Title: Prevalence of known risk factors in uruguayan women treated for breast cancer at a University Hospital.

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Abstract

**Purpose:** In Uruguay, breast cancer has the highest incidence and mortality related to cancer in women. The knowledge of the distribution of risk factors related to disease development supports the implementation of prevention strategies in routine clinical practice. This study aimed to determine the epidemiological profile for breast cancer and the frequency of mammographic surveillance in the surveyed population.

**Material and Methods:** A survey was conducted among Uruguayan women diagnosed with breast cancer who were assisted in the Mastology Unit of the Oncology Service of the Hospital de Clínicas from September 1, 2018 to March 1, 2020.

**Results:** This study included 398 respondents, with a median age at diagnosis of 61 years (34–86 years). A total of 310 respondents (78%) had one or more risk factors. Most women aged over 50 years (264 out of a total of 338 [78.1%]) underwent mammographic surveillance at least biannually.

**Conclusions:** Consistent with international reports, most respondents had a risk factor. Among the group of respondents aged over 50 years, most underwent mammographic and clinical surveillance at least biannually. Although it is only possible to formulate conclusions about the surveyed women because of the study design , the obtained data further our understanding of the epidemiological profile of the Uruguayan population, which can contribute to prevention practices.

**Introduction:**

Cancer is an important epidemiological issue in Uruguay. Considering both sexes, cancer is the second cause of death, after cardiovascular diseases, and accounts for almost a quarter (24.6%) of all deaths registered in the country per year. Almost 16,179 new cases are registered per year, and more than 7,995 Uruguayans die of the disease (1,2).

As observed worldwide, breast cancer (BC) is the most frequent cancer diagnosed among women in Uruguay and the main cause of cancer-related deaths. Approximately 1,926 new cases are registered each year, and approximately 670 women die from this disease. In Uruguay, 1 in 11 women will develop BC over the course of a lifetime. The median age of the patients diagnosed with their first invasive BC in 2012–2016 was 63 years (51–74 years). Most patients (69.5%) are diagnosed at an early stage, which reinforces the importance of secondary prevention for this pathology (3,4).

There has been a decrease in the mortality rate of this disease in recent years, which could be associated with an increase in early detection, improved treatments, and integration of interdisciplinary teams for this pathology (2), but BC continues to represent a great burden, both socially and economically, due to its impact on the affected person and their environment. The economic burden of BC for the society is defined by direct and indirect costs. The direct costs are those related to medical care, and the indirect costs include absenteeism from work, disability, and widows’ and orphan’s pensions. Hence, it is important to develop policies and programs for the prevention and control of such diseases.

The primary prevention of BC is focused on adjusting the risk factors that are subject to change and promoting the protective factors. As with most cancers, the etiology of BC is unknown, but several risk factors have been implicated in its genesis. These can be classified as modifiable and non-modifiable (Table 1). Determining the distribution of risk factors is essential for implementing health promotion interventions in the community to promote the well-being and health of women.

The Clinical Practice Guidelines for Early Detection of Breast Cancer of the Ministry of Public Health (*Ministerio de Salud Pública* [MSP]) has recommended that systematic mammography screening should be performed every 2 years for women aged 50–69 years, an age range in which the benefit of mammography screening is greater and the risks are lower (overdiagnosis, false positives). The potential benefits and risks of conducting this study should be individualized and analyzed in women aged 40–49 years and 70–74 years.

This study aimed to determine the epidemiological profile of BC and the frequency of clinical and mammographic surveillance of patients diagnosed and treated for BC in the Mastology Teaching Unit (*Unidad Docente Asistencial de Mastología* [UDAM]) of the Oncology Service of the *Hospital de Clínicas*.

Material and methods

This was an observational and prospective study that included patients aged over 18 years who were diagnosed with BC and were assisted at the UDAM of the Oncology Service of the *Hospital de Clínicas* from September 1, 2018 to March 1, 2020. All patients signed an informed consent form and authorized the use of the information in this study.

This survey was designed *ad hoc* to investigate the main risk factors for developing the disease, the level of education, and the completion of the breast examination and mammography screening in a comprehensible manner (Annex 1). It comprised 15 closed, dichotomous, or multiple-choice questions. These were designed to determine the prevalence of the main risk factors for BC, the level of education, the smoking habits, and the frequency with which the breast examination and mammography screening are performed.

The included variables were as follows: age at diagnosis, anthropometric measurements (height and weight at puberty, at diagnosis, and at present), family history of BC, personal history of proliferative breast diseases, high breast density, hormonal factors, alcohol consumption, and physical exercise.

The anthropometric data were based on the patients’ reports on weight at diagnosis, at present, and at puberty, and whether the weight variation was greater than 10% (between puberty and diagnosis) was considered. The weight and height data were used to determine the body mass index (BMI), and the World Health Organization classification was used, which considers the following: normal BMI, 20 to 24.99 kg/m2; overweight, 25 to 29.9 kg/m2; and obesity, 30 kg/m2 or more (5) .

Since there were no previous values, the sample size was calculated to estimate a ratio assuming an inaccuracy of 0.05 and an expected ratio of 0.5, which resulted in the requirement of including 384 patients.

The data were collected, analyzed, and compared with the available Uruguayan data.

The proposed study was conducted in accordance with the international ethical standards for biomedical research, “MERCOSUR rules for clinical trial regulations” and the “Declaration of Helsinki,” and with the research regulations approved by the National Ethics Committee in 2019.

Results

The study included 398 respondents. The median age of the respondents at diagnosis was 61 years (34–86 years). At the time of diagnosis, 28.6% (95% confidence interval [CI] 24.1%–33.0%, 114 patients) were aged 50–59 years and 56.3% (95% CI 51.4%–61.2%, 224 patients) were aged 60 years old or older. Most respondents (356 patients [89.4%], 95% CI 86.4%–92.4%) were postmenopausal. The rest of the data is shown in Table 2.

Regarding the level of education, most patients completed primary education: 116 (29.1%, 95% CI 24.6%–33.5%) completed primary education, 102 (25.6%, 95% CI 21.3%–29.9%) started secondary education, and 24 (6%, 95% CI 3.7%–8.3%) attended tertiary education. The rest of the data are shown in Table 2.

A total of 310 respondents (78%, 95% CI 73.8%–82%) had one or more risk factors for BC. Of these, 175 (45%, 95% CI 40.1%–49.9%) had only one risk factor, 75 (18.8%, 95% CI 14.96%–22.64%) had two risk factors, and only 56 (14.2%, 95% CI 10.7%–17.5%) had three or more risk factors. The distribution of the risk factors is shown in Figure 1.

A total of 360 (93%, 95% CI 90.5%–95.5%) respondents had children: 312 (84.3%, 95% CI 80.6%–88.01%) had children before the age of 30 years, and most (254 patients [63.8%], 95% CI 59.0%–68.52%) breastfed for more than 6 months.

A total of 136 respondents (34.7%, 95% CI 29.5%–38.9%) had a family history of BC: 90 (22.6%, 95% CI 18.5%–26.7%) had at least one affected first-degree relative, 60 (15%, 95% CI 11.6%–18.6%) had at least one affected second-degree relative, 45 (10%, 95% CI 7.1%–13%) had two or more affected relatives, and 34 (8.5%, 95% CI 5.8%–11.2%) had two or more affected relatives with one being a first-degree relative. Of the 136 respondents with a family history of BC, 24 had a family member diagnosed with BC before the age of 50 years, and 12 had a family member diagnosed before the age of 45 years.

Among the postmenopausal respondents, 320 (80.4%, 95% CI 76.5%–84.3%) went through menopause at the age of 45–55 years, 18 (4.5%, 95% CI 2.5%–6.5%) had a late menopause (after the age of 55 years), and 59 (14.8%, 95% CI 11.3%–18.3%) had an early menopause (before the age of 45 years). Most respondents (374 [94%], 95% CI 91.7%–96.3%) did not receive hormone replacement therapy (HRT). Of the 20 respondents who received HRT, 12 received combined HRT for 3 years, 6 with progestogens for 3 years, and no data were available for 2 respondents.

Regarding the risk factors related to lifestyle, the mean BMI at the time of diagnosis was 28.2 kg/m2. Moreover, 126 patients (31.7%, 95% CI 27.1%–36.3%) were overweight (BMI, 25–29.9), 132 (33.2%, 95% CI 28.6%–37.8%) were obese (BMI ≥30), and 140 (35.2%, 30.5%–39.9%) had a normal weight (BMI ≤25). Most patients (286 [71.9%], 95% CI 67.5%–76.3%) had a weight gain of more than 10% since puberty at the time of diagnosis.

A total of 306 respondents (76.9%, 95% CI 72.8%–81.0%) exercised regularly: most (234 [58.8%], 95% CI 54.0%–63.6%) walked for at least 30 minutes thrice a week, and the other respondents performed other types of exercise (28, bicycle riding; 14, yoga; 4, tai chi; 8, performed exercise using several machines; 6, gymnastics; 4, swimming; and 4, Pilates exercise). The rest of the respondents (23.1%, 95% CI 19.0%–27.2%) were sedentary.

More than half of the respondents (296 [74.4%], 95% CI 70.1%–78.7%) did not consume alcohol. Of the total of alcohol consumers, 56 (54.9%, 95% CI 45.2%–64.6%) consumed less than three drinks per week.

Regarding smoking, most respondents (258 [64.8%], 95% CI 60.1%–69.5%) did not smoke, 96 (24.1%, 95% CI 20.0%–28.3%) were former smokers, and 44 (11%, 95% CI 8.0%–14.2%) were smokers.

Of the 338 patients aged over 50 years at diagnosis, 264 (78.4%, 95% CI 74.0%–82.8%) underwent mammographic and clinical surveillance at least biannually; the rest did not undergo mammographic surveillance or breast examination on a regular basis. Of the 268 postmenopausal respondents who underwent mammographic surveillance, 88 (32.8%, 95% CI 27.2%–38.4%) had high-density breasts, and 24 of these (8.9%, 95% CI 5.6%–12.4%) underwent a breast biopsy.

Discussion

The etiology of BC is unknown, although several studies have investigated the risk factors that can predict and quantify the risk of developing the disease. However, BC is sporadic most of the time, and it is not possible to identify the risk factors other than sex and age.

BC was diagnosed after the age of 50 years in 84.9% of our patients, with a median age at diagnosis of 61 years, which is consistent with national (4) and international reports (6).

Of the 398 respondents, 310 (78%) had one or more risk factors for BC, which is higher than the frequency of 43% according to the National Breast Cancer Program (*Programa Nacional de Cáncer de Mama*) (7) and of 48% according to our team (8). This can be explained by the fact that these studies included healthy patients, whereas our study included patients with BC.

Moreover, our results are similar to those reported in a study by Hines *et al*. that found that 62%–75% of non-Hispanic patients diagnosed with BC had at least one risk factor for the development of the disease (9).

Of all respondents, 136 (34.7%) had a family history of BC, and 90 (22.6%) had an affected first-degree relative. This value is higher than that of international reports, with values ranging from 15% to 25% (9,10). However, only 24 respondents had a family member diagnosed with BC before the age of 50 years and 12 before the age of 45 years. These results suggest that family history could play an important role in the development of BC in our population, although a control group would be required to confirm it. This can be due, at least in part, to the association between the family history of BC, and the risk of BC is attributable not only to hereditary genetic factors but also to other factors, such as environmental and shared lifestyle, or a combination of both.

Regarding protective factors, most respondents (306, 76.6%) practiced physical exercise, and only 23.4% were sedentary. Although the populations are different, this result is similar to that found in the First National Survey for Risk Factors for Chronic Non-Communicable Diseases (CNCD), with 22.8% of sedentary females aged 25–64 years and 28% of females aged 55–64 years (11).

Although childbirth before the age of 30 years and lactation are considered protective factors in the genesis of BC, most respondents had children before the age of 30 years (312, 86.6% of this subgroup), and most (254 patients, 70.5%) breastfed for more than 6 months.

A total of 102 (25.7%) consumed alcohol, which is lower than the 37.4% reported in the first CNCD, and most of those who consumed alcohol (56, 54.9%) did it less than three times a week.

Although it is difficult to analyze the association between smoking and the development of BC, since up to 50% of female smokers consume alcohol, several studies suggest that there is a higher risk of developing BC in the smoking population (12), and this was, therefore, included in the investigated risk factors. Only 44 respondents (11.1%) were smokers, which is lower than the 25.4% reported in the second CNCD. However, it should be noted that 96 respondents (24.1%) were former smokers, which could reflect the impact of the implementation of an important set of actions by the state, adapting the measures proposed by the framework convention on tobacco control.

The association between a high BMI and the risk of developing BC in postmenopausal women is also known (13). In our study, 126 respondents (31.7%) were classified as overweight (BMI, 25–29.9) and 132 (33.2%) as obese (BMI ≥30). These results are similar to those reported by the second CNCD, with values of 32.7% and 29.2% (15), respectively. Since overweight and obesity were the most frequent risk factors and considering that overweight, obesity, and nutrition-related diseases (cardiovascular, metabolic, mental health, and osteoarticular diseases) are the causes of the main risk factors that affect the morbidity and mortality in our country, the education of postmenopausal patients would be of great importance, both to those diagnosed with BC and those healthy, to maintain a normal body weight as a preventive measure.

Our results show that some of the risk factors found in Uruguay are similar to those found in developed countries, which is most likely associated with factors inherent to the western lifestyle. In particular, this involves demographic factors (the risk of experiencing cancer in general, and CM in particular, is associated with age) and overweight and obesity.

Regarding the level of education, it could be related to the accessibility of the patients to the available information on the early detection and timely treatment of BC. In this context, most of the included patients (320, 80.4%) had completed primary education and at least started secondary education, and most of the respondents aged over 50 years underwent mammographic and clinical surveillance at least biannually (264 patients, 78.1% of this subgroup). Such a relatively high percentage probably reflects not only the level of education but also that of the prevention campaigns performed by the Honorary Commission for the Fight Against Cancer (*Comisión Honoraria de Lucha Contra el Cáncer* [CHLC]) and the MSP. Therefore, the continuation of BC early detection programs should be considered a priority.

This explains that most patients were diagnosed with BC following screening mammography (258 patients, 76.3%) or medical examination (56 patients, 16.5%) and only 24 patients (6%) following breast self-examination.

Among the strengths of this study, the number of included patients, the incorporation of all age groups, and the assessment of modifiable and non-modifiable risk factors are considered worth noting.

However, when interpreting the obtained results, it should be kept in mind that the survey was performed on patients assisted at the UDAM of the Oncology Service of the *Hospital de Clínicas*, which could have introduced biases and, consequently, limit the possibility of extrapolating the results to the general population. Therefore, further studies on risk and protective factors for BC in a larger population, including patients assisted in private institutions and from the interior of the country, are required.

Conclusions

Although it is only possible to formulate conclusions about the women included in the survey due to the characteristics of the study, the collected data allow us to better understand the epidemiological profile of the Uruguayan population, which can contribute to prevention practices. According to international reports, most respondents had a risk factor other than sex to develop the disease. The percentage of respondents with a family history was higher than that found internationally. Most respondents aged over 50 years underwent mammographic and clinical surveillance at least biannually. This undoubtedly reflects the impact of the prevention campaigns performed by the CHLC and MSP.

Acknowledgment We thank all our patients who agreed to respond to our survey and oncology residents who helped distributing the surveys.

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