
Hypertension and Breast Cancer Risk in Chile - a Case-control Study

Ana Pereira¹², Maria Luisa Garmendia¹²*, Maria Elena Alvarado¹, Cecilia Albala²

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.

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

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 5 to 14 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
Ana Pereira et al. 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.

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).

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.

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Exposure variables

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

<table>
<thead>
<tr>
<th></th>
<th>All sample</th>
<th>p-value</th>
<th>Only Postmenopausal Women</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N  %</td>
<td>N  %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sociodemographic characteristics</td>
<td>170 100</td>
<td>170 100</td>
<td>116</td>
<td>100 116</td>
</tr>
<tr>
<td>Age (years) (mean, SD)</td>
<td>56.5 12.3</td>
<td>55.2 10.4</td>
<td>0.287</td>
<td>62.4 9.7</td>
</tr>
<tr>
<td>Total years of formal education (years) (mean, SD)</td>
<td>9.6 4.2</td>
<td>8.5 3.6</td>
<td>0.010</td>
<td>8.7 4.0</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>Alcohol intake once per week or more (n, %)</td>
<td>64 37.7</td>
<td>58 34.1</td>
<td>0.498</td>
</tr>
<tr>
<td></td>
<td>Years of smoking (years) (mean, SD)</td>
<td>13.4 15.5</td>
<td>9.7 13.5</td>
<td>0.968</td>
</tr>
<tr>
<td></td>
<td>Fruit and vegetable intake (n, %)</td>
<td>35 20.6</td>
<td>35 20.6</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>1st quartile</td>
<td>45 26.5</td>
<td>43 25.3</td>
<td>0.259</td>
</tr>
<tr>
<td></td>
<td>2nd quartile</td>
<td>46 27.1</td>
<td>50 29.4</td>
<td>0.316</td>
</tr>
<tr>
<td></td>
<td>3rd quartile</td>
<td>44 25.9</td>
<td>42 24.7</td>
<td>0.273</td>
</tr>
<tr>
<td></td>
<td>4th quartile</td>
<td>62 36.5</td>
<td>65 38.2</td>
<td>0.703</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>85 50.0</td>
<td>87 51.2</td>
<td>0.533</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>23 13.5</td>
<td>18 10.6</td>
<td>0.180</td>
</tr>
<tr>
<td>Morbidity</td>
<td>Type 2 Diabetes mellitus (self-report, treatment or glagemia ≥126) (n, %)</td>
<td>22 15.2</td>
<td>15 10.0</td>
<td>0.180</td>
</tr>
<tr>
<td></td>
<td>HOMA-IR &gt;2.5 (n, %)</td>
<td>93 54.7</td>
<td>95 55.9</td>
<td>0.817</td>
</tr>
<tr>
<td></td>
<td>Obesity (BMI ≥30), (n, %)</td>
<td>55 32.4</td>
<td>67 39.4</td>
<td>0.175</td>
</tr>
<tr>
<td>Gynecobstetrics characteristics</td>
<td>Menopause (n, %)</td>
<td>122 71.8</td>
<td>116 68.2</td>
<td>0.478</td>
</tr>
<tr>
<td></td>
<td>Ever use of oral contraceptive (n, %)</td>
<td>71 41.8</td>
<td>81 47.7</td>
<td>0.275</td>
</tr>
<tr>
<td></td>
<td>Ever use of hormone replacement therapy (n, %)</td>
<td>41 24.4</td>
<td>60 35.3</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>Number of full-term pregnancies (mean,SD)</td>
<td>2.7 2.1</td>
<td>2.8 1.6</td>
<td>0.709</td>
</tr>
<tr>
<td></td>
<td>Family history of BC (1st relative) (n, %)</td>
<td>37 21.8</td>
<td>33 19.4</td>
<td>0.592</td>
</tr>
</tbody>
</table>

**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, gynecobstetric, 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 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

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>All sample</th>
<th>Only Postmenopausal women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Blood Pressure ≥140/90 (mmHg)</td>
<td>3.13</td>
<td>1.78;5.49</td>
</tr>
<tr>
<td>Systolic blood pressure ≥140 (mmHg)</td>
<td>3.58</td>
<td>1.89;6.79</td>
</tr>
<tr>
<td>Diastolic blood pressure ≥90 (mmHg)</td>
<td>3.36</td>
<td>1.72;6.59</td>
</tr>
<tr>
<td>Blood Pressure ≥130/85 (mmHg)</td>
<td>2.07</td>
<td>1.33;3.22</td>
</tr>
<tr>
<td>Systolic blood pressure ≥130 (mmHg)</td>
<td>2.38</td>
<td>1.47;3.83</td>
</tr>
<tr>
<td>Diastolic blood pressure ≥85 (mmHg)</td>
<td>2.30</td>
<td>1.41;3.76</td>
</tr>
</tbody>
</table>

*p value <0.05

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, McEliot 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 (Toniole 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.

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References


