RESEARCH ARTICLE

Hypertension and the Risk of Breast Cancer in Chilean Women: a Case-control Study

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Abstract

Background: Breast cancer is the most common cancer in women worldwide. Although different metabolic factors have been implicated in breast cancer development, the relationship between hypertension and breast cancer has not been elucidated. Aim: To evaluate hypertension as a risk factor for breast cancer in Chilean women of low and middle socio-economic status. Methods: We conducted an age-matched (1:1) case-control study in 3 hospitals in Santiago, Chile. Breast cancer cases (n=170) were histopathologically confirmed. Controls had been classified as Breast Imaging Reporting and Data System I (negative) or II (benign findings) within 6 months of recruitment. Blood pressure was measured using a mercury sphygmomanometer and standardized procedures. We used 2 hypertension cut-off points: blood pressures of ≥140/90 mmHg and ≥130/85 mmHg. Fasting insulin and glucose levels were assessed, and anthropometric, sociodemographic, and behavioral information were collected. Odds ratios and 95% confidence intervals were estimated for the entire sample and restricted to postmenopausal women using multivariable conditional logistic regression models. Results: Hypertension (≥140/90 mmHg) was significantly higher in cases (37.1%) than controls (17.1%) for the entire sample and in postmenopausal pairs (44.0% compared to 23.8%). In crude and adjusted models, hypertensive women had a 4-fold increased risk of breast cancer (adjusted odds ratio: 4.2; 95% confidence interval: 1.8; 9.6) compared to non-hypertensive women in the entire sample. We found a similar association in the postmenopausal group (adjusted odds ratio: 2.8; 95% confidence interval: 1.1; 7.4). A significant effect was also observed when hypertension was defined as blood pressure of ≥130/85 mmHg. Conclusion: A significant association was found between hypertension and breast cancer over the entire sample and when restricted to postmenopausal women. Hypertension is highly prevalent in Latin America and may be a modifiable risk factor for breast cancer; therefore, a small association between hypertension and breast cancer may have broad implications.

Keywords: Breast neoplasms - hypertension - case-control study - postmenopause - risk factors

Asian Pacific J Cancer Prev, **13 (11)**, 5829-5834

Introduction

Breast cancer (BC) is the most common female cancer (excluding non-melanoma skin cancer) in both developed and developing regions, and it accounts for 23% of all female cancers worldwide. The highest incidence rates, which are observed in developed countries with the exception of Japan, are greater than 80 per 100,000; however, in developing regions, the incidence rates are less than 40 per 100,000 women. Differences in mortality rates are less marked between the different regions because of better survival in developed regions, in which the mortality rate ranges from 6-19 per 100,000 women (Porter 2009; Ferlay et al., 2010). Chile, a post-transitional country, is no exception to the burden of BC. In 2008, the estimated age-adjusted incidence (to the World Standard Population) of BC was 40.1 per 100,000 woman-years, and it was the second leading cause of cancer-related deaths with a mortality rate of 11.0 per 100,000 woman-years (Chilean Ministry of Health 2008).

Well-known risk factors for BC risk include family history of BC, reproductive factors, obesity after menopause, physical inactivity, and higher socioeconomic status (Hunter and Willett, 1993; Madigan et al., 1995; Key et al., 2001). In the past few years, extensive efforts have been dedicated to understanding the relationship between obesity-related conditions, such as insulin resistance, type 2 diabetes mellitus, metabolic syndrome, and hypertension (HT), and BC risk (Xue and Michels, 2007; Bjorge et al., 2010; Ronco et al. 2012a; 2012b). Information regarding the relationship between HT, a highly prevalent disease in most countries, and breast cancer risk is scarce and inconsistent (Peeters et al., 2000; Largent et al., 2006; 2007; 2010; Reeves et al., 2012). Inflammation, sexual

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hormones, high body mass index, and inhibition of apoptosis after long exposure to high blood pressure are possible mechanisms that explain the relationship between HT and BC risk (Largent et al., 2006).

Considering that hypertension is highly prevalent in Chile (25% in adult women) (Ministerio, 2010) and that the relationship between HT and BC is not clearly established, the objective of our study is to evaluate the association between HT and BC in pre- and postmenopausal Chilean women of low and middle socio-economic status.

Materials and Methods

Study design

The present study is based on an age matched case-control study conducted in 3 main hospitals at Santiago de Chile during 2005 to determine the relationship between insulin resistance and BC. We will briefly summarize the methodology of the original article, but further details have been published elsewhere (Garmendia et al., 2007).

A case was defined as a female patient with a histopathologically confirmed primary BC tumor (ductal or lobular), who was recruited within 2 months of diagnosis (incident cases). BCs histopathologically confirmed as Paget's disease, cystosarcoma phyllodes, angiosarcoma, and primary lymphoma were excluded from the study (Greene et al., 2006). All prospective cases were identified through hospital databases and were categorized as pre- or postmenopausal BC. There were 195 eligible patients of whom 14 (7.2%) refused to participate and 11 (5.6%) did not attend the appointment. Finally, 170 BC cases, of which 116 were postmenopausal women, were included in the analysis.

Controls were identified from mammography services at each hospital from the same time period that each BC case was recruited for the study. Controls were individually matched by 5-year age intervals and neighborhood residence at a ratio of 1:1. We randomly selected women who met the following eligibility criteria: (i) a screening mammography conducted in the last 6 months prior to recruitment with no evidence of malignancy in the images, i.e., Breast Imaging Reporting and Data System (BI-RADS) I (negative) or II (benign findings) (Balleyguier et al., 2007) and (ii) no personal history of BC.

All cases and controls were invited to an appointment at each corresponding hospital. They underwent a face-to-face interview, blood pressure measurement, anthropometric measures, and an overnight fasting blood sample collection carried out by trained nurses.

Exposure variables

Blood pressure was measured using a mercury sphygmomanometer by nurses who received special training for standardizing blood pressure measurements. The measurement was carried out after 10 minutes of chair rest during which women were sitting with their arm lying on a Table. The measurement was recorded twice at an interval of 5 minutes in order to diminish error. The mean difference between the first and second measurements was 1.7 mmHg (SD±10.6) for systolic pressure and 1.6 mmHg (SD±10.4) for diastolic pressure. We used the average of the first and the second measurements to determine systolic and diastolic pressure. In our analysis, we considered 2 definitions of high blood pressure: 140/90 mmHg or greater, defined by the Joint National Committee (JNC VII) (Chobanian et al., 2003), and 130/85 mmHg or greater, defined by the Third Adult Treatment Panel (ATP III) (National Cholesterol Education Program (NCEP), 2002).

Co-variables

We used a structured questionnaire to acquire information related to sociodemographic status, lifestyle, morbidity, and gyneco-obstetric characteristics. The sociodemographic characteristics investigated included age as a continuous variable and the total number of years of formal education. With regard to lifestyle, we determined alcohol use as weekly consumption (yes/no), years of smoking, fruit and vegetable consumption (by a food frequency questionnaire categorized by quartile; first quartile corresponded to lowest consumption), and physical activity levels (low, moderate, and high levels measured using the International Physical Activity Questionnaire) (Craig et al., 2003). As a morbidity variable, we included type 2 diabetes mellitus defined by self-report of previous diagnosis or treatment or fasting glycemia with a blood glucose level of ≥126 mg/dL. The gyneco-obstetric variables evaluated were self-report of menopausal status, number of full-term pregnancies, use of oral contraceptives at any time (yes/no), use of hormone replacement therapy (HRT) at any time (yes/no), and first relative maternal family history of BC (yes/no).

Weight and height were measured using a calibrated physician's mechanical scale; all women were barefoot and were wearing light clothes at the time of measurement. We calculated body mass index (BMI) as weight in kilograms divided by height in meters squared. Obesity was defined as a BMI of ≥30 kg/m^2 (World Health Organization, 1995).

Overnight fasting blood samples were collected between 8 and 9 am using Vacutainer tubes containing the anticoagulant EDTA. All samples were centrifuged within 2 hours from collection and analyzed at the laboratory of the Clinical Hospital University of Chile. Plasma glucose and insulin levels were measured using the glucose-oxidase method and enzyme-linked immunosorbent assay (ELISA), respectively. We used the Homeostasis Model Assessment Index (HOMA-IR) to define insulin resistance; the cut-off point was 2.5 or greater (Matthews et al., 1985).

Statistical analysis

Descriptive analyses of covariates between cases and controls were compared using a paired t-test or chi-square test.

The selection of possible confounders was assessed using directed acyclic graphs (DAGs) (Greenland et al., 1999; Robins, 2001; Hernan et al., 2002), which are based on scientific knowledge rather than statistical findings. This strategy identified the following as possible confounders in the relationship between high blood

pressure and BC: age, menopause, educational level, fruit and vegetable intake, physical activity, parity, alcohol use, smoking, insulin resistance, diabetes treatment, obesity, use of oral contraceptive, and hormonal therapy replacement. Age and place of residence were controlled using the matching procedure.

We used conditional logistic regression models (with the confounders defined above) to estimate the crude and adjusted odds ratios (ORs) and 95% confidence intervals (95%CIs) between high blood pressure and BC. We repeated the analysis using different outcomes for blood pressure, as defined previously, and by each component of the definition (high systolic blood pressure or high diastolic blood pressure, independently). The analysis was carried out for the entire sample and stratified by menopausal status, because prior studies suggest that different mechanisms are involved in the etiopathogenesis of BC in pre- and postmenopausal women (Xue and Michels, 2007). In this study, we report only the results of the entire sample and those restricted to postmenopausal women, because the premenopausal BC sample was not large enough to detect a sensible effect size. All analyses were performed using Stata 10.0 software.

Ethics

The study was approved by the Ethical Committee Board of the Faculty of Medicine at the Universidad de Chile. All participants signed informed consent prior to participating in the study.

Results

Table 1 summarizes the sociodemographic, gyneco-obstetric, lifestyle, and morbidity characteristics among BC cases and controls. The mean age was 55.1 (SD: 11.5) years in the entire sample and 61.4 years (SD: 8.9) years among postmenopausal women. BC cases had more years of formal education and a lower proportion of HRT use compared to those in the entire sample or among postmenopausal women ($p<0.05$). Obesity was higher in postmenopausal controls than in BC cases, but this difference did not reach statistical significance.

The prevalence of HT, defined as a pressure of 140/90 mmHg or more, was significantly higher in cases (37.1%) than in controls (17.1%) in the entire sample, as well as in postmenopausal pairs (44.0% compared to 23.8%). This association was observed when analysis was restricted to either the systolic blood pressure or diastolic blood pressure components. When a blood pressure of 130/85 mmHg or more was used to define HT, the prevalence of HT increased among cases and controls, but statistical differences among them were similar to those obtained using the previous definition of HT (Figure 1).

In crude and adjusted models, we observed a positive relationship between HT and BC independent of the blood pressure definition used, in the entire sample. Women with HT (with a blood pressure of 140/90 mmHg or more) had a 4-fold increased risk of BC (ORadj: 4.2; 95%CI: 1.8; 9.6) than those without HT in the entire sample. A significant,

Table 1. Descriptive Characteristics of Co-variables in Cases and Controls in the Entire Sample and Restricted to Postmenopausal Women

	All sample					Only Postmenopausal women				
	Cases		Controls			Cases		Controls		
	N	%	N	%	p-value	N	%	N	%	p-value
	170	100	170	100	116	100	116	100		
Sociodemographic characteristics										
Age (years) (mean, SD)	56.5	12.3	55.2	10.4	0.287	62.4	9.7	60.3	8.0	0.064
Total years of formal education (years) (mean, SD)	9.6	4.2	8.5	3.6	0.010	8.7	4.0	7.7	3.4	0.040
Lifestyle										
Alcohol intake once per week or more (n, %)	64	37.7	58	34.1	0.498	47	40.5	41	35.3	0.419
Years of smoking (years) (mean, SD)	13.4	15.5	9.7	13.5		13.1	16.4	9.3	13.0	
Fruit and vegetable intake (n, %)					0.968					0.992
1st quartile	35	20.6	35	20.6		28	24.1	28	24.1	
2nd quartile	45	26.5	43	25.3		30	25.9	29	25.0	
3rd quartile	46	27.1	50	29.4		31	26.7	33	28.5	
4th quartile	44	25.9	42	24.7		27	23.3	26	22.4	
Physical activity (n, %)					0.703					0.157
Low	62	36.5	65	38.2		45	38.8	45	38.8	
Moderate	85	50.0	87	51.2		53	45.7	62	53.5	
High	23	13.5	18	10.6		18	15.5	9	7.8	
Morbidity										
Type 2 Diabetes mellitus (self-report, treatment or glicemia ≥126) (n, %)	22	15.2	15	10.0	0.180	20	20.4	15	14.0	0.225
HOMA-IR >2.5 (n, %)	93	54.7	95	55.9	0.817	71	61.2	65	56.0	0.424
Obesity (BMI ≥30), (n, %)	55	32.4	67	39.4	0.175	38	32.8	51	44.0	0.079
Ginecoobstetrics characteristics										
Menopause (n, %)	122	71.8	116	68.2	0.478					
Ever use of oral contraceptive (n, %)	71	41.8	81	47.7	0.275	41	35.3	50	43.1	0.226
Ever use of hormone replacement therapy (n, %)	41	24.4	60	35.3	0.029	36	31.6	57	49.1	0.007
Number of full-term pregnancies (mean,SD)	2.7	2.1	2.8	1.6	0.709	3	2.4	3	1.7	0.949
Family history of BC (1st relative) (n, %)	37	21.8	33	19.4	0.592	25	21.6	21	18.1	0.510

Table 2. Crude and Adjusted Odds Ratio (OR) and 95% Confidence Intervals (95%CI) of Breast Cancer in Relation to High Blood Pressure (According to JNCVII and ATPIII), Systolic and Diastolic Blood Pressure in the Entire Sample and Restricted to Postmenopausal Women

Blood Pressure	All sample				Only Postmenopausal women			
	OR	95%CI	OR*	95%CI	OR	95%CI	OR**	95%CI
Blood Pressure ≥140/90 (mmHg)[1]	3.13	1.78;5.49	4.18	1.81;9.64	2.71	1.47;5.00	2.84	1.09;7.39
Systolic blood pressure ≥140 (mmHg)[1]	3.58	1.89;6.79	3.24	1.38;7.63	3.09	1.57;6.10	2.44	0.93;6.36
Diastolic blood pressure ≥90 (mmHg)[1]	3.36	1.72;6.59	4.27	1.53;11.87	2.60	1.25;5.39	2.03	0.62;6.65
Blood Pressure ≥130/85 (mmHg)[2]	2.07	1.33;3.22	2.55	1.33;4.89	2.05	1.22;3.45	2.37	1.01;5.55
Systolic blood pressure ≥130 (mmHg)[2]	2.38	1.47;3.83	2.75	1.40;5.41	2.10	1.23;3.58	2.19	0.95;5.06
Diastolic blood pressure ≥85 (mmHg)[2]	2.30	1.41;3.76	2.6	1.28;5.28	2.17	1.24;3.79	2.05	0.85;4.94

*adjusted by alcohol use, fruit and vegetable intake, physical activity, type 2 diabetes, menopause, use of oral contraceptives, use of hormone replacement therapy, obesity, years of formal education, smoking, number of living births. **adjusted by alcohol use, fruit and vegetable intake, physical activity, type 2 diabetes, use of oral contraceptives, use of hormone replacement therapy, obesity, years of formal education, smoking, number of living births. [1]Defined by JNCVII. [2]Defined by ATPIII

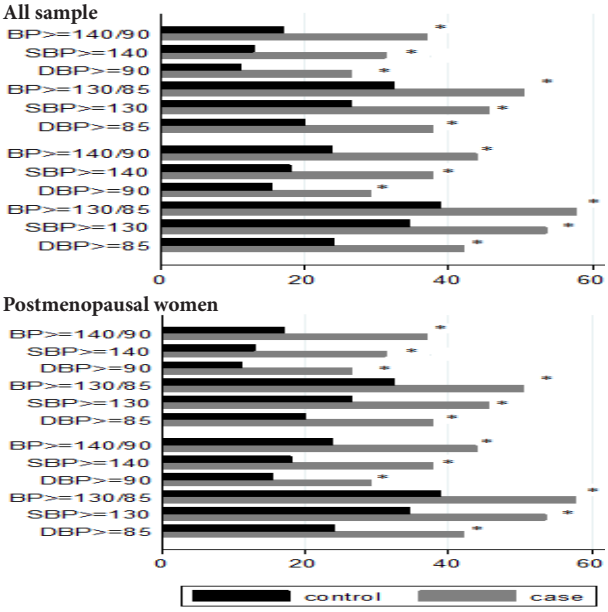

Figure 1. Distribution of High Blood Pressure (BP), Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP) in Cases and Controls in the Entire Sample and Restricted to Postmenopausal Women. *p value <0.05

but smaller, effect was observed if we considered HT as 130/85 mmHg or greater. In both definitions, the effect was similar when systolic and diastolic blood pressures were analyzed independently.

In the group of postmenopausal women, the strength of the association between blood pressure and BC was 2-3 times higher in women with HT than in those without HT, both in crude and adjusted models. Similar to the analysis of the entire sample, the magnitude of the association was larger using the JNC VII definition of HT (Table 2).

Discussion

To the best of our knowledge, this is the first study assessing the relationship between high blood pressure and BC in Latin American post-menopausal women; we discovered a strong association between high blood pressure (defined by JNC VII and ATPIII) and increased risk of BC. Hypertensive women had twice the risk of developing BC compared to non-hypertensive women in our entire sample and among postmenopausal women. The association remained significant when assessing systolic and diastolic blood pressure separately, but only when the entire sample was considered. We were not able to evaluate this association in premenopausal women because of the small number of these cases in our study. However, the strength of the relationship was higher in the entire sample than in postmenopausal women, suggesting a possible effect of HT on premenopausal BC.

The relationship between HT and BC is controversial. Some studies report a weak-to-moderate association between HT and BC in postmenopausal women (Soler et al., 1999; Largent et al., 2006; Kabat et al., 2009; Rosato et al., 2011), but this is not consistent with other studies (Lindgren et al., 2007; Agnoli et al., 2009; Bjorge et al., 2010; Reeves et al., 2012). Some authors suggest that the observed association between HT and BC is confounded by obesity, which is a risk factor for both postmenopausal BC and HT (Franceschi et al., 1990; La Vecchia et al., 1997). A cohort study of 20,555 women followed for up to 20 years showed a small effect between HT and BC, which was non-significant after adjusting for BMI (Peeters et al., 2000). However, 2 case control studies found a 20% increased risk of BC in postmenopausal women with HT after controlling for BMI (Soler et al., 1999; Rosato et al., 2011). Furthermore, a large cohort study of approximately 5,000 postmenopausal women supported this positive association after adjusting for BMI, albeit only when considering high diastolic blood pressure (Kabat et al., 2009). In our study, obesity was not related to BC because our controls had a higher BMI than the BC cases; therefore, we found a strong relationship between HT and BC after controlling for obesity.

Multiple authors have questioned whether HT, per se, is a risk factor for the genesis of BC; it has been proposed that anti-HT drugs used for HT treatment may play a role in BC development (Mackenzie et al., 2012). A prospective follow-up of 73,742 patients (self-reported data) showed that long-term use of any anti-HT drug for more than 5 years resulted in a small increase in BC risk (Largent et al., 2010). This association has been found in women whose anti-HT drugs include diuretics, and a possible pathway for BC development might be an increase in insulin resistance (Li et al., 2003; Largent et al., 2006). However, in a cohort study with a mean

follow-up of 27 years, only a small effect was found in women who had high diastolic blood pressure and were not using anti-HT drugs at baseline (Lindgren et al., 2007). In addition, pooled analysis of 5 case-control studies did not find an association between anti-HT drugs and BC risk (Grossman et al., 2002). Therefore, there is not enough evidence to conclude whether HT or the drugs used for the treatment of HT are responsible for the small increased risk. In our study, we were not able to assess the influence of anti-HT drugs on BC risk for several reasons. First, a misclassification error may occur if a patient's HT was controlled by treatment; thus, a patient could be classified incorrectly as normal. However, this error should be non-differential between BC cases and controls, because we used incident cases; BC cases and controls had the same opportunity to receive treatment at primary health units. Second, according to the National Health Survey, only 25% of women with HT receiving treatment in Chile achieve normal blood pressure levels with anti-HT drugs (Ministerio, 2010). Finally, our statistical models were adjusted for insulin resistance, controlling the possible effect of diuretics on BC risk.

Different mechanisms have been proposed for the relationship between HT and BC. First, high blood pressure itself provides an environment for developing BC; this is mediated by the inhibition of apoptosis after long-term exposure to HT (Hamet, 1997). Alternatively, BC and HT share a common pathophysiological pathway mediated by adipose tissue (Largent, McEligot et al. 2006); women with more adipose tissue are more likely to be in a state of chronic inflammation, which increases the risk of both BC (Balkwill et al., 2005) and HT (Li et al., 2005). Furthermore, steroid hormones such as estradiol are involved in the genesis of BC and may protect against HT (Dubey et al., 2002). Finally, as previously discussed, the association may be confounded by BMI and diabetes; HT is associated with higher levels of insulin and insulin growth factors (Giovannucci, 1995), which stimulate cell proliferation, thereby increasing the risk of mutagenesis (Toniolo et al., 2000; Muti et al., 2002).

The objective and standardized measuring of blood pressure carried out by trained personnel is a major strength of our study. Most case-control studies use self-reported HT data, which can be affected by recall bias. Moreover, we used incident cases of BC confirmed by histopathology, suggesting that HT preceded the onset of BC. We were also able to guarantee that controls were free of disease at the time of recruitment, because the inclusion criteria required a normal mammogram within 6 months. Controlling for potential metabolic confounders, such as insulin resistance and obesity, is another strength of our study.

Our study also has several limitations. First, as mentioned, we did not record data pertaining to anti-HT drug use and the time from HT diagnosis. Second, some of our confounding variables (for example, fruit and vegetable intake and physical activity levels) were self-reported data, which are subject to response bias. Finally, we did not have a large enough sample size to observe a relationship between HT and BC in premenopausal women.

We conclude that HT is significantly associated with BC for women living in a post-transitional country. However, further studies are needed to confirm this relationship independently in pre- and postmenopausal women. HT is highly prevalent in Latin America and may be a modifiable risk factor for BC; therefore, even a small effect between HT and BC could have extensive, population-wide implications.

Acknowledgements

This work was supported by National Commission for Scientific and Technological Research (CONICYT), Chile Government, Grant FONISSAO4I2119.

We would like to thank study participants for being generous with their time, and interviewers for their dedication to study. We also thank staff at 3 participant hospitals, San Juan de Dios, San Borja Arriaran, and Oriente Dr. Luis Tisne of Ministerio de Salud (Chile) for their contribution to this research.

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