RESEARCH ARTICLE

# Risk Factors for Breast Cancer in Postmenopausal Women in Brazil

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## Abstract

**Purpose: To analyze risk factors for postmenopausal breast cancer. Methods: The present case-control study included 600 women treated at a cancer center reference hospital in a municipality in the South of Brazil. Results: Totals of 100 patients and 500 control subjects were evaluated. The mean age of the women was 52.5 ± 11.9 years; the average was 57.4 ± 11.8 years, and the average age of the control subjects was 51.5 ± 11.7 years. The risk factors for breast cancer that were considered included an age ≥ 40 years, postmenopausal status, a body mass index (BMI) ≥ 30 kg/m$^2$, and reduced physical activity. Variables like postmenopausal status and an obese BMI were associated with cases of breast cancer. Women who were postmenopausal or obese were 3.80 or 1.80 times more likely to develop breast cancer, respectively, and physically inactive women were 1.72 times more likely to develop breast cancer. Conclusions: Obesity and postmenopausal status are associated with the occurrence of breast cancer in this population. Being over 40 years of age was also a statistically significant factor for postmenopausal women.**

**Keywords:** Breast cancer - case-control study - reproductive factors - risk factors - obesity - overweight

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## Introduction

Breast cancer is the second most common cancer worldwide and the fifth leading cause of cancer-related deaths overall (WHO, 2012). In the United States, breast cancer has the highest mortality rate among cancers in women, with 122 deaths per 100.000 women, and the second highest incidence, with 21.5 cases per 100.000 women, according to the latest statistics available from 2011 (U.S. Cancer Statistics Working Group, 2014). Among women, breast cancer is the most common type of cancer worldwide, accounting for 25% of new cases diagnosed in 2012, and the second cause of cancer death in more developed regions (WHO, 2012).

In Latin America, breast cancer is the most common type of cancer in women (Ferlay et al., 2010; Forouzanfar et al., 2011), and mortality rates for this disease are higher than in developing countries, even though morbidity rates are lower (Jemal et al., 2011; Siegel et al., 2012), indicating that there are still many gaps in the epidemiology of this disease (Amadou et al., 2014). Several risk factors have previously been identified and described in the literature.

In Brazil, projections for 2014 and 2015 estimate that there will be 57.120 new breast cancer cases, with a risk of occurrence of 56.09 cases per 100,000 women (Brazil, 2014). This high prevalence has been attributed to both reproductive and hormonal factors, including age at menarche, age at first birth, number of pregnancies, menopausal status, hormone replacement therapy, and use of oral contraceptives (Ferlay et al., 2010).

According to the Brazilian Ministry of Health, the main risk factors for breast cancer are linked to age, genetics, and endocrine factors. These factors primarily include a family history of breast cancer, early menarche, late menopause, an age at first birth of greater than 30 years, nulliparity, the use of hormonal contraceptives, the use of hormone replacement therapy (HRT) to treat the effects of menopause, exposure to ionizing radiation under 40 years of age, genetic susceptibility, obesity (especially after menopause), and alcohol consumption (Brazil, 2013).

Although some Brazilian studies have been conducted, much controversy still exists regarding the etiology of breast cancer because the early identification of risk factors can increase the chances of detection and expand the treatment possibilities, resulting in better survival rates (Anjos et al., 2012). The risk factors, however, are still quite complex and often contradictory, but determining their identity is crucial because it helps to identify population groups who are more prone to the disease and directly address these cases, seeking to avoid/reduce the

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morbidity and mortality.

Thus, the objective of this study was to analyze the risk factors for breast cancer associated with menopause.

## Materials and Methods

A case-control study was conducted that included 600 women treated at a cancer center reference hospital in a Brazilian municipality in the Central North mesoregion of Parana state, Brazil. Data were collected from October 2013 through October 2014. Women with a histologically confirmed diagnosis of breast cancer discovered within six months from the time of the interview were evaluated as potential cases. For the control group, women who visited the hospital for routine breast exams during the same period were randomly selected. The study excluded women who had a breast cancer recurrence, had any history of cancer, or were diagnosed more than six months prior to the date of the interview.

The cases were collected by identifying patients diagnosed with breast cancer who were undergoing treatment during the selected study period (October 2013 to October 2014), totaling 100 women. Five control subjects were included for each case, resulting in a total of 500 control subjects. Structured questionnaires were administered after informed consent was obtained. The study was approved by the Standing Committee on Ethics in Human Research of the State University of Maringa [Universidade Estadual de Maringa] (Opinion no. 353.649).

The following sociodemographic variables were evaluated in the study: educational level (none, <8 years, and ≥8 years of education); marital status (single, married/stable, and widowed/divorced); and color/race (white, black, mixed, or Asian). The following variables considered risk factors for breast cancer were also evaluated: age (<40 or ≥40 years); age at menarche (<14 years or ≥14 years); parity (≤ 3 or >3 pregnancies); age at first birth (<21 or ≥21 years); breastfeeding history (<12 or ≥12 months); abortion history (yes or no); menopause (pre- or postmenopausal), where postmenopausal women were considered those naturally undergoing menopause or who underwent a total hysterectomy; age at menopause (<50 or ≥50 years); hormone replacement therapy and contraceptive use in the past (yes or no); family history of breast cancer (first-, second-, and third-degree relatives); pre-diagnosis weight (self-reported weight during the last six months prior to diagnosis) or current weight for the control subjects; and height. The body mass index (BMI) was calculated using the following formula: weight (kg)/ height (m)2. The values were classified according to World Health Organization criteria (WHO, 2013), stratified for a BMI <30.0 kg/m$^2$ or ≥30.0 kg/m$^2$ (obesity).

Physical activity followed the American guidelines for physical activity (US Department of Health And Human Services, 2008), which consider at least 150 minutes of physical activity of moderate intensity or 75 minutes of vigorous aerobic physical activity in a week to have beneficial health effects for adults; women were considered to be active when they met this requirement and inactive when they did not.

For the statistical analyses, the data were tabulated using descriptive analysis (mean and standard deviation), and a crude analysis using the crude odds ratio (OR) was performed. The chi-square test and Fisher's exact test were used, when applicable, to determine whether an association existed between the variables and cases of breast cancer. In the next step, variables were selected that had a descriptive level of significance of less than 0.20 for multivariate analysis and logistic regression to examine the relationship between independent variables and the outcome variable. These analyses were performed using Statistica 7.1, and a 5% level of significance was used.

## Results

The analysis included 100 (16.7%) case patients and 500 (83.3%) control subjects. The mean age of the women was 52.53 ± 11.94 years; the case patients had an average age of 57.44 ± 11.80 years, and the control subjects had an average age of 51.54 ± 11.74 years (<0.001) (descriptive data).

The sociodemographic characteristics of women indicated that 80.8% were white, and 46.0% had ≥ 8 years of formal education. Regarding the marital status, 69.2% were married or had a stable union. There were no significant differences between the case and control subjects (Table 1).

The characteristics that were considered risk factors for breast cancer included an age ≥ 40 years, postmenopausal status, a BMI ≥ 30 kg/m$^2$, and physical inactivity (Table 2).

In the logistic regression analysis, the variables

**Table 1. Distribution of Breast Cancer and Control Subjects According to the Sociodemographic Variables**

| Variable | Case | Control | Odds ratio | p |
|---|---|---|---|---|
| | n (%) | n (%) | (CI) | |
| Educational level (years of study) | | | | |
| None | 9 (16.4) | 46 (83.6) | 1.00 (0.42-2.32) | 0.99 |
| < 8 | 46 (17.1) | 223 (82.9) | 1.06 (0.66-1.70) | 0.80 |
| ≥ 8 | 45 (16.3) | 231 (83.7) | 1.00 | |
| Marital status | | | | |
| Single | 10 (24.4) | 31 (75.6) | 1.80 (0.78-4.07) | 0.12 |
| Married/Stable union | 63 (15.2) | 352 (84.8) | 1.00 | |
| Widowed/ divorced | 27 (18.8) | 117 (81.3) | 1.29 (0.76-2.18) | 0.31 |
| Color/Race | | | | |
| White | 81 (16.7) | 404 (83.3) | 1.00 | |
| Black | 5 (19.2) | 21 (80.8) | 1.19 (0.38-3.46) | 0.78 |
| Mixed | 13 (14.9) | 74 (85.1) | 0.88 (0.44-1.72) | 0.68 |
| Asian | 1 (50.0) | 1 (50.0) | 4.99 (0.01-89.38) | 0.30* |

*Fisher's exact test

**Table 2. Bivariate Analysis of Breast Cancer and Control Patients According to the Risk Factors Assessed**

| Variable | Case | Control | Odds ratio | p |
|---|---|---|---|---|
| | n (%) | n (%) | (CI) | |
| Age (years) | | | | |
| < 40 | 6 (8.0) | 69 (92.0) | 1.00 | |
| ≥ 40 | 94 (17.9) | 431 (82.1) | 2.51 (1.01-6.62) | 0.03 |
| Age at menarche (years) | | | | |
| < 14 | 62 (15.2) | 345 (84.8) | 1.16 (0.46-3.16) | 0.74 |
| ≥ 14 | 36 (18.9) | 154 (81.1) | 1.00 | |
| Parity (number of pregnancies) | | | | |
| ≤ 3 | 75 (17.3) | 359 (82.7) | 1.18 (0.70-1.99) | 0.51 |
| > 3 | 25 (15.1) | 141 (84.9) | 1.00 | |
| Age at first birth (years) | | | | |
| < 21 | 38 (13.6) | 241 (86.4) | 1.00 | |
| ≥ 21 | 49 (18.6) | 214 (81.4) | 1.45 (0.89-2.37) | 0.11 |
| Breastfeeding (months) | | | | |
| < 12 | 25 (15.6) | 135 (84.4) | 1.02 (0.59-1.76) | 0.94 |
| ≥ 12 | 52 (15.4) | 286 (84.6) | 1.00 | |
| History of abortion | | | | |
| Yes | 23 (14.9) | 131 (85.1) | 0.83 (0.49-1.42) | 0.48 |
| No | 75 (17.4) | 356 (82.6) | 1.00 | |
| Menopause | | | | |
| Premenopausal | 17 (7.8) | 201 (92.2) | 1.00 | |
| Postmenopausal | 83 (21.7) | 299 (78.3) | 3.28 (1.84-5.93) | < 0.001 |
| Age at menopause (years) | | | | |
| < 50 | 47 (18.9) | 202 (81.1) | 0.66 (0.40-1.09) | 0.08 |
| ≥ 50 | 40 (26.1) | 113 (73.9) | 1.00 | |
| Prior hormone replacement | | | | |
| Yes | 10 (11.9) | 74 (88.1) | 0.64 (0.30-1.34) | 0.20 |
| No | 90 (17.4) | 426 (82.6) | 1.00 | |
| Prior contraceptive use | | | | |
| Yes | 63 (16.4) | 322 (83.6) | 0.94 (0.59-1.51) | 0.78 |
| No | 37 (17.2) | 178 (82.8) | 1.00 | |
| Family history of breast cancer | | | | |
| First-degree relative | 8 (28.6) | 20 (71.4) | 0.58 (0.17-1.96) | 0.32 |
| Second-degree relative | 3 (16.7) | 15 (83.3) | 0.29 (0.05-1.41) | 0.08* |
| Third-degree relative | 13 (40.6) | 19 (59.4) | 1.00 | |
| Physical activity | | | | |
| Active | 23 (9.2) | 228 (90.8) | 1.00 | |
| Inactive | 77 (22.1) | 272 (77.9) | 2.81 (1.66-4.77) | <0.001 |
| BMI (kg/m$^2$) | | | | |
| < 30 | 68 (14.8) | 391 (85.2) | 1.00 | |
| ≥ 30 | 32 (22.47) | 109 (77.3) | 1.69 (1.03-2.77) | 0.02 |
| WC (cm) | | | | |
| < 80 | 12 (18.2) | 54 (81.8) | 1.00 | |
| ≥ 80 | 88 (16.5) | 446 (83.5) | 1.13 (0.55-2.28) | 0.72 |

BMI: Body mass index; WC: waist circumference; CI: confidence interval. *Fisher's exact test

postmenopausal status and BMI ≥ 30 kg/m$^2$ were associated with cases of breast cancer. Women who were postmenopausal, had a BMI ≥ 30 kg/m$^2$, and were physically inactive were 3.80, 1.80, and 1.72 times more likely to develop breast cancer, respectively (Table 3).

The analysis of risk variables for breast cancer based on menopausal status indicated that 87.2% of women ≥ 40 years of age were postmenopausal (Table 4), and 87.5% were obese.

## Discussion

ABrazil is located in South America, which is the continent with the fastest population growth in the world (World Development Indicators, 2010). This growth, combined with an aging population, has been accompanied by an increase in unhealthy lifestyles characterized by physical inactivity, poor eating habits, excessive alcohol consumption, tobacco use, excessive exposure to sunlight,

and increasing urbanization (Gross et al., 2013), factors that have been associated with an increase in non-communicable diseases including cancer (Amadou et al., 2014). Currently, breast cancer is the leading type of cancer among women worldwide (WHO, 2012).

In a large study based on data from the Women's Health Initiative that analyzed more than 800 potential risk factors for breast cancer in an attempt to identify new predictors and confirm previously established risk factors, the authors concluded that some of the most frequently studied risk factors may not be as important as once thought and are investigated at the expense of other less studied factors, which may be relevant determinants for breast cancer (Hartz and He, 2013).

Thus, the contextual basis for this research was to identify significant risk factors in the prevention of breast cancer.

In the present study, an age at first childbirth of over 21 years and early menarche were not associated with the occurrence of breast cancer. However, increasing age had a large effect on the risk of breast cancer and was significantly associated with breast cancer in the bivariate analysis, as described by another study (Bhadoria et al., 2013).

It should be noted that some studies claim that Latin American women are more likely to develop breast cancer at a younger age. However, having a more advanced stage of cancer at diagnosis compared to Western women (Lee et al., 2012; Justo et al., 2013), may be explained by more limited access to health care and mammography, in addition to the lack of follow-up after an abnormal mammogram (Breen et al., 2007; Stuver et al., 2011). Moreover, a lack of health care coverage for Latin American populations has been described (Knaul et al., 2011).

Similarly to this study, other studies have not observed an association between a history of abortion and breast cancer (Karim et al., 2015), even in large population studies (Reeves et al., 2006; Karim et al., 2015).

Although previous use of oral contraceptives and hormone replacement therapy were not associated with the development of breast cancer in this study, this is one of the most disputed controversies among risk factor studies, which often disagree. The use of these methods has increased since the late 1960s, following changes in women's lifestyles. Data from the United Nations show that 28% of women in the United Kingdom (2008-9), 40.6% in France (2008), and 16.3% in the United States have used oral contraceptives (United Nations, 2013). Thus, the relationship between the use of oral contraceptives among women of reproductive age and the risk of breast cancer has not been elucidated (Ichida et al., 2015). Despite the benefits described in the literature associated with oral contraceptive use, such as reduction in menorrhagia, irregular menstruation, functional ovarian

**Table 3. Multivariate Analysis of Breast Cancer and Control Patients According to Risk Factors**

| Variable | Adjusted OR | Odds ratio (CI) | p |
|---|---|---|---|
| Age (years) | | | |
| ≥ 40 | 1.03 | 0.37-2.91 | 0.94 |
| Age at 1st birth | | | |
| ≥ 21 | 1.37 | 0.88-2.14 | 0.88 |
| Menopause | | | |
| Postmenopausal | 3.80 | 1.89-7.60 | <0.001 |
| Age at menopause (years) | | | |
| < 50 | 0.71 | 0.43-1.15 | 0.17 |
| BMI (kg/m2) | | | |
| ≥ 30 | 1.80 | 1.11-2.94 | 0.01 |
| Physical activity | | | |
| Inactive | 1.72 | 1.07-2.77 | 0.02 |

BMI: body mass index; CI: confidence interval

**Table 4. Risk Factor Analysis of Breast Cancer Cases According to Menopausal Status**

| Variable | Premenopausal | Postmenopausal | Odds ratio | p |
|---|---|---|---|---|
| | n (%) | n (%) | (CI) | |
| Age (years) | | | | |
| < 40 | 5 (83.3) | 1 (16.7) | 1.00 | |
| ≥ 40 | 12 (12.8) | 82 (87.2) | 34.17 (3.33-84.74) | <0.001 |
| Prior hormone replacement | | | | |
| Yes | - | 10 (100.0) | ND | 0.20 |
| No | 17 (18.9) | 73 (81.1) | 1.00 | |
| Prior contraceptive use | | | | |
| Yes | 12 (19.0) | 51 (81.0) | 0.66 (0.18-2.30) | 0.47 |
| No | 5 (13.5) | 32 (86.5) | 1.00 | |
| Physical activity | | | | |
| Active | 1 (4.3) | 22 (95.7) | 1.00 | |
| Inactive | 16 (20.8) | 61 (79.2) | 5.77 (0.73-123.4) | 0.11 |
| BMI (kg/m$^2$) | | | | |
| < 30 | 13 (19.1) | 55 (80.9) | 1.00 | |
| ≥ 30 | 4 (12.5) | 28 (87.5) | 1.65 (0.44-6.68) | 0.41 |

BMI: Body mass index; ND: not determined

cysts, benign breast disease, premenstrual syndrome, and iron deficiency/anemia (Caserta et al., 2014), the fear of an increased risk of breast cancer leads to low adherence to their use (among Japanese women, for example) (Ichida et al., 2015). According to the Clinical Practice Guidelines for Breast Cancer from the Japanese Breast Cancer Society from 2013, the use of oral contraceptives may increase the risk of breast cancer, but there is no consensus on the period of use, previous use, or drug composition (Ichida et al., 2015). In a study with non-Asian populations, oral contraceptive use was associated with a 4.6-fold greater risk of breast cancer (Anothaisintawee et al., 2014). Similar results were seen for Asian women (but with higher doses) (Vaisy, Lotfinejad and Zhian, 2014), Saudi Arabian women (Karim et al., 2015), and for women in other studies (Suhrke and Zahl, 2015). Increased exposure to estrogen has also been considered a risk for breast cancer in younger women (Assis et al., 2013). Other studies, however, have not found an association between oral contraceptive use and cases of breast cancer (Karim et al., 2015; Ichida et al., 2015).

Exposure to estrogen may be endogenous (as in the case of early menarche, late menopause, and older age at first childbirth) or exogenous, including hormone replacement therapy or the use of oral contraceptives (WHO, 2015; Zhang et al., 2012).

In the present study, in addition to an age of over 40 years, as noted above, postmenopausal status was also considered a risk factor for breast cancer, as was a BMI ≥ 30 kg/m2 (obesity). The multivariate analysis indicated that these two variables were statistically significant. Postmenopausal women, obese women, and physically inactive women were 3.80, 1.80, and 1.72 times more likely to develop breast cancer, respectively.

Obesity is worth mentioning due to its high prevalence worldwide and because it is preventable. In addition, a reduction in obesity would also decrease numerous chronic diseases. Data from the World Health Organization show that more than 50% of people are overweight or obese (WHO, 2015), and in Brazil, data from the Surveillance of Risk and Protective Factors for Chronic Diseases Telephone Survey - 2104 [Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico -VIGITEL] show that 52.5% of the Brazilian population over 18 years of age is overweight (BRASIL, 2014), which indicates the need for continued studies on the association of this risk factor with breast cancer.

Several studies have confirmed that obesity has been linked to an increased risk of breast cancer (Minatoya et al., 2014; Kabat et al., 2014; Guo et al., 2015), and a poor prognosis (Robinson, Bell and Davis, 2014; Copson et al., 2015; Herlevic et al., 2015). In recent years, the literature has also demonstrated the association between obesity and breast cancer in postmenopausal women. A controlled randomized observational study reported that postmenopausal women who were treated with estrogen in combination with progestin had an increased risk of breast cancer (Chlebowski et al., 2013). At that time, the authors concluded that high circulating concentrations of estrogen were associated with an increased risk of breast cancer (Kaaks et al., 2005). In addition, some studies have noted that hormonal changes after menopause are associated with adiposity (Rose and Vona-Davis, 2009).

However, some studies have found that obesity is not associated with decreased survival in populations with a high prevalence of obesity or in individuals with breast cancer, concluding that other factors may contribute to the poor prognosis of patients with breast cancer observed in populations with low rates of obesity (Herlevic et al., 2015).

Another important factor to be considered for obese postmenopausal women is that women who are very obese are significantly less likely to participate in mammography screening than normal-weight women (Hellman et al., 2015).

A meta-analysis that included 82 studies on BMI and breast cancer mortality concluded that for every 5 kg/m2 increase in BMI, the increased risk of mortality prior to diagnosis is 17%, and in the 12 months after diagnosis, the value is 11%. (Chan et al., 2014).

Several studies support the recommendation to be physically active (US Department of Health and Human Services, 2008) following a diagnosis of breast cancer, as such activity has many health benefits (Branstrom et al., 2015) and improves a patient's quality of life (Pinto, Dunsiger, and Waldemore, 2013), even if the exercises are of low intensity (Branstrom et al., 2015). Higher levels of physical activity are associated with fewer treatment-related side effects, an improved quality of life, improved survival, a lower risk of recurrence, and lower mortality rates (Speck et al., 2010; Ibrahim and Al-Homaidh, 2011).

Maintaining an adequate level of physical activity, a healthy diet, and a healthy body weight are among the twelve ways to prevent cancer that are described in the fourth edition of the European Code Against Cancer (Schuz et al., 2015). Thus, physical activity should be encouraged in this population (Branstrom et al., 2015).

However, some studies have shown that breast cancer patients have lower levels of physical activity (Devoogdt et al., 2010) are more sedentary, and perform lower intensity physical activities than healthy individuals (Phillips et al., 2015). In a study consisting of self-reported data, approximately 70% of patients who had a previous breast cancer diagnosis did not perform the recommended level of physical activity of at least 150 minutes per week of moderate to vigorous intensity exercise (Kim et al., 2013). Those data were confirmed in our study, in which women who did not participate in regular physical activity were 1.72 times more likely to develop breast cancer.

A prospective study that evaluated physical activity in postmenopausal women and the occurrence of breast cancer found that the incidence of breast cancer among less physically active women was 40% higher than that in women who had higher rates of physical activity, and obese women had a 58% higher incidence of breast cancer than normal weight women (Bellocco et al., 2015). A lower risk of developing breast cancer was evident with 95-130 minutes of weekly physical activity, and stronger effects were observed among postmenopausal women (Si et al., 2015).

This study has some limitations; for instance, most patients had less than eight years of formal education,

which may have contributed to an information bias. Relying on individuals to remember past personal information introduces the possibility that individuals who are affected by a disease will misremember information. Self-reported data could lead to underestimation of information regarding certain health-related behaviors. In addition, the BMI was used to classify obesity, and although this index is almost universally used, it has limitations such as not distinguishing between lean mass and fat mass and not describing the distribution of body fat.

In conclusion, the risk factors for breast cancer that were considered included an age ≥ 40 years, postmenopausal status, obesity, and reduced physical activity. Variables postmenopausal status and an obese BMI were associated with cases of breast cancer. For healthcare professionals, knowing the risk factors associated with breast cancer among Brazilian women can help guide the development of health policies by focusing on the risk factors found in this population, such as obesity and physical inactivity, and emphasizing your actions in the age group more than 40 years and menopausal status. Working on these questions, according to our study, it will be possible to reduce the morbidity and mortality of this important disease.

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