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Factors associated with gestational breast cancer: case-control study

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Abstract *The prevalence of gestational breast cancer (GBC) is 1:3,000-10,000 pregnancies. This study aims to identify the risk factors associated with GBC. This case-control study was conducted in the period between January 2004 and December 2014 at a reference maternity hospital for high-risk pregnancies in Rio de Janeiro. Two controls were selected for each case, totaling 21 GBC cases and 42 controls. Data were collected through a review of medical and hospitalization and delivery records. Reproductive, obstetrical, sociodemographic and health-related characteristics were investigated. Results: The mean age of pregnant women in both groups was 35.5 years. Menarche's mean age was also similar (12.3 years) in both groups. Mother's age at first pregnancy was > 30 years in 28.6% of the patients with GBC and in 2.4% of the control group (p = 0.03). Crude and adjusted odds ratio and their respective CI 95% were calculated through conditional logistic regression paired by mother's age. The results show that the risk for GBC increases 27% for each additional year of mother's age at first pregnancy (p < 0.02) and that mothers with lower schooling had higher risk of GBC (OR = 8.49). Conclusion: Our data confirm the association of primiparity over 30 years of age and low level of schooling with GBC.*

Key words *Breast neoplasms, Pregnancy*

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Introduction

Breast cancer is the second most frequent neoplasm in the world and is most common among women, accounting for 22% of new cases each year. In Brazil, breast cancer mortality rates remain high, probably because the disease is still diagnosed in advanced stages. Some 75,000 cases have been estimated for 2014[1].

Gestational breast cancer (GBC) is defined as one that is diagnosed during pregnancy, or up to one year after delivery and with a prevalence during the pregnancy-puerperal cycle of one case in every 3,000-10,000 pregnancies, depending on the population studied[2].

GBC prevalence tends to increase due to postponed pregnancy age. It usually is diagnosed at an advanced stage, with a poorly differentiated histological level and worse prognosis[3]. Breast physiological changes during pregnancy generate an increase in breast density, hampering clinical examination and mammography and mammographic ultrasonography interpretation, which delays diagnosis[4].

The concurrent occurrence of breast cancer and pregnancy continues to be a challenge that generates distress to pregnant woman, family and professionals involved, due to the dilemma between the ideal therapy for mothers and the well-being of fetuses.

GBC risk factors are still not well understood[5]. In the short term, pregnancy and postpartum are associated with transient increase in the risk of breast cancer, regardless of age. The higher risk period ranges from 10 to 15 years after women's first pregnancy up to 25 years, while it may remain for 30-50 years if the first birth occurred at age 30 or older[6,7]. The transient increase in postpartum risk is aggravated by a concomitant family history of breast cancer. Therefore, a woman 30 years of age or older with a family history is three times more likely to be at risk than those without relatives with breast cancer[7].

The protective effect of pregnancy increases with parity and the early age of the first gestation[8]. Thus, the first pregnancy before the age of 30 reduces the risk by 25% compared to nulliparous women. If the first pregnancy occurs before the age of 20, the risk is 30% lower than in the first year after the age of 35.[7,8]

Because it is a disease with great emotional, social, psychological and aesthetic impact, this study aims to identify the risk factors associated with GBC.

Methodology

Study population and study design

This is an observational study with a case-control design. The study population consisted of 63 pregnant women aged between 25 and 43 years, paired by age, admitted between January 2004 and December 2014 at the Perinatal Center of the Pedro Ernesto University Hospital of the State University of Rio de Janeiro (HUPE/UERJ), a reference maternity hospital for high-risk pregnancies, Vila Isabel district, Rio de Janeiro, RJ.

Sample size

The sample size calculated with the Fleiss method consisted of 63 participants, with 21 cases and 42 controls. The percentage of 32% of pregnant women with a first pregnancy age greater than 30 years in the general population[9] and 69% among pregnant women with breast cancer, 95% confidence level and study power of 80% were considered.

Selection of cases and controls

Cases were defined as women who were diagnosed with breast cancer during the current pregnancy, including all 21 pregnant women with breast cancer admitted during the study period, after confirmation by histopathological diagnosis. The control group included pregnant women with the same age of the cases or at most, plus/minus one year, without malignant neoplasms and who had delivered, at most, three months before or after the pregnant woman included as a case. When more than two pregnant women met the selection criteria for controls, we selected those with the closest delivery date to the case. Two controls were selected for each case.

Our maternity hospital is a reference for cases of malignant neoplasms. Most pregnant women with breast cancer come from the National Cancer Institute José Alencar Gomes da Silva (INCA), a specific body of the Ministry of Health for the national policy of prevention, diagnosis and treatment of cancer. The remainder are referred by other health facilities that can perform treatment and control of the disease during pregnancy. Prenatal care is provided to these pregnant women in our hospital, but some prefer to continue the follow-up of pregnancy in a health facility near their residence. Admissions due to

Ciência & Saúde Coletiva, 24(6):2361-2369, 2019

gestational complications and for the resolution of delivery occur at our maternity hospital.

Data collection

Interviews or questionnaires were not used as data collection tool. The Obstetrics Service of the HUPE/UERJ Perinatal Center records data of pregnant women in a document called hospitalization and delivery summary (SIP), which is divided into three (data on admission, delivery and development until hospital discharge). This document is retrieved from medical records at the time of discharge from the hospital and delivered to the administration office of the service in order to be entered in the maternity hospital database. Breast cancer cases during pregnancy were identified by consulting the variable "diagnosis" of the database. The next step was a survey of data contained in the SIP. Patient charts aided in the search for data that were incomplete or did not exist in the SIP and were important for the preparation of the study. Data collection was performed in 2015.

The following sociodemographic variables were analyzed: age (<35 years, ≥35 years); mother's age at the first pregnancy (≤30 years,> 30 years), ethnicity (white, non-white) and schooling level (illiterate/elementary school, secondary school/higher education). Health-related questions evaluated were body mass index (BMI) (<30 kg/m^2, ≥ 30 kg/m^2), tobacco use, alcohol use, breast cancer family history and use of previous hormonal contraception. The reproductive and obstetric characteristics analyzed were age at menarche (up to 11 years, >11 years); sexarche (≤17 and >17 years); number of pregnancies (<4; 4-10); parity (<3; 3-6); history of abortion (spontaneous or induced); type of delivery (caesarean section; vaginal); gestational age (≥37 weeks; <37 weeks); birth weight (<2,500g; ≥2,500g); and 1st and 5th minute Apgar (<7; ≥7). Variables were categorized according to the mean or with commonly used clinical criteria. The histological tumor type and breastfeeding were also studied. The information collected was reviewed and coded by researchers. To ensure entry quality, data were entered twice and checked in the Epi-Info 3.5.2 program (*US Centers for Disease Control and Prevention*), which was used for database construction and statistical analysis.

Data review

Frequencies, means and standard deviations of the factors studied between cases and controls were calculated. Statistical tests (Student's t and Fisher's test) were used to compare the characteristics between cases and controls. The adjusted odds ratios (OR) and their 95% CI were calculated using conditional logistic regression (pairing by mother's age). The selection of variables to be included in the model considered scientific knowledge on the subject. We also used the AIC criterion for the specification of the final model[10]. With breast cancer as the dependent variable, independent variables included in the model were mother's age at the first gestation (in years), family history, early menarche (age of menarche £12 years vs. >12 years), high parity (parity>3 live births vs. £ 3 live births) and low schooling (illiterate/elementary school vs. secondary school/higher education). We used the R-Project program, version 3.2.4 in the analyses.

Ethical aspects

HUPE Research Ethics Committee approved this study (CAAE 0221.0.228.000-10), ensuring the data anonymity and confidentiality.

Results

The mean age of pregnant women in both groups was approximately 35.5 ± 5.2 years (p = 0.50). In both groups, 33.3% were aged between 25 and 34 years. The breast cancer group showed lower schooling level (52.4%) than controls (21.4%) (p = 0.01) (Table 1).

The mean BMI of the case group was normal (27.1 ± 4.3) and that of the control group showed a tendency to overweight (33.2 ± 7.7) (p = 0.001). No significant difference was found between the groups in relation to variables ethnicity, tobacco use, alcohol use, breast cancer family history and use of previous hormonal contraception (Table 1).

The case group evidenced age of first pregnancy over 30 years in 28.6% versus 2.4% in the control group (p = 0.03). The mean age of menarche was similar in both groups (12.3 years), and the event occurred before 11 years of age in 28.6% of patients in the case group and 21.4% in the control group (p = 0.37). The case group showed late first sexual intercourse, with a mean age of 19.5 years, whereas in the control group it was 17.4 years (p = 0.04). There was no significant difference between the number of pregnancies, deliveries or abortions, nor in the type of delivery between the groups studied. The Apgar score was similar in both groups (Table 2).

Table 1. Sociodemographic and health characteristics of the pregnant women.

Variable	Categories	Case Group n (%)	Control Group n (%)	p-value
Age (years)	< 35	7 (33,3)	14 (33,3)	0,50
	≥ 35	14 (66,7)	28 (66,7)	
	Mean ± SD	35,5±5,2	35,5±5,1	0,96
Ethnicity	White	4 (19)	18 (28,6)	0,19
	Non-white	17 (81)	28 (62,2)	
Schooling	Illiterate / Elementary	11 (52,4)	9 (21,4)	0,01
	Secondary /Higher	10 (47,6)	33 (78,6)	
BMI	< 30	16 (76,2)	18 (43,9)	0,01
	≥ 30	5 (23,8)	24 (57,1)	
	Mean ± SD	27,1±4,3	33,2±7,7	0,01
Alcohol use	No	19 (90,5)	39 (92,9)	0,54
	Yes	2 (9,5)	3 (7,1)	
Smoking	No	20 (95,2)	34 (81,0)	0,12
	Yes	1 (4,8)	8 (19,0)	
Breast cancer family history	No	18 (85,7)	35 (83,3)	0,56
	Yes	3 (14,3)	7 (16,7)	
Previous use of hormonal contraception	No	3 (18,8)	3 (10,3)	0,36
	Yes	13 (81,2)	26 (89,7)	

SD, standard deviation; BMI, body mass index.

Breastfeeding in the current gestation corresponded to 88.1% of pregnant women in the control group and 10% in the case group. Stages of breast cancer among pregnant women resulted in three patients (15%) in stage IIB and 18 patients (85%) in stages III and IV. The infiltrating ductal carcinoma was the predominant histological type in 95% (20) of the cases and one patient (4.8%) had a phyllodes tumor.

Treatment during pregnancy consisted of mastectomy in 14.3% (3), mastectomy and chemotherapy (CT) in 19% (4) and exclusive CT in 38% (8). Six patients (28.6%) were not treated in the service, since one patient died due to pulmonary-borne sepsis and five patients arrived at the service to interrupt the pregnancy due to clinical or obstetric complications.

Analyzing the mother's characteristics, estimates of the adjusted analysis (paired by mother's age) indicate that the higher the mother's age in the first pregnancy, the greater the probability of breast cancer (OR = 1.27) and that mothers with low schooling were more likely to have breast cancer (OR = 8.49) (Table 3).

Discussion

Without a doubt, the main risk factor for breast cancer is being female. Being over 35 is the second most important factor[11].

Our study was developed with prevalent GBC cases in a decade (2004-2014), where one-third of the case group was below 35 years of age (Table 1). Bell et al.[7] showed that only 14.3% of women aged < 35 years had GBC.

Andersson et al.[12] describe that GBC among Swedish women aged 15-44 years corresponds to 7% of all breast cancer cases in this age group, confirming their rarity. Between 1963 and 1974, the most affected group was 25-29 years (31.5% of cases) and then 30-34 years (17.9%), numbers that changed to 27.9% and 23.6%, respectively, in 1990-2002. As women tend to delay motherhood, GBC age tends to increase and get closer to the breast cancer age in non-pregnant women[12].

GBC risk factors are still not well established and the literature shows few studies that include women diagnosed with breast cancer during pregnancy. Hou et al.[5] developed the first study to evaluate GBC-associated risk factors with data from a Nigerian cohort collected over a decade, the same time span as in this study. However, authors called GBC carriers women who developed breast cancer in the period up to five years after the first birth (divided into two groups: up to two years and 3-5 years postpartum) and compared them with women with breast cancer diagnosis after five years of childbirth (non-GBC cases), and with controls with the same delivery interval, but without the disease. The reproductive factors studied were age at menarche, parity, age

Ciência & Saúde Coletiva, 24(6):2361-2369, 2019

Table 2. Reproductive and obstetric characteristics of the patients.

Variable	Category	Case Group	Control Group	p-value
		n (%)	n (%)	
Age at 1st pregnancy (years)	≤ 30	15 (71.4)	41 (97.6)	0.01
	> 30	6 (28.6)	1 (2.4)	
	Mean ± SD	25.3 ± 6.7	21.9 ± 5.2	0.03
Menarche (years)	≤ 11	6 (28.6)	9 (21.4)	0.37
	> 11	15 (71.4)	33 (78.6)	
	Mean ± SD	12.3 ± 1.8	12.3 ± 1.4	0.71
Sexarche (years)	≤ 17	7 (33.3)	25 (59.5)	0.04
	>17	14 (66.7)	17(40.5)	
	Mean ± SD	19.5 ± 5.1	17.4 ± 2.7	0.03
Number of pregnancies (1 to 10)	< 4	13 (61.9)	22 (52.4)	0.33
	≥ 4	8 (38.1)	20 (47.6)	
	Mean ± SD	3.7 ± 2.3	3.5 ± 1.7	0.74
Parity (0 to 6)	< 3	13 (61.9)	24 (57.1)	0.79
	≥ 3	8 (38.1)	18 (42.9)	
	Mean ± SD	2.2 ± 1.7	2.2 ± 1.5	0.91
Abortion	No	13 (61.9)	22 (52.4)	0.33
	Yes	8 (38.1)	20 (47.6)	
	Mean ± SD	0.6 ± 0.9	0.7 ± 0.8	0.57
Type of delivery	Cesarean section	12 (60.0)	27 (64.3)	0.48
	Vaginal	8 (40.0)	15 (35.7)	
Gestational age (weeks)	< 37	9 (42.9)	7 (17.5)	0.06
	≥37	12 (57.1)	33 (82.5)	
Birthweight	≤ 2,500g	8 (40.0)	9 (21.4)	0.11
	> 2,500g	12 (60.0)	33 (78.6)	
APGAR 1st minute	< 7	4 (21.1)	7 (17.1)	0.48
	≥ 7	15 (78.9)	34 (82.9)	
APGAR 5th minute	< 7	1 (5.3)	1 (2.4)	0.15
	≥ 7	18 (94.7)	40 (97.6)	

SD, Standard deviation.

Table 3. Association between maternal age at first pregnancy and gestational breast cancer (paired analysis).

Independent variables1:	Crude OR	CI 95%	p-value	Adjusted OR	CI 95%	p-value
Age at 1st pregnancy	1.12	1.01; 1.24	0.04	1.27	1.05; 1.54	0.02
BC family history	0.83	0.15; 4.52	0.82	3.29	0.32; 33.60	0.32
Early menarche	1.35	0.38; 5.26	0.61	4.17	0.02; 2.36	0.22
High parity	1.04	0.29; 3.64	0.96	2.25	0.26; 19.09	0.45
Low schooling	5.06	1.34; 19.03	0.02	8.49	1.55; 46.51	0.02

95% CI, 95% confidence interval; OR, Odds Ratio [1]Conditional logistic regression model (paired by maternal age) to explain the occurrence of breast cancer according to the characteristics: age at first pregnancy (years), breast cancer family history, early menarche (age ≤12 vs. > 12 years), high parity (> 3 vs. ≥ 3 live births) and low schooling (illiterate/primary school vs. secondary school/higher education).

at first delivery, duration of breastfeeding and abortion. The group that showed GBC up to two years postpartum had BRCA1 and BRCA2 with higher frequency (p = 0.03) and the first delivery occurred at a later age (25.9 ± 4.6 vs. 21.9 ± 4.6; p = 0.001). However, no significant associations remained after adjustment for confounding factors[5].

Mother's age at the first pregnancy is cited in the literature as an established risk factor for breast cancer[5-7,11-13]. The risk of developing breast cancer in women who had their first child after

30 years of age is approximately twice the risk of those delivering younger than 20 years[10]. If the first birth occurred after the age of 35, this risk is greater than in nulliparous women. Having a second child at an early age reduces the risk of breast cancer[13].

Our study showed that the probability of GBC increases 27% for each year over the age of the first pregnancy (p-value < 0.02). This is the first study that included pregnant women not affected by breast cancer as controls, with similar age and time of delivery, which may have contributed to making the group more homogeneous.

Other authors confirm this association. Bell et al.[7] studied women with breast cancer and investigated whether the diagnosis occurred in pregnancy or up to one year postpartum (13 and 9 women, respectively, were included as GBC), comparing them with 377 women in the non-GBC group. They concluded that women with first pregnancy after 35 years of age are at higher risk of developing breast cancer in life than nulliparous women. This risk is reduced in subsequent pregnancies, although the age of the first delivery continues to influence the risk[7]. Merviel et al.[8] observed low parity and late age in the first gestation in the high-risk group for breast cancer, where more than 30% of the women were nulliparous or primiparous, 20.6% had their first pregnancy after 30 years and only 8.7% before 20 years. In the low-risk group, the mean age at the first pregnancy was 22.8 ± 3.9 years, while in the high-risk group this was 37.6 ± 2.3 years (p < 0.00001)[8].

The explanation for the late first pregnancy to be a risk factor for breast cancer are the increased estrogen concentrations that are positively associated with breast cancer risk before the age of 40, corroborating with the theory that the hormonal changes that occur during pregnancy play a role in their development[13,14]. Pregnant women less than 25 years of age and who have elevated HCG levels during the first quarter of gestation are 33% less likely to be diagnosed with breast cancer after 50 years. It is believed that the conclusion of a gestation at a young age is the necessary factor to fully differentiate the mammary epithelium and protect against cancer in the future[14].

According to Ardalan et al.[15], mother's age in the first full-term pregnancy is the only factor established to influence this risk significantly. GBC increases proportionately as women delay reproduction. Associations among other characteristics of pregnancy and GBC risk show conflicting results[15].

Other potential risk factors include a family history of breast cancer, use of hormonal contraceptives, alcohol consumption, height and body mass index (BMI). Age at diagnosis, ethnicity, and schooling level are possible confounding factors[5].

In our study, most sociodemographic, health, and reproductive variables did not show association with GBC. There were differences in the bivariate analysis between three variables cited in the literature as confounding factors with discordant results, according to several authors, namely: schooling, BMI and sexarche (Tables 1 and 2).

In relation to the sexarche, this factor alone is probably not relevant, but it is related to the age of the first gestation. In the literature, we found only one article, with an African population, that found association between first sexual intercourse before 15 years of age and reduced risk of breast cancer (OR=0.46, 95% CI 0.27-0.79), but due to the high parity found in the region, it is not possible to generalize these findings[16]. In this study, there was a significant difference when the cut-off point was established by the mean (17 years). However, when comparing adolescents younger than 15 years with the group aged ≥15 years, the result was similar in both groups (p=0.68).

As for the lower BMI found in our study in the case group, this may be because they show the disease at the time of pregnancy. According to McPherson et al., obesity is associated with twice the risk of postmenopausal breast cancer, whereas among premenopausal women, it is associated with a reduced incidence[13]. However, these results are controversial or unconfirmed by other authors. Merviel et al.[8] reaffirm that overweight and obesity decrease the risk of breast cancer in menacme, Troisi et al.[17] (OR = 0.76, 95% CI 0.65-0.90), whereas Hou et al.[5] found no association with BMI, because it may vary according to ethnicity and hormonal status.

Schooling is a controversial factor in the literature and can be a confounding factor, since results are divergent. Some studies did not find a significant difference[16] and others report a higher level of education among the cases[10], which is not in agreement with the findings of this study, requiring additional studies to confirm the actual association.

Other variables consecrated in the literature as breast cancer risk factors did not show significance for GBC in this study. Breast cancer family history increases the risk by 80% when in first-degree relatives, threefold if in two first-degree cases and fourfold if in three or more rela-

tives[8]. Hou et al.. argue that breast cancer family history may be a strong predictor, particularly for GBC up to two years postpartum (OR=3.28, 95% CI 1.05-10.3)[5]. Women with breast cancer family history are at increased risk for the disease at an early age and appear to be at a greater risk of breast cancer in the first five years after first delivery than women without a family history, although not all studies confirm this observation[7].

Parity ≥ 3 was described by Ghiasvand et al.[11] to have a strong protective effect for the development of non-gestational breast cancer ($p < 0.001$). However, Hou et al.[5]. found no association between parity and abortion with GBC. The trend towards reduced parity and breastfeeding time may partly explain the increased incidence of breast cancer among young Iranians[11].

Likewise, we did not observe a statistically significant difference concerning birthweight and preterm birth rate. Regarding Apgar score, while more women with GBC had newborns with Apgar < 7 in the first minute, approximately 95% of the cases and controls showed good recovery of newborns in the fifth minute with Apgar ≥ 7.

Ardalan and Bungum[15] observed that when pregnancy reaches 40 weeks, protection against breast cancer development is set, perhaps because breast cells have more time to complete differentiation and maturation, a process that begins in the third quarter of gestation.

While the case group showed lower gestational age and lower birthweight, these results did not show any significance. Amant et al.[18] studied 129 children from mothers with breast or hematologic cancer exposed during pregnancy to chemotherapy or radiotherapy. They observed that the frequency of small for gestational age (SGA) was higher in mothers with GBC, but the treatment did not cause cognitive, cardiac or general health damage in early infancy, indicating that pregnancy does not justify delayed start of mother's disease treatment.

Mogos et al.[19] observed a high risk of low birthweight (24%) and preterm birth (33%) in pregnant women with a diagnosis of reproductive cancer (uterus, ovary, cervix, fallopian tubes, vagina, vulva and breast).

Regarding breastfeeding, 90% of the cases did not breastfeed in the current pregnancy, whereas non-breastfeeding was 11.9% in the control group. This result may be related to the fact that women in the case group underwent chemotherapy, which contraindicates breastfeeding. We did not have access to information about breastfeeding in previous pregnancies. In the study by Bell et al.[7] only two patients breastfed among the nine patients who had a diagnosis of breast cancer within one year of delivery. Prolonged breastfeeding (> 37 months) has an inverse association with the risk of developing breast cancer, with a protective relationship that persisted after adjusting for potential confounding factors, such as parity, age at first delivery, age at menarche and educational level[11,20].

The protective action mechanisms of breastfeeding in protecting against breast cancer are still uncertain. The main hypotheses include that breastfeeding promotes breast tissue differentiation; causes prolonged hormonal changes, probably estrogen decline and prolactin increase, suppressing ovulation. It is one of the few potentially modifiable protective factors that are used for women at risk[20].

The burden of delaying motherhood beyond the age of 30 increases the transient risk of breast cancer for two reasons: elevated peak of breast cancer incidence in the early postpartum years and the increased risk of persisting for 30-50 years post-partum[6].

One of the limitations of the study is the incorrect completion of medical records, with many missing data or omission of information by patients. In addition, the low frequency of the disease did not allow us to evaluate a large number of cases, although our study included cases that occurred in a period of 10 years. The lack of specific studies on breast cancer during the gestational period hindered comparison of our results in several aspects.

In conclusion, our data confirm the association between low schooling and primiparity over the age of 30 and GBC. However, further studies on young women are required to explore unknown risk factors. Considering the great impact of breast cancer on the lives of affected pregnant women with compromised quality of life, especially in the functional and social aspects[21], we reiterate the importance of anamnesis and thorough physical breast examination during prenatal and puerperal periods.

Collaborations

DLM Monteiro, AJB Trajano, NCP Rodrigues participated in the project design, methodology and data analysis and interpretation. DLM Monteiro, CL Nunes, CA Antunes, EM Almeida, DBS Barmpas and ALC Magalhães participated in the writing of the article.

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