression in breast cancer and its association with risk factors in Mexican women. *Asian Pac J Cancer Prev*, **15**, 3805-9.

Gates MA, Xu M, Chen WY, et al (2012). Wolpin BM. ABO blood group and breast cancer incidence and survival. *Int J Cancer*, **130**, 2129-37.

Ji Y, Sheng L, Du X, et al (2014). Clinicopathological variables predicting HER-2 gene status in immunohistochemistry-equivocal (2+) invasive breast cancer. *J Thorac Dis*, **6**, 896-904.

Justo N, Wilking N, Jönsson B, et al (2013). A review of breast cancer care and outcomes in Latin America. *Oncol*, **18**, 248-56.

Keyhani E, Muhammadnejad A, Behjati F, et al (2013). Pazhoomand. Angiogenesis markers in breast cancer--potentially useful tools for priority setting of anti-angiogenic agents. *Asian Pac J Cancer Prev*, **14**, 7651-6.

Lutgendorf S, Sood A (2011). Biobehavioral Factors and Cancer Progression: Physiological Pathways and Mechanisms. *Psychosom Med*, **73**, 724-30.

Lyon: International Agency for Research on Cancer; 2013.

Maschio LB, Madallozo BB, Capellasso BA, et al (2014). Immunohistochemical investigation of the angiogenic proteins VEGF, HIF-1α and CD34 in invasive ductal carcinoma of the breast. *Acta Histochem*, **116**, 148-57.

Melhem-Bertrandt A, Chavez-MacGregor M, Lei X, et al (2011). Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. *J Clin Oncol*, **29**, 2645-52.

Pervaiz F, Rehmani S, Majid S, et al (2015). Evaluation of Hormone Receptor Status (ER/PR/HER2-neu) in Breast Cancer in Pakistan. *J Pak Med Assoc*, **65**, 747-52.

Petric M, Martinez S, Acevedo F, et al (2014). Correlation between Ki67 and histological grade in breast cancer patients treated with preoperative chemotherapy. *Asian Pac J Cancer Prev*, **15**, 10277-80.

Quốc Lu'o'ng KV, Nguyễn LT (2012). The roles of beta-adrenergic receptors in tumorigenesis and the possible use of beta-adrenergic blockers for cancer treatment: possible genetic and cell-signaling mechanisms. *Cancer Management Res*, **4**, 431–45.

Rummel S, Shriver CD, Ellsworth RE (2012). Relationships between the ABO blood group SNP rs505922 and breast cancer phenotypes: a genotype-phenotype correlation study. *BMC Med Genet*, **13**, 41.

Sood AK, Bhatty R, Kamat AA, et al (2006). Stress hormone mediated invasion of ovarian cancer cells. *Clin Cancer Res*, **12**, 369–75.

Tang J, Li Z, Lu L, et al (2013). Seminars in Cancer Biology β-Adrenergic system, a backstage manipulator regulating tumour progression and drug target in cancer therapy. *Semin Cancer Biol*, **23**, 533-42.

Tirona MT, Sehgal R, Ballester O (2010). Prevention of breast cancer (part I): Epidemiology, risk factors, and risk assessment tools. *Cancer Invest*, **28**, 743-50.

Villarreal-Garza C, Aguila C, Magallanes-Hoyos MC, et al (2013). Breast cancer in young women in Latin America: an unmet, growing burden. *Oncol*, **18**, 1298-306.

Wang T, Li Y, Lu HL, et al (2016). β-adrenergic receptors: New target in breast cancer. *Asian Pac J Cancer Prev*, **16**, 8031-39.

Yang E, Bane CM, MacCallum RC, et al (2002). Stress-related modulation of matrix metalloproteinase expression. *J Neuroimmunology*, **133**, 144–50.

Zhang D, Ma Q, Wang Z, et al (2011). β2-adrenoceptor blockage induces G1/S phase arrest and apoptosis in pancreatic cancer cells via Ras/Akt/NFκB pathway. *Molecular Cancer*, **10**, 146.