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Effects of risk factors in the likelihood of breast cancer subtypes in Brazilian women

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ABSTRACT

Introduction: Breast cancer is a heterogenous disease with multiple causes and it lacks more investigation related to its risk factors. **Objective:** To evaluate the likelihood of breast cancer subtypes according to the positivity to estrogen and progesterone receptors (ER+ and PR+ respectively), with or without the expression HER2, related to the following risk factors: age, parity, diabetes mellitus, arterial hypertension, occurrence of familiar cancer case and body mass index (BMI). **Methods:** The sample with 79 individuals was divided into three subtypes 1 (ER+/PR-), 2 (ER+/PR+) and 3 (RE+/RP+/HER+) and then analyzed by quantitative methods using Ordinal Generalized Linear Models (OGLM) for estimating the marginal effects of risk factors for the studied subtypes, and modeling the heteroscedasticity in terms of error. **Results:** It were observed the following statistically significant positive effects: (1) age for the tumoral subtype 1 (ER+/PR-) and (2) parity for the subtype 2 (ER+/PR+); while the significant negative effects were: (1) age for subtype 3 (ER+/PR+/HER2+); (2) parity for both 1 (ER+/PR-) and 3 (ER+/PR+/HER2+) subtypes; and arterial hypertension for subtype 1 (ER+/PR-). There were no statistically significant effects for BMI, Diabetes mellitus and occurrence of familiar cancer variables on the studied tumoral subtypes. **Conclusion:** The risk factos age and parity demonstrated varied effects for the breast cancer subtypes according the expression of estrogen, progesterone and HER2 receptors.

Keywords: breast neoplasm; parity; risk factors; age; hypertension.

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INTRODUCTION

Breast cancer is the most incident malignant neoplasm in the female population, excluding non-melanoma skin cancer, and responsible for the highest mortality rate for women worldwide[1]. Despite the efforts of the female population and public policies for prevention and early detection of the disease, the worldwide mortality rate has increased in recent decades, with an average annual increase of 0.7 per 100,000 inhabitants from 1990 to 2015[2]. In Brazil, it was estimated the emergence of 66,280 new cases of breast cancer for each year of the triennium 2020-2022, with an estimated risk of 61.61 new cases per 100,000 women[3].

The onset of breast cancer is multifactorial[4]. The risk factors can be divided into three groups: (1) genetic and hereditary[5]; (2) environmental and behavioral[6]; and (3) gynecological and reproductive[7], with age-dependent distribution (below or above 50 years)

and association with family history of cancer cases in first-degree relatives[8,9]. These factors can be considered modifiable or not. The former includes smoking, alcohol consumption, overweight, and obesity, for example, while the non-modifiable ones refer to those such as genetic mutations and family history of cancer. The variable spectrum of risk factors, added to the subjectivity of the patient to the carcinogenesis process, culminates in a heterogeneous disease with several possible clinical and histological forms[10]. Epithelial cell carcinoma is the most common histological type and is divided into in situ and invasive lesions. The invasive carcinoma of no special type accounts for most cases (70-75%), followed by lobular carcinomas (10-14%)[11].

The search for more specific methods to have a more accurate characterization of breast cancer led to the proposition of molecular classifications by immunohistochemistry - IHC, in the following types: luminal, amplified HER2 and triple negative (TN)[12]. The luminal subtypes are the most frequent and have a gene expression similar to the luminal breast epithelium, being classified into luminal A and B, with expression of estrogen receptor (ER) positive and/or progesterone receptor (PR) positive. Tumors with human epidermal growth factor receptor-2 (HER2) amplification represent 15-20% of malignant breast neoplasms and this type of change causes the activation of the cell proliferation pathway - RAS/RAF/MEK/ERK[13]. TN subtypes are characterized by the absence of ER, PR and HER2 expression, being a genetically heterogeneous group[14]. This classification has changed the form of the clinical management of breast cancer with the proposition of approaches focused on tumor biology, electing patients to hormone therapy (RE+) or inclusion of immunotherapy (HER2+) in the therapeutic scheme[15].

Due to the benefits for therapy and prognostic value for breast cancer, the expression of ER, RP and HER2 has been studied in relation to risk factors for the disease. A study by Yang et al.[16] demonstrated associations between reproductive risk factors (age at menarche, parity, age at first pregnancy), body mass index (BMI) and family history of cancer in a first-degree relative and molecular subtypes classified by positive or negative labeling for ER, RP, HER2 and other markers for TN type. Logistic regression models were used to estimate associations between the factors analyzed and the molecular subtypes. The results showed clear association between the studied factors and hormone receptor-positive tumors.

Despite the epidemiology of breast cancer being one of the most studied[17], only half of the occurrence of cases is explained by well-established risk factors, with a large majority of undefined causes. This reflects the need to improve the evaluation of the interaction between risk factors by seeking to understand the intricate biological network between etiologic factors, or even identify differences between tumor subtypes using new research methods[4]. For example, evidence has shown the relationship between breast cancer, diabetes mellitus and hypertension, and the relationship between overweight and obesity with metastasis and mortality from the disease[18-20]. However, more studies are needed to further elucidate these relationships.

Thus, this research extends the investigation regarding breast cancer risk factors by analyzing the probability of hormone receptor positive (RE+ and/or RP+) tumor subtypes, with or without HER2 expression, in relation to the following factors: age, birth, diabetes mellitus, hypertension, occurrence of familial breast cancer, and BMI by Ordinal Generalized Linear Models (OGLM).

METHODS

Study design and population

The study is classified as observational, analytical and cross-sectional[21]. The research participants were patients, all female, diagnosed with breast cancer and treated at Casa de Saúde Nossa Senhora do Perpétuo Socorro (CSNSPS), during the period from 2010 to 2018. CSNSPS is a private hospital based in the municipality of Garanhuns located in the interior of Pernambuco, 230 km from the state capital, which provides oncology care mainly through the Unified Health System (SUS). CSNSPS is the reference service for the region known as Agreste Meridional (Southern Agreste), the headquarters of one of the state health regions, known as the V region, made up of 21 municipalities with a population of more than half a million inhabitants.

The eligibility criteria were: i) diagnosis confirming for breast cancer; ii) disease framed in stages 1 to 4; and iii) presentation of pathological examination and IHC. Patients with incomplete data or no IHC result were excluded from the sample.

Sample and data collection

Data were collected, from June to November 2018, through a documental survey in the patients' records, resulting in a database with information from 149 patients. After exclusion of observations with missing and inconsistent data, the sample resulted in n=79. Table 1 presents the variables used in the study with respective rationales[22-27] for their use.

Data analysis

After tabulation, the data were analyzed using quantitative methods. The research developed by Parise et al.[22], Li et al.[8] and Yang et al.[16] used mainly logit regression to identify the effects studied. However, the logit model requires the error term of the regression to have logistic distribution, its failure to meet biases not only the standard error, but also the coefficients. Since breast cancer research still lacks certainty about its determinants, it is natural that the estimated models are not

Table 1: Description of the variables used in the research.

Name	Variable Description	Expected results	Rationale
Dependent Variable			
Tumor subtype	It is an ordinal variable according to the expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 receptor, with values 1 (RE+/RP-), 2 (RE+/RP+) and 3 (RE+/RP+/HER2+).		Perou et al.[12] Parise et al.[13] Yang et al.[16]
Independent variables			
Age (years)	This is the age of the patient at the time of the first diagnosis for breast cancer.	(+)	Parise et al.[22] Wong et al.[23]
Childbirth (unit)	This is the number of births the patient had before the first diagnosis.	(-)	Yang et al.[16] Ma et al.[24]
Diabetes (binary)	Identifies if the patient has diabetes mellitus.	(+)	Attner et al.[25]
Hypertension (binary)	Identifies if the patient has hypertension.	(+)	Bosco et al.[26]
Mother with breast cancer (binary)	Identifies whether the patient's mother had breast cancer.	(+)	Collaborative Group on Hormonal Factors in Breast Cancer[9]
BMI (unit)	This is the patient's Body Mass Index.	(+)	Suzuki et al.[27] Yang et al.[16]

homoscedastic due to the omission of relevant and unknown variables, and it is therefore necessary to consider heteroscedasticity in the estimation. In this sense, the research overcomes this difficulty and innovates by estimating the marginal effects by the Ordinal Generalized Linear Models (OGLM), modeling heteroscedasticity, and its coefficients are unbiased[28,29]. The statistically positive or negative effect occurs when the null hypothesis of indifference of the observed variable is rejected, using the p-value of the z-test for the regression coefficients estimated by the OGLM.

Table 2: Descriptive statistics of the variables used in the research.

Variable	Average	Standard deviation	Minimum	Maximum
Age (years)	55.96	12.67	26.00	85.00
Birth (units)	3.56	4.08	0.00	19.00
Diabetes mellitus (binary)	0.31	-	0.00	1.00
Hypertension (binary)	0.30	-	0.00	1.00
Mother with cancer (binary)	0.16	-	0.00	1.00
BMI (units)	26.84	5.38	12.3	40.25

Ethical considerations

The study followed the resolution nº 466/2012 of the National Health Council (CNS) and was approved by the Research Ethics Board from Universidade de Pernambuco under CAAE nº: 82425617.4.0000.5207.

RESULTS

Table 2 presents the descriptive statistics of the studied sample of 79 patients, 12 (15.2%) from tumor subtype 1 (ER+/PR-), 55 (69.6%) from tumor subtype 2 (ER+/PR+) and 12 (15.2%) from tumor subtype 3 (ER+/PR+/HER2+). The mean age of breast cancer patients was 55.96 ±12.67 years. The patients had a mean of 3.56 deliveries. Hypertension affected 30% of the patients, while diabetes mellitus (DM) affected 31% of the sample. In addition, on average, the patients were overweight, with a BMI of 26.84 (Kg/m^2).

Table 3 presents the results of coefficient and marginal effect estimation by OGLM to identify the effect of the independent variables on the studied breast cancer subtypes.

The obtained results show that the marginal effects of the variables studied are different and depend on the positivity for the receptors (ER, PR and HER2) evaluated. Age had a statistically positive effect on the grade of tumor subtype 1 (ER+/PR-). In the subtype classified as 3 (ER+/PR+/HER2+), age showed a negative effect, while the RE+/RP+ subtype did not show any statistically significant effect. Thus, it is interesting to note that the higher age of the patients reduces the probability of occurrence of subtypes 1 (ER+/PR-) and 3 (ER+/PR+/HER2+).

The number of deliveries of patients also showed effects in the different tumor subtypes. In subtypes 1 (ER+/PR-) and 3 (ER+/PR+/HER2+) a greater number of deliveries reduces the probability of their occurrence, while for subtype 2, the effect is positive. On the other hand, hypertension showed a statistically significant and negative effect only in the first tumor subtype 1 (ER+/PR-). In other words, the probability of occurrence is reduced in this tumor subtype when the patient is hypertensive.

The variables Diabetes mellitus, Mother with Cancer and BMI did not show any statistically significant effect on tumor subtypes with the method used. Finally, the modeling of the variance by the variable birth was statistically significant, that is, the treatment of heteroscedasticity was relevant for obtaining unbiased coefficients of the study.

Table 3: Estimation results with the Ordinal Generalized Linear Model (OGLM) regression.

Variable	Coefficient	Standard Error	Z	Marginal Effect		
				Value of the dependent variable		
				1 (ER+/PR-)	2 (ER+/PR+)	3 (ER+/PR+/HER2+)
Age (years)	-0.021	(0.011)	-1.89*	0.004***	-0.001	-0.003*
Birth (units)	-0.051	(0.021)	-2.44**	-0.029***	0.073***	-0.044**
Diabetes mellitus (binary)	0.298	(0.299)	1.00	-0.058	0.011	0.047
Hypertension (binary)	0.426	(0.250)	1.70*	-0.083*	0.016	0.067
Mother with cancer (binary)	-0.353	(0.391)	-0.90	0.069	-0.013	-0.056
BMI (units)	-0.020	(0.023)	-0.88	0.004	-0.001	-0.003
Sigma (ln)						
Childbirth	-0.193	(0.058)	-3.32***			

*p≤0.10, **p≤0.05 e ***p≤0.01

DISCUSSION

In this study, a sample of breast cancer patients was separated into three subtypes according to the expression of hormone receptors for estrogen (ER) and progesterone (PR), and HER2 receptors. The groups formed were then analyzed with respect to the factors age, birth, diabetes mellitus, hypertension, occurrence of cancer in family, and BMI by Ordinal Generalized Linear Models (OGLM). Breast tumors have been classified from IHC labeling for ER and RP[12]. Tumors expressing ER (ER+) or PR (PR+), collectively referred to as hormone receptor positive (HR+) tumors, are more responsive to endocrine therapy and demonstrate different profiles for risk factors[16]. To further corroborate for molecular subtyping, tagging for HER2 identifies a subgroup of breast tumors with a worse prognosis, but which benefit from monoclonal antibody therapy as adjuvant for patients with amplification and/or overexpression of the corresponding gene[4]. The results obtained allowed us to identify the effect of the variables age, delivery, and hypertension on subtypes 1 (ER+/PR-), 2 (ER+/PR+) and 3 (ER+/PR+/HER2+).

Age is the most important single risk factor for cancer in general and influences the morphological and molecular heterogeneity of specific types of cancer[4]. Average age found in the sample was 55.96 ± 12.67 years, which is higher than the Brazilian mean age at diagnosis, which is 49.0 years (45.5-52.6)[30]. Anderson et al.[31] showed the existence of two main groups of breast cancer according to age at diagnosis, in a bimodal distribution pattern or age peaks around 50 and 70 years. The bimodality in disease onset is also accompanied by a bimodal pattern for RE positivity. Cancers with negative labeling for ER (ER-) are dominant for the group diagnosed near the age of 50, while ER+ tumors are more common near the age of 70. This distribution may explain the difference found between the sample studied and the data for the Brazilian population, because here, all patients were ER+, with a mean age over 50 years.

With increasing age, tumors are more likely to be ER+. Young women are more likely than older women, and African American and Hispanic women are more likely than white women to have the ER-/PR-/HER2- or TN13 subtype. Thus, age is used as a predictive factor of increased risk, affecting, for example, the overall survival rates and the frequency in the occurrence of metastases. Tumors with poor prognosis are associated with a younger age group, while tumors with better prognosis are associated with a later age group[32]. The data obtained for the sample studied showed a statistically positive effect for subtype 1 (ER+/PR-) and a negative effect for subtype 3 (ER+/PR+/HER2+). These results are supported by data indicating that patients with TN, HR+/HER2+ and HR-/HER2+ profiles are 10-30% less likely to be diagnosed compared to patients HR+/ HER2−[33].

Factors related to a woman's reproductive life, in turn, are associated with the development of breast cancer[34]. For example, nulliparous women have an increased risk of breast cancer, if compared to women with children (relative risk 1.2-1.7). Although parity confers an increased risk of breast cancer in the first five years after delivery, parity confers a protective effect over time[35]. In the sample studied, the average number of births was twice as high (3.56 births) as the birth rate of the Brazilian population, which is 1.74 children per woman in 2014[36].

Reproductive factors are explained by the hormonal action on female breasts that leads to the development of sporadic breast cancer. Homones such as estrogen and progesterone stimulate the development of the breasts during puberty, menstrual cycles, and pregnancy. During menstrual cycles, stimulation by estrogen and progesterone increases cell proliferation and can cause damage to cellular DNA. The repetition of this process with each cycle, coupled with defects in the repair systems, can lead to the accumulation of mutations that generate pre-malignant cells and then transformed tumor cells. At this stage, hormones stimulate the growth of these cells and the proliferation of stromal cells that support cancer development[10].

The studies performed with regard to parity indicate lower risks for multiparous women versus nulliparous women for breast tumors of type Luminal A. In other words, ER+ with or without positivity for PR[16,37]. According to Fortner et al.[38], multiparous women have lower risk of having ER+ breast cancer (vs. nulliparous women, hazard ratio 0.82 [0.77-0.88]), as well

as an inverse association between Luminal B subtype and higher number of deliveries. However, it remains unclear how parity decreases the risk for breast cancer. The explanation found so far is related to a probable protective effect conferred by hormonal changes during pregnancy, which results in a more differentiated mammary gland that is less susceptible to changes in specific cell subpopulations[7].

The effect of parity in the sample studied was evidenced by the results obtained by OGLM: the highest parity had a negative effect for the subtypes (ER+/PR-) and 3 (ER+/PR+/HER2+), while for subtype 2 (ER+/PR+), the effect was positive. In other words, tumor subtypes with PR- or HER2+ suffer a negative effect of parity, and parity positively influences the PR+ profile without HER2 expression. This result can be explained by the greater exposure of female breasts to a distinct profile, with various hormones, including progestin[7], during the gestational period, leading to a likely activation and expression of these receptors throughout life and after the cellular transformation processes that occur in carcinogenesis. It is important to note that most studies seek association between parity and risk or protective effect for a specific molecular profile[16,38]. The opposite was analyzed here; the variable "births" explains the presence of subtypes according to the positivity for the hormone receptors studied. The positive effect for the ER+/PR+ subtype confirms the indication for these patients of tamoxifen therapy, and the expression of PR can be used for indication to treatment with aromatase inhibitors[7,15]. That is, parity explains the expression profile of hormone receptors in the sample studied.

Excess body fat can progressively cause or exacerbate a spectrum of comorbidities, including type 2 diabetes mellitus, hypertension, and breast cancer mortality[18]. Therefore, these three variables were studied in this study. Clinical and preclinical data have provided evidence that obesity may worsen breast cancer incidence, severity, and mortality[18]. The sample studied had a mean BMI in the overweight range (26.84 kg/m^2), but there was no significant effect for the tumor subtypes studied. Obesity measured by BMI has presented variable results, menopausal-associated and, regarding the relative risk for breast cancer, especially the hormone receptor-positive subtypes, due to a probable greater peripheral conversion of estrogen[16].

Considering hypertension and diabetes mellitus, 30% of the sample studied presented both comorbidities. In Brazil, the proportion of individuals aged 18 years or older reporting a diagnosis of hypertension was 21.4% in 2013, with a higher proportion of women (24.2%). While for diabetes mellitus, the proportion in the country was 6.2% of the population aged 18 years or older, with a higher proportion among women (7.0%), both comparisons in relation to males[39]. Of the two comorbidities studied, only hypertension showed a negative effect for hormone subtype 1 (ER+/PR-). A recent systematic review with meta-analysis showed that hypertensive individuals have an increased risk for breast cancer[20]. The data obtained here indicate that if the patient is hypertensive, the occurrence of the ER+/PR- subtype will be reduced. That is, besides the hypertensive woman being more susceptible to developing the disease[40], this comorbidity may influence the expression and consequent biological behavior of the tumor. It is noteworthy that there is no literature evaluation similar to the one developed here, requiring, therefore, further study on the mechanism between hypertension and expression of hormone receptors in breast tumors.

In summary, the results obtained allow the conclusion that the variables age, childbirth and hypertension have effects on breast tumor subtypes related to the profile of receptors for estrogen and progesterone, in addition to HER2. The effects were varied by subtype, with the positive effects of age for subtype 1 (ER+/PR-) and delivery for subtype 2 (ER+/PR+) being statistically significant. Hypertension had a weak negative effect only for subtype 1 (ER+/PR-). From a methodological point of view, this work contributes to OGLM being used to understand the complex biology of breast cancer, specifically related to those expressing hormone receptors, opening the way for further analyses with more variables and larger samples. Finally, we emphasize that it was possible to treat heteroscedasticity in order to obtain unbiased coefficients for the study.

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