Breast cancer risk factors that are identical and differential associated with menopause status of women in Northeast Brazil

Kedma Anne Lima Gomes

State University of Paraíba (UEPB)

Aline Ferreira de Araújo Jerônimo

State University of Paraíba (UEPB)

Raissa de Oliveira Ramos

State University of Paraíba (UEPB)

Lorena Sofia dos Santos Andrade

State University of Paraíba (UEPB)

Mathias Weller (✉ mathiasweller@uepb.edu.br)

State University of Paraíba (UEPB) <https://orcid.org/0000-0002-5881-4256>

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Abstract

Background: This case-control study was aimed at the identification of factors that modify breast cancer risk in a population from Northeastern Brazil. Breast cancer risk factors in this population are poorly understood.

Methods: Data of 291 patients with invasive breast cancer and 291 healthy controls were obtained from medical records and personal interviews. Odds ratios (OR) and confidence intervals (CI) were determined using univariate and multiple regression analysis.

Results: Oral contraceptive use increased the risk of breast cancer among pre- and post-menopause women 3.661 (95% CI: 1.81-7.39; $p < 0.001$) and 3.086 (95%CI: 1.85-5.79; $p < 0.001$) times. Family history increased the risk of breast cancer among pre- and post-menopause women 3.791 (95%CI: 1.85-7.77; $p < 0.001$) and 3.538 (95%CI: 2.16-5.79; $p = 0.000$) times. Risk of breast cancer among post-menopause women who regularly consumed alcohol was 4.21 (95%CI: 2.08-8.50; $p < 0.001$) times increased compared to women who did not consume alcohol. Obese and overweight post-menopause women had 2.117 (95%CI: 1.15-3.88) and 1.217 (95%CI: 0.74-2.19) times increased risk, compared to women with normal weight ($p = 0.044$). Waist-to-hip ratio > 0.8 increased the risk of breast cancer among pre-menopause women 2.026 (0.94-4.38; $p = 0.067$) times in the univariate analysis. Nulliparous post-menopause women had 2.667 (95%CI: 1.30-5.50; $p = 0.070$) times increased risk. Univariate analysis of nulliparity among pre-menopause women indicated 2.59 (OR= 0.386; 95%CI: 0.15-0.98; $p = 0.038$) times decreased risk.

Conclusions: Oral contraceptive use, family history and alcohol consumption increased the risk of breast cancer among pre- and post-menopause women. High body mass index increased the risk only among post-menopause women, whereas unadjusted high waist-to-hip ratio increased the risk of pre-menopause women. Nulliparous pre-menopause women tended to have decreased risk, whereas nulliparous post-menopause women tended to have increased risk of breast cancer.

Background

Breast cancer (BC) is the most common cancer worldwide and between 2005 and 2015, the disease incidence increased from 1.7 to 2.4 million cases worldwide [1]. This increase was mostly observed in developing countries due to changing lifestyle and longer life expectation, whereas in most developed countries, the incidence remained stable, or even declined [2]. With more than 209 million inhabitants, Brazil is the largest country of Latin American. For the year 2018, 59,700 new cases of the disease were predicted and BC is currently contributing to 29.5% of all neoplasms among women [3]. In the two largest urban centers of Brazil, São Paulo, respectively, Rio de Janeiro and also other regions in Southern, Southeastern and Midwestern Brazil, over the last 10 years, BC incidence has stabilized [3]. This is in contrast to the Northeastern region, where BC incidence increased between 2005 and 2018 from 27.23 to 63.98 new cases per 100,000 women [3, 4].

In literature, it is well established that reproductive, respectively, anthropometric and lifestyle related factors, modify the risk of BC [5 - 8]. It was estimated that about one third of all post-menopausal BC cases in the

United States are caused by modifiable and therefore preventable, lifestyle-related risk factors [9]. In the United Kingdom, 6.9% of all breast cancer cases were attributed to obesity and overweight, as a single risk factor for the disease [6]. Brazilian case-control BC studies identified family history, poor diet, low physical activity, high body mass index (BMI), alcohol consumption, low *versus* high number of children and use of oral contraceptives, as risk factors for the disease [10 - 12]. These studies referred to data from populations from Southern and Southeastern regions of Brazil. Only few studies addressing the identification of risk factors were performed in Northeastern Brazil, a region where BC incidence is increasing: Lima and colleagues (2008), attributed increased BC risk to poor diet of women, including high intake of red and processed meat [13]. A recent case-control study of a population from Northeastern Brazil identified menarche age ≤ 12 years, one *versus* ≥ 2 children and time interval before first and last gestation of >10 years as risk factors for BC, whereas total lifetime breastfeeding >24 month decreased the risk of BC [14]. Another recent study identified obesity and overweight as risk factor for BC [15].

Since 2003, Brazil has a public program for early detection of breast cancer and mammography screening is propagated in the month of October ("Outubro rosa"). In Northeastern Brazil, most women rely on information about BC on television and very few information is given about preventable risk factors, respectively modifiable factors that decrease the risk of BC [16]. There is an urgent need to identify BC risk factors in this population and if modifiable, to propagate their prevention in health campaigns. The present case-control study focused on identification of lifestyle-related and reproductive risk factors in a population from Northeastern Brazil. The identification of several risk factors indicates remarkable differences of pre- and post menopause women that were not reported in previous studies with any Brazilian population.

Methods

Study population

Patients were eligible if diagnosed within 36 months from recruitment with invasive BC and aged 18 years or older. Patients with *in situ* tumors were excluded from the study. Patients with breast cancer recurrence were also excluded from the study. Data from breast cancer patients were sampled in two reference centers for breast cancer treatment in the state of Paraíba, Northeastern Brazil: The "Fundação Assistencial da Paraíba" Hospital (FAP) in Campina Grande and "Napoleão Laureano" Hospital (HNL) in João Pessoa. Both public hospitals receive mainly low-income patients and treat more than 95% of all BC cases in the state. Patients seeking for treatment come from regions as far as 600 km from the reference centre. João Pessoa, capital of the state of Paraíba, has about 0.8 million inhabitants and is located on the coast. Campina Grande, with about 0.4 million inhabitants, the second most populated urban centre in Paraíba, is located about 120 km away from the capital in the inland of the state. Similarly to other states of Northeastern Brazil, Paraíba has mixed-ethnicity population composed of Indigenous, African and European ancestry.

Data of controls were obtained from both public hospitals and in three public health care centers. Many patients were from rural areas. Therefore, a comparable part of controls was also recruited from rural areas: Two of the three health care centers were in rural areas, about 40km away from Campina Grande. Women

with any type of cancer were excluded from the study as controls. Women with any other chronic disease, like diabetes and heart disease were also excluded as controls. Furthermore, it was avoided to interview more than one healthy women of the same family. Controls were randomly selected in health care centers and directly asked by one of the authors to participate as volunteers. Most controls (>60%) accompanied children or grandchildren for vaccine or other medical examination. Other controls visited the health care center mainly because of injuries, colds or gastrointestinal infections. Controls interviewed in hospitals were healthy companions of non-cancer patients. Controls were eligible for the study if they were aged over 18 years old and agreed to participate in the study. Participation rate of patients and controls was about 90% and 85%.

Data sampling

Breast cancer patients and controls were interviewed between March 2017 and January 2019. The study included 291 women with invasive operable breast cancer, diagnosed and treated between 2016 and 2019. No significant differences were observed between patients of both reference centers. A structured questionnaire was applied to interview patients in chemotherapy and radiotherapy units of both hospitals. Clinical and histopathological data of patients were obtained from medical records. Height and weight had been measured in both reference centers before any therapeutic treatment and were also obtained from medical records. The same questionnaire was applied to interview healthy controls in waiting rooms of health care centers. All interviews were performed by one of the authors.

Body mass index (BMI) was defined according to the World Health Organization [17]: Underweight: $< 18.5 \text{ kg/m}^2$; normal weight: $18.5\text{--}24.99 \text{ kg/m}^2$; overweight: $25.0\text{--}29.99 \text{ kg/m}^2$; obesity $\geq 30.0 \text{ kg/m}^2$. Waist-to-hip ratio (WHR) was defined according to previous studies [20]: Normal weight: ≤ 0.8 ; Obesity and overweight: > 0.8 .

Minimum wage and multiple values were used to characterize income. This is a popular and well-known method to define economic level among low- and middle-class subjects. Information about ethnic origin was self-reported by participants. Educational level was defined as follows: 1. Incomplete elementary school with duration of less than nine years was defined as “Basic”; 2. Elementary school with duration of nine years was defined as “Low” 3. High school with duration of 12 years was defined as “middle”. 4. Higher educational levels were defined as “high”. Data about ethnic origin were self-reported by participants. Women were asked if they used ever or never oral contraceptives. When asked about family history, interviewed women often confounded BC with other types of cancer. Therefore present information about family history referred to different types of cancer and not to BC alone. Family history included BC and other types of cancer among first- degree relatives. Physical activity was defined as any type of regular low, moderate or strong body movement.

Statistical analysis

All statistical analyses were performed using the SPSS STATISTICS™ software (SPSS; IBM company; version 24). The t-test was applied to compare continuous variables. Pearson's Chi-Square (χ^2) test was applied to compare categorized variables. To quantify associations among single risk factors for BC, nominal logistic regression analysis was applied. Data of controls served as reference group. Results were presented as adjusted odd ratios (OR), 95% confidence interval (CI) and p-value of likelihood ratio tests. Significant univariate regression analysis variables were used for regression modeling with multiple adjusted variables: Variables with significance level less than 0.2 in the univariate analysis were included in the model. Then, variables with significance level less than 0.05 were kept in the model. Backward selection was used when significant variables were selected. The final model was tested for fitness using the likelihood ratio test.

Results

Basic socio- demographic and anthropometric characteristics of cases and controls were summarized in Table 1. Of all 582 women, 181 showed pre-menopause status, whereas 401 showed post-menopause status (Table 1). As variables of pre- and post-menopause women showed remarkable differences, data were stratified for menopause status. Mean waist-to-hip ratio (WHR) of 88 pre-menopause cases was 0.872 ($s = 0.07$) compared to 0.848 ($s = 0.08$) of 93 controls ($p = 0.036$; Table 1). Of all pre-menopause women, 28 (31.82%) cases and 16 (17.20%) controls informed Caucasian ethnic origin ($p = 0.025$; Table 1). The mean age of 203 post-menopause cases and 198 controls was 59.70 ($s = 10.09$) and 62.15 ($s = 9.84$) years ($p = 0.015$; Table 1). The mean body mass index (BMI) of post-menopause cases and controls was 28.31 ($s = 5.20$) and 26.67 ($s = 4.58$) ($p = 0.001$; Table 1). In contrast to pre-menopause women, WHR and marital status were not significantly different between post-menopause cases and controls ($p = 0.149$; $p = 0.055$; Table 1). Of the 401 post-menopause women, 131 (64.53%) cases and 152 (76.77%) controls had low income ($p = 0.026$).

In the univariate regression analysis, pre-menopause nulliparous women had 2.59 (OR = 0.386; 95%CI: 0.15–0.98) decreased risk of BC compared to parous women ($p = 0.038$; Table 2). The comparison of WHR among pre- menopause women indicated that those with value > 0.8 , had 2.026 (95%CI: 0.94–4.38) times increased risk of the disease, compared to women with WHR of ≤ 0.8 ($p = 0.067$; Table 2). In the adjusted multiple analysis model, only variables oral contraceptive use, family history and alcohol consumption remained heterogeneously distributed between pre-menopause cases and controls (Table 2): Oral contraceptive use and family history increased the risk of BC by 3.610 (95%CI: 1.77–7.38) and 3.791 (95%CI: 1.85–7.77) times, compared to women who claimed not to have used oral contraceptives before disease diagnosis, respectively, without family history ($p < 0.001$; $p < 0.001$; Table 2). Consumption of alcohol increased risk of BC 2,059 (95%CI: 0.90–4.73) times, compared to women who never consumed it ($p = 0.086$; Table 2).

In the group of post-menopause women with age at menarche < 12 years, the risk of the disease increased 1.918 (95%CI: 1.01–3.66) times compared to women with age at menarche ≥ 12 years ($p = 0.044$; Table 2). In the adjusted multiple analysis model, variables nulliparity, oral contraceptive use, family history, BMI and alcohol consumption remained heterogeneously distributed between post-menopause cases and controls

(Table 2): In contrast to pre-menopause women, nulliparity tended to increase the risk of BC among post-menopause women. Nulliparous women had 2.667 (95%CI: 1.30–5.50) times increased risk of the disease compared to parous women ($p = 0.070$; Table 2). Post-menopause women, who used oral contraceptives and had positive family history of BC, had 3.086 (95%CI: 1.85–5.79) and 3.576 (95%CI: 2.21–5.79) times increased risk of the disease ($p < 0.001$; $p < 0.001$; Table 2). In contrast to pre-menopause women, increased BMI among post-menopause women was positively associated with risk of the disease: Obese and overweight women had 2.117 (95%CI: 1.15–3.88) and 1.271 (95%CI: 0.74–2.19) increased risk of the disease compared to women with normal weight ($p = 0.048$; Table 2). Post-menopause women who consumed any type of alcohol had 4.21 (95%CI: 2.08–8.50) times increased risk of the disease compared to those who did not consume alcohol ($p < 0.001$; Table 2).

Breastfeeding had no significant impact on risk of BC among parous women ($p = 0.081$ Table 2). Parous cases and controls had on average 3.27 ($s = 2.21$) and 3.12 ($s = 2.56$) children ($p = 0.479$), respectively. In the multiple analysis model, women with one and two, respectively three children, had a 2.52 (OR = 0.397; 95%CI: 0.21–0.76) and 1.61 (OR = 0.621; 95%CI: 0.38–1.02) times decreased risk of disease compared to women with more than three children ($p = 0.016$; Table 2). Similarly, as in the case of post- and pre-menopause women, oral contraceptive use, family history and alcohol consumption were associated with increased risk of the disease ($p < 0.001$; $p < 0.001$; $p < 0.001$; Table 2).

Of all 582 women, 189 (64.95%) cases and 98 (33.68%) controls had used contraceptives ($p = 0.000$). The mean time of oral contraceptive use between cases and controls was 69.15 ($s = 67.57$) and 82.79 ($s = 68.99$) months ($p = 0.101$), respectively. Of all 582 women, 86 (29.55%) cases and 26 (8.94%) controls consumed alcohol ($p = 0.000$). Alcohol consumption between cases and controls was on average 4.74 ($s = 5.16$) and 3.08 ($s = 5.36$) times per month ($p = 0.168$).

Discussion

In the present study, oral contraceptive use, family history and alcohol consumption were positively associated with risk of BC. Their effect was similar among pre- and post-menopausal parous women, respectively. Anthropometric measures BMI and WHR in contrast, were differently associated with risk of BC between pre- and post-menopause women. Reproductive risk factors age at menarche and nulliparity also showed remarkable differences between pre- and post-menopause women.

Age at menarche < 12 years increased the risk of the disease among post-menopause women, but not among pre-menopause women. However, this effect remained not significant after data adjustment. In agreement with present results, recent studies carried out in Thailand, Brazil and Norway revealed increased risk of BC associated with younger age at menarche [14, 19, 20].

Post-menopause nulliparous women of the present study had increased risk of the disease. Among pre-menopause women in contrast, nulliparity as a single variable, decreased the risk of BC, but had no significant effect after data adjustment. Parity is a well-established modulator of risk of BC [21]. Previous studies have associated nulliparity with an overall increased risk of the disease [20, 22]. Nulliparity as a risk

factor for BC was also identified in a previous study carried out in Brazil [14]. Furthermore, the effect of parity depends on menopause status: Parous pre-menopause women, mainly at the age of 35 or older, had increased risk of the disease until 15 years after delivery [23]. Among post-menopause women in contrast, nulliparity was associated with increased risk of the disease, explaining the general protective effect of parity, as most BC cases are found among post-menopause women [21]. The dual effect of parity that depends on menopause status, may be also present in the present population, reducing risk among pre-menopause women, increasing the risk among post-menopause women, respectively. However, present data indicated the effect of parity, comparing nulliparous and parous women, but did not establish a positive association between high number of children and reduced risk among post-menopause women. Furthermore, in contrast to present results the protective effect of parity among parous women generally increases with higher number of children [21].

The use of oral contraceptives increased the risk of BC between pre- and post-menopause women in the present study. Previous findings support the idea that the use of oral contraceptives increases the risk of BC: In literature, oral contraceptive use is a well-established risk factor for BC [5, 19, 22]. A previous Brazilian study also identified oral contraceptive use for more than five years as risk factor for BC among women aged ≥ 45 years [24]. Studies have indicated that the risk of BC increases only during or after recent use: Recent use of oral contraceptives was associated with increased risk of the disease among young women [25]. An observational study conducted for more than four decades in the United Kingdom showed that the risk of BC decreased approximately five years after stopping use of oral contraceptives [26]. Present data also indicated that positive family history increased the risk of BC of both pre- and post-menopause women. In agreement with present results, recent studies performed in Thailand and Brazil, also identified first- degree family history of BC as a variable that increased the overall risk of the disease [10, 19].

According to the World Health Organization (WHO), between 2010 and 2014, overweight and obesity increased from 51.10% to 54.10%, respectively, from 17.80% to 20.00% among Brazilian adults [17]. In the present study, anthropometric measures BMI and WHR showed differences between pre- and post-menopause women: Results have indicated that obesity and overweight, determined as BMI, was positively associated with risk of BC among post- menopause women, but not among pre- menopause women. Obesity and overweight are considered the most important modifiable lifestyle-related risk factor among women, especially due to its impact on BC [6]. In studies that used anthropometric measures, obesity and overweight increased the overall risk of BC [15, 19, 20, 22]. A recent study performed in Southern Brazil, associated obesity, respectively high BMI, to increased risk of BC among post-menopause women and to decreased risk of BC among pre-menopause women [11]. Similarly, recent studies, all based on BMI, identified obesity and overweight as risk factors for BC among post- menopause women, whereas results for pre- menopause women remained conflicting [5, 27]. A recent study performed in the United Kingdom revealed that low BMI and low waist-to-hip ratio increased the risk of pre-menopause women, whereas both measures were positively associated with risk of BC among post-menopause women [6]. In a meta-analysis, Amadou and colleagues (2013) pointed out that increased BMI of post-menopause women was positively associated with BC, whereas high WHR increased the risk of both pre-menopause and post-

menopause women [18]. The present results about BMI, were consistent with most previous studies. However, in the case of WHR, univariate analysis of present data indicated borderline significance among pre –menopause women, but not among post- menopause women. Only obese pre-menopause women tended to have increased risk of the disease.

Pre- and post-menopause women of the present study, who consumed some type of alcohol, had increased risk of the disease. This effect was strong for post-menopause women, but weak for pre-menopause women. A recent study carried out in Rio de Janeiro, Brazil, also identified alcohol consumption as a risk factor for BC [12]. A previous study indicated that even low doses of alcohol could increase the risk of BC and that there is a positive relationship between dose of alcohol and risk of the disease [28]. The effect of alcohol on the etiology of BC could be by epigenetic mechanisms [29]. A recent study on pre-menopause women suggested that alcohol had negative effect only on individuals who also had family history of BC and lower folic acid intake [30]. Therefore, the effect of alcohol depends on the context of other risk factors and this may also explain why in other previous studies, alcohol consumption had no impact on the risk of BC [30].

The low availability of data may have impaired the establishment of a positive association between dose of alcohol consumption and risk of BC. It was also not possible to identify any possible protective effect of breastfeeding and high number of children for parous and post-menopause women, respectively. Low number of data generally leads to lower resolution and therefore may have obscured significant associations between BC and such factors. The study established an overall positive association between use of oral contraceptives and risk of BC, but important data about the time interval between last use of oral contraceptives and disease diagnosis were missing. The study included patients who received diagnosis of disease within the last three years. Therefore, another limitation of the present study may have been recall biases of interviewed women and information about risk factors may have been confounded. Furthermore, a selection bias of controls and patients cannot be excluded.

Conclusion

The present results indicated that family history and several lifestyle-related factors increased the risk of BC among women in this study: Family history and oral contraceptive use increased the risk of BC among post- and pre-menopause women. Increased risk of women, who consumed alcohol, was more pronounced among post-menopause than pre- menopause women. Obesity and overweight, measured by BMI, increased the risk of BC among post-menopause women, but not among pre-menopause women. In the univariate analysis, early age at menarche increased the risk of BC among post-menopause women and WHR had borderline significance among pre-menopause women. Nulliparity increased risk of post-menopause women and reduced risk of pre- menopause women. These findings are in agreement with most previous case-control studies about risk factors for BC. Future studies should include larger groups of patients and controls. Furthermore, regarding alcohol consumption, the effect of different doses should be analyzed and in the case of oral contraceptive use, time interval between last use and BC diagnosis should be integrated. Avoiding modifiable behaviors such as alcohol consumption and poor diet should be

propagated by health authorities mainly during public health campaigns like “Outubro Rosa”, that focuses so far nearly exclusively on mammography screening, but not on risk factors.

Abbreviations

MS: Mammography screening.

Declarations

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Ethical approval and consent to participate

The data sampling protocol was reviewed and approved by the Brazilian National Ethics Research Committee (CAAE plataforma Brasil: 22358113.1.0000.5187). Written informed consent was obtained from each participant of the study.

Consent for publication

Consent to publish data anonymously was obtained from each participant of the study.

Availability of data

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no interests that compete with any of the contents of the manuscript.

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Authors' contributions

KALG, AFAJ, ROR and LSSA performed interviews and tabulation of data. KALG and MW performed data analysis. MW performed study design and manuscript draft. Authors equally contributed to conception and critical review of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Basic socio- demographic and anthropometric characteristics of women, stratified for menopause status.

Pre menopause women (N= 181)				
		Case (N= 88)	Control (N= 93)	<i>p</i>
Mean Age		42.63 (s = 7.93)	42.68 (s = 8.32)	0.965
Mean BMI		27.63 (s = 5.09)	26.69 (s = 4.45)	0.194
Mean Waist- Hip ratio		0.872 (s = 0.07)	0.848 (s = 0.08)	0.036
		N (%)	N (%)	
Income	Low	56 (65.88%)	68 (73.12%)	
	Middle	20 (23.53%)	15 (16.13%)	
	High	9 (10.59%)	10 (10.75%)	
	Missing	3		
Private health insurance	Yes	17 (19.32%)	23 (24.73%)	0.474
	No	71 (80.68%)	70 (75.27%)	
Education level	Analphabetic	0	1 (1.08%)	0.680
	Basic	31 (35.63%)	29 (31.18%)	
	Low	15 (17.24%)	12 (12.90%)	
	Middle	27 (31.04%)	33 (35.48%)	
	High	14 (16.09%)	18 (19.36%)	
	Missing	1		
Civil state	Stable union	56 (64.37%)	46 (49.46%)	0.051
	No stable union	31 (35.63%)	47 (50.54%)	
	Missing	1		
Ethnic origin	Mixed	60 (68.18%)	77 (82.80%)	0.025
	Caucasian	28 (31.82%)	16 (17.20%)	
Post menopause women (N= 401)				
		Case (N= 203)	Control (N= 198)	
Mean Age		59.70 (s= 10.09)	62.15 (s= 9.84)	0.015
Mean BMI		28.31 (s= 5.20)	26.67 (s= 4.58)	0.001
Mean Waist- Hip ratio		0.894 (s= 0.06)	0.886 (s= 0.06)	0.149

		N (%)	N (%)	
Income	Low	131 (64.53%)	152 (76.77%)	0.026
	Middle	64 (31.53%)	40 (20.20%)	
	High	8 (3.94%)	6 (2.03%)	
Private health insurance	Yes	27 (13.30%)	21 (10.61%)	0.249
	No	176 (86.70%)	177 (89.39%)	
Education level	Analphabetic	12 (5.91%)	4 (2.02%)	0.200
	Basic	99 (48.77%)	112 (56.57%)	
	Low	27 (13.30%)	25 (12.63%)	
	Middle	46 (22.66%)	44 (22.22%)	
	High	19 (9.36%)	13 (6.56%)	
Civil state	Stable union	76 (38.38%)	98 (48.28%)	0.055
	No stable union	122 (61.62%)	105 (51.72%)	
	Missing	5		
Ethnic origin	Mixed	70 (34.48%)	62 (31.31%)	0.525
	Caucasian	133 (65.52%)	136 (68.69%)	

Table 2. Risk factors of breast cancer of pre menopause, post menopause and parous women.

		N (%)	N (%)	OR _{CRUDE} (95% CI)	P _{LRT}	OR _{ADJUSTED} (95% CI) ¹	P _{LRT}
Pre menopause women (N= 181)							
		Case (N= 88)	Control (N= 93)				
Age categories	< 30	3 (3.41%)	4 (4.3%)	0.750 (0.08-6.71)	0.818		
	31-39	28 (31.82%)	27 (29.03%)	1.037 (0.19-5.6)			
	40-49	45 (51.13%)	44 (47.31%)	1.023 (0.2-5.34)			
	50-59	9 (10.23%)	15 (16.13%)	0.600 (0.10-3.63)			
	≥ 60	3 (3.41%)	3 (3.23%)	1			
Age at menarche	< 12	13 (14.77%)	13 (13.98%)	1.067 (0.47-2.45)	0.879		
	≥ 12	75 (85.23%)	80 (86.02%)	1			
Nulliparity	Yes	7 (7.96%)	17 (20.48%)	0.386 (0.15-0.98)	0.038		
	No	81 (92.04%)	76 (81.72%)				

Oral contraceptive use	Yes	67 (76.14%)	37 (39.78%)	4.829 (2.54- 9.18)	<0.001	3.661 (1.81-7.39)	<0.001
	No	21 (23.86%)	56 (60.22%)	1		1	
Abortion	Ever	24 (28.57%)	17 (18.28%)	1.788 (0.88- 3.63)	0.105		
	Never	60 (71.43%)	76 (81.72%)	1			
	Missing	4					
Family history	Yes	52 (59.09%)	19 (20.43%)	5.626 (2.91- 10.88)	<0.001	3.791 (1.85-7.77)	<0.001
	No	36 (40.91%)	74 (79.57%)	1		1	
BMI	Obesity	22 (25.88%)	24 (25.81%)	1.324 (0.62- 2.83)	0.291		
	Overweight	36 (42.35%)	30 (32.26%)	1.733 (0.87- 3.45)			
	Normal	27 (31.77%)	39 (41.93%)				
	Missing	3					
Waist- hip ratio	> 0.8	74 (86.05%)	70 (75.27%)	2.026 (0.94- 4.38)	0.067		
	≤ 0.8	12 (13.95%)	23 (24.73%)	1			

	Missing	2					
Physical activity	No	52 (59.09%)	52 (55.91%)	1.139 (0.63-2.06)	0.666		
	Yes	36 (40.91%)	41 (44.09%)	1			
Smoking	Ever	17 (19.32%)	17 (8.43%)	1.070 (0.51-2.26)	0.858		
	Never	71 (80.68%)	76 (91.57%)	1			
Alcohol consumption	Yes	30 (34.09%)	13 (14.13%)	3.143 (1.51-6.55)	0.002	2,059 (0.90-4.73)	0.086
	No	58 (65.91%)	79 (85.87%)			1	
	Missing		1				
Post menopause women (N= 401)							
		Case (N= 203)	Control (N= 198)				
Age categories	< 40	5 (2.46%)	1 (0.50%)	5.735 (0.64-51.54)	<0.001		
	40-49	29 (14.29%)	4 (2.02%)	8.316 (2.65-26.06)			
	50-59	66 (32.51%)	92 (46.47%)	0.823 (0.47-1.44)			

	60-69	69 (33.99%)	62 (31.31%)	1.277 (0.72-2.27)			
	≥ 70	34 (16.75%)	39 (19.70%)	1			
Age at menarche	< 12	29 (14.43%)	16 (8.08%)	1.918 (1.01-3.66)	0.044		
	≥ 12	172 (85.57%)	182 (91.92%)	1			
	Missing	2					
Nulliparity	Yes	32 (15.76%)	17 (8.59%)	1.992 (1.07-3.72)	0.027	2.667 (1.30-5.50)	0.070
	No	171 (84.24%)	181 (91.41%)	1		1	
Oral contraceptive use	Yes	122 (60.10%)	61 (30.81%)	3.383 (2.24-5.12)	<0.001	3.086 (1.85-5.79)	<0.001
	No	81 (39.90%)	137 (69.19%)	1			
Abortion	Ever	53 (27.75%)	51 (26.02%)	1.092 (0.70-1.71)	0.701		
	Never	138 (72.25%)	145 (73.98%)	1		1	
	Missing	12	2				
Family history	Yes	115 (56.55%)	47 (23.74%)	4.199 (2.73-6.45)	<0.001	3.576 (2.21-5.79)	<0.001

	No	88 (43.35%)	151 (76.26%)	1		1	
BMI	Obesity	68 (34.87%)	40 (20.20%)	2.386 (1.42-4.00)	0.030	2.117 (1.15-3.88)	0.048
	Overweight	70 (36.00%)	78 (39.40%)	1.260 (0.79-2.01)		1.271 (0.74-2.19)	
	Normal	57 (29.23%)	80 (40.40%)	1		1	
	Missing	8					
Waist- hip ratio	> 0.8	182 (90.10%)	182 (91.92%)	0.800 (0.40-1.59)	0.524		
	≤ 0.8	20 (9.90%)	16 (8.08%)	1			
	Missing	1					
Physical activity	No	94 (46.30%)	110 (55.56%)	0.690 (0.47-1.02)	0.064		
	Yes	109 (53.70%)	88 (44.44%)	1			
Smoking	Ever	91 (44.83%)	74 (37.37%)	1.361 (0.91-2.03)	0.129		
	Never	112 (55.17%)	124 (62.63%)	1			
Alcohol consumption	Yes	56 (27.59%)	13 (6.57%)	5.421 (2.86-10.29)	<0.001	4.21 (2.08-8.50)	<0.001

	No	147 (72.41%)	185 (93.43%)			1	
Parous women only (N= 509)							
		Case (N= 252)	Control (N= 257)				
		N (%)	N (%)	OR_{CRUDE} (95% CI)	P_{LRT}	OR_{ADJUSTED} (95% CI)²	P_{LRT}
Age categories	< 30	3 (1.19%)	3 (1.17%)	1.400 (0.26-7.52)	0.008		
	31-39	31 (12.30%)	25 (9.73%)	1.736 (0.83-3.62)			
	40-49	66 (26.19%)	41 (15.95%)	2.254 (1.18-4.29)			
	50-59	62 (24.60%)	95 (36.96%)	0.914 (0.50-1.67)			
	60-69	65 (25.80%)	58 (22.57%)	1.569 (0.84-2.93)			
	≥ 70	25 (9.92%)	35 (13.62%)	1			
Menopause status	Pre	80 (31.75%)	77 (29.96%)	1.087 (0.75-1.58)	0.663		
	Post	172 (68.25%)	180 (70.04%)	1			

Age at menarche	< 12	37 (14.68%)	22 (8.56%)	1.838 (1.05-3.22)	0.030		
	≥ 12	215 (85.32%)	235 (91.44%)	1			
Number of children	1	40 (15.94%)	55 (21.40%)	0.568 (0.34-0.95)	0.081	0.397 (0.21-0.76)	0.016
	2-3	124 (49.40%)	134 (52.14%)	0.723 (0.49-1.08)		0.621 (0.38-1.02)	
	> 3	87 (34.66%)	68 (26.46%)	1		1	
	Missing	1					
Age at first life birth	< 20	90 (36.15%)	103 (40.08%)	1.143 (0.64-2.05)	0.288		
	20- 29	133 (53.41%)	120 (46.69%)	1.449 (0.82-2.56)			
	≥ 30	26 (10.44%)	34 (13.23%)	1			
	Missing	3					
Reproductive period³	≤ 10	139 (65.57%)	138 (67.98%)	0.897 (0.60-1.35)	0.602		
	> 10	73 (34.43%)	65 (32.02%)	1			
Lifetime breastfeeding	Never	32 (12.75%)	37 (14.40%)	0.799 (0.47-	0.571		

				1.37)			
	≤ 12	101 (40.24%)	111 (43.19%)	0.841 (0.58-1.22)			
	> 12	118 (47.01%)	109 (42.41%)	1			
	Missing	1					
Oral contraceptive use	Yes	177 (70.24%)	87 (33.85%)	4.611 (3.17-6.70)	<0.001	3.785 (2.47-5.81)	<0.001
	No	75 (29.76%)	170 (66.15%)	1		1	
Abortion	Ever	75 (29.88%)	68 (26.46%)	1.184 (0.80-1.74)	0.391		
	Never	176 (70.12%)	189 (73.54%)	1			
	Missing	1					
Family history	Yes	148 (58.73%)	58 (22.57%)	4.883 (3.32-7.18)	<0.001	3.899 (2.53-6.02)	<0.001
	No	104 (41.27%)	199 (77.43%)	1		1	
BMI	Obesity	85 (34.98%)	58 (22.57%)	2.198 (1.40-3.46)	0.003		
	Overweight	90 (37.04%)	97 (37.74%)	1.392 (0.91-2.12)			
	Normal	68	102	1		1	

		(27.98%)	(39.69%)				
	Missing	9					
Waist- hip ratio	> 0.8	222 (89.16%)	224 (87.16%)	1.211 (0.71-2.08)	0.487		
	≤ 0.8	27 (10.84%)	33 (12.84%)	1			
	Missing	3					
Physical activity	No	129 (51.19%)	144 (56.03%)	0.823 (0.58-1.17)	0.273		
	Yes	123 (48.81%)	113 (43.97%)	1			
Smoking	Ever	99 (39.29%)	86 (33.46%)	1.287 (0.90-1.85)	0.172		
	Never	153 (60.71%)	171 (66.54%)	1			
Alcohol consumption	Yes	77 (30.56%)	23 (8.98%)	4.457 (2.69-7.39)	<0.001	2.991 (1.69-5.28)	<0.001
	No	175 (69.44%)	233 (91.02%)	1		1	
	Missing		1				

Odds ratios (OR), confidence intervals (95% CI) and significance level of likelihood ratio tests (P_{LRT}) of variables are shown for cases stratified for pre and post menopause, respectively, parous women. Control served as reference group. Variables of univariate analysis (OR_{CRUDE}) were used for modelling ($OR_{ADJUSTED}$).

¹Adjusted for age as continuous variable, age at menarche and smoking; ²Adjusted for age as continuous variable, age at menarche and menopause status.