Histological and Immunohistochemical Characteristics for Hereditary Breast Cancer Risk in a Cohort of Brazilian Women

Características histológicas e imunohistoquímicas para risco hereditário de câncer de mama em uma coorte de mulheres brasileiras

Renata Mendes de Freitas¹,², Maximiliano Ribeiro Guerra¹, Vivian Assis Fayer¹, Angélica Atala Lombelo Campos¹, Jane Rocha Duarte Cintra³, Joan Warren⁴, Rafaela Russi Ervilha¹, Camila Damasceno de Paula¹, Maria Teresa Bustamante-Teixeira¹

¹Department of Public Health, Faculdade de Medicina, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil
²Epidemiology of Congenital Malformations Laboratory, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil
³Oncology Institute, Hospital 9 de Julho, Juiz de Fora, MG, Brazil
⁴Independent Researcher, Washington, United States

Address for correspondence Renata Mendes de Freitas, PhD, Rua José Lourenço Kelmer, s/n, Juiz de Fora, MG, Brazil (e-mail: renatafreitas.mendes@gmail.com).© 2022. Federação Brasileira de Ginecologia e Obstetrícia. All rights reserved.

Keywords
► breast cancer
► hereditary breast and ovarian cancer syndrome
► cohort studies
► immuno-histochemistry
► genetic counseling

Abstract

Objective The study aimed to characterize the clinical, histological, and immunohistochemical profile of women with invasive breast cancer, according to the risk for Hereditary Predisposition Breast and Ovarian Cancer Syndrome in a Brazilian population.

Methods This is a retrospective study performed from a hospital-based cohort of 522 women, diagnosed with breast cancer treated at an oncology referral center in the Southeast region of Brazil, between 2014 and 2016.

Results Among the 430 women diagnosed with invasive breast cancer who composed the study population, 127 (29.5%) were classified as at increased risk for hereditary predisposition to breast and ovarian cancer syndrome. There was a lower level of education in patients at increased risk (34.6%) when compared with those at usual risk (46.0%). Regarding tumor characteristics, women at increased risk had higher percentages of the disease diagnosed at an advanced stage (32.3%), and with tumors >2cm (63.0%), with increased prevalence for both characteristics, when compared with those at usual risk. Furthermore, we found higher percentages of HG3 (43.3%) and Ki-67/C21 >25% (64.6%) in women at increased risk, with prevalence being about twice as high in this group. The presence of triple-negative tumors was observed as 25.2% in women at increased risk and 6.0% in women at usual risk, with the
Breast cancer has a multifactorial etiology associated with hormonal, reproductive, genetics, lifestyle-related factors, and it is more frequent in post-climacteric women. Most of these tumors originate in the ductal epithelium and acquire an invasive capacity. However, other histological types are found due to the great heterogeneity and different carcinogenic profiles of the tumors.

Molecular biology has allowed the investigation of several genes associated with carcinogenesis, including the analysis of gene expression profiles of breast cancers, which makes it possible to correlate them with disease prognosis and with response to treatment. In clinical practice, the immunohistochemical technique enables a quick, simple, and low-cost analysis of the expression of proteins that compose the tumor; additionally, it can evaluate the tumor grade and identify the molecular subtypes of breast cancer. Some characteristics of the breast tumor are essential for the clinical follow-up of the patients. The cell proliferation marker Ki-67 has an increased expression in breast tumors that may be associated with a higher risk of recurrence and worse prognosis. The histological grade given by the Nottingham Classification System refers to the sum of the tubular grade, nuclear grade, and mitotic index scores, indicating the degree of differentiation of the tumor tissue, which also influences the prognosis. Furthermore, it is noteworthy that the size of the tumor is related to the probability of recurrence and lymph node involvement.

The hereditary condition is the cause identified in 10 to 25% of breast and ovarian cancers, involving mutations in genes of high and moderate penetrance, such as the BRCA1 and BRCA2 genes. The National Comprehensive Cancer Network (NCCN) defines criteria that help identify women prone to hereditary breast cancer. These criteria take into account the clinical manifestation of pre-climacteric ages and more aggressive breast carcinogenesis, with a prevalence of absence of biomarkers being 2.5 times higher among women in the increased risk group.

**Conclusion**  From the clinical criteria routinely used in the diagnosis of breast cancer, the care practice of genetic counseling for patients at increased risk of hereditary breast cancer in contexts such as Brazil is still scarce.

**Resumo**  O presente estudo buscou caracterizar o perfil clínico, histológico e imunohistoquímico de mulheres com câncer de mama invasivo segundo o risco para a Síndrome de Predisposição Hereditária ao Câncer de Mama e Ovário em uma população brasileira. Trata-se de um estudo retrospectivo realizado a partir de uma coorte hospitalar composta por 522 mulheres diagnosticadas com câncer de mama entre 2014 e 2016 assistidas em um centro de referência oncológica localizado na região sudeste brasileira. Entre as 430 mulheres diagnosticadas com câncer de mama invasivo que compuseram a população de estudo, 127 (29,5%) foram classificadas como de risco aumentado para a síndrome de predisposição hereditária ao câncer de mama e ovário. Verificou-se menor nível de escolaridade nas pacientes com risco aumentado (34,6%) quando comparadas àquelas consideradas como de risco habitual (46,0%). Quanto às características do tumor, as mulheres de risco aumentado apresentaram maiores percentuais de doença diagnosticada em estádio avançado (32,3%) e com tumores >2cm (63,0%), com prevalência aumentada para ambas as características, quando comparadas àquelas de risco habitual. Ainda nas mulheres de risco aumentado, foram encontrados maiores percentuais de GH3 (43,3%) e K-i-67 ≥ 25% (64,6%), com prevalência cerca de duas vezes maior neste grupo. A presença de tumores triplo-negativos foi observada em 25,2% nas mulheres de risco aumentado e 6,0% nas mulheres de risco habitual, com prevalência de ausência de biomarcadores 2,5 vezes maior entre as mulheres do grupo de risco aumentado. A partir dos critérios clínicos rotineiramente utilizados no diagnóstico do câncer de mama, a prática assistencial do aconselhamento genético para as pacientes com risco aumentado de câncer de mama hereditário em contextos como o do Brasil ainda é escarça.
prevalence of bilaterality, triple-negative subtype tumors diagnosed up to 60 years old, Ashkenazi Jewish ancestry, and an association with other malignant neoplasms that affect family members, such as ovarian, endometrial, pancreas, bowel, prostate, and male breast cancer.7–9

Furthermore, the NCCN (2020)5 and other medical organizations suggest potential candidates to specialists that would benefit from genetic testing and counseling, based mainly on personal and family history of cancer.8–10 Family history is an important means used to identify individuals at risk of hereditary cancer; however, recommendations based on family history for genetic screening may be limited due to a poor family history, limited to first-degree relatives or to information inconsistently documented by professionals.7,9–11

Therefore, frequent reviews of the recommendation guidelines to assess Hereditary Breast and Ovarian Cancer (HBOC) syndrome have been performed to advance the diagnosis and management of women with HBOC syndrome, which has enabled the incorporation of new and more comprehensive criteria.6,10

In Brazil, there are few studies on the genetic profile of patients and family members at risk for HBOC syndrome.12 This study seeks to characterize the clinical, histological, and immunohistochemical profile of women with invasive breast cancer, according to the risk for HBOC syndrome in a Brazilian population.

Methods

This is a retrospective study, performed from a hospital-based cohort, consisting of 522 women diagnosed with breast cancer between 2014 and 2016, and treated at an oncology referral center in the Zona da Mata of Minas Gerais, in the southeastern region in Brazil.

Sociodemographic, clinic, and pathological data were extracted from medical records, and additional information was obtained through interviews with patients, as well as from analysis of pathological anatomy and immunohistochemical test results.

Through the criteria used to assess hereditary breast cancer risk, recommended by the NCCN (2020),9 women were classified into two categories: increased and usual risk for hereditary breast cancer. The group with increased risk for hereditary breast cancer considered the presence of at least one of the clinical criteria for HBOC Syndrome, such as: age at diagnosis ≤ 45-years-old; triple-negative subtype diagnosed in women aged ≤ 60 years; diagnosis of breast cancer between 46–50-years-old, with at least one first or second-degree relative with malignant neoplasm in the breast or ovary; and a personal history of breast cancer with the presence of secondary malignant tumor in the same organ.9 The group with usual risk for hereditary breast cancer was considered as the same found in the asymptomatic female population, which has environmental and hormonal factors as the main risk conditions for the development of the disease.

The study excluded women with in situ breast cancer (n = 42) and those without information about at least one of the biomarkers of the tumor for estrogen, progesterone, and HER-2 (n = 50).

The characterization of the pathological profile of breast carcinoma was performed using the following variables: stage at diagnosis (early – I, intermediate – II, advanced stage – III and IV), histological type (ductal, lobular, others), tumor size (≤ 2 cm, > 2 cm), lymph node involvement, histological grade (HG1–well differentiated, HG2–moderately differentiated, HG3–poorly differentiated), Ki-67 cell proliferation index (< 25%, ≥ 25%). Considering the relationship between the increased expression of Ki-67 and HG3, according to Gong et al.5 and Delpech et al.11 perineural invasion, vascular invasion, inflammatory infiltrate, multifocality, multicentricity, intraductal component, estrogen and progesterone hormone receptors (HR), HER-2 receptor, and immunohistochemical biomarkers (present: HR+ and HER-2+ or HR– and HER-2–; absent: HR– and HER-2–). And considering the presence of HER-2 only in tumors reported as 2+ or 3+ with confirmation by in situ hybridization technique.14

From analyses stratified according to risk for hereditary breast cancer, the mean and respective 95% confidence interval (95% CI) for age at diagnosis, as well as absolute numbers and percentages for categorical variables were presented. The difference in the distribution of categorical variables according to the risk for hereditary breast cancer was assessed using the chi-square test (χ²), and the significance level considered was 5%. For these variables were estimated the prevalence ratios (PR) and the respective 95% confidence interval (95% CI). The analysis was performed using the STATA (StataCorp. College Station, TX, USA) software, version 16.0.

The study was approved by the Research Ethics Committee of Federal University of Juiz de Fora (CEP/UFJF), CAAE: 5342919.0.0000.5147.

Results

Among the 430 women diagnosed with invasive breast cancer who composed our study population, 127 (29.5%) were classified as at increased risk for HBOC Syndrome, according to the criteria recommended by the NCCN (2020).9 For women at increased risk, the mean age was 42 years (95% CI: 40.9–44.0), and for those with usual risk, it was 63 years (95% CI: 61.9–64.2).

The majority of women were white (72.3%), with more than eight years of education (55.8%), and users of the public health service (60.5%). There was a lower level of education in patients at increased risk (36.4%) compared to those considered to be at usual risk (46.0%) (PR = 0.70; 95% CI: 0.52–0.96) (Table 1).

Most of the investigated patients did not mention a history of breast cancer in the family (69.5%). However, for women at increased risk, 39.4% had a positive history of cancer in up to third-degree relative. When we considered only first-degree relatives with breast cancer in the group of women at increased risk (20.5%), a 50% higher prevalence was found in the increased risk group than in the usual risk group (PR = 1.5; 95% CI: 1.09–2.14). Regarding
anatomopathological characteristics of the population of the study, it was observed that 74.4% had early-stage/intermediate type, 82.3% had invasive ductal histological type, tumor size > 2 cm (54.2%), non-involved lymph nodes (50.9%), histological grade 2 (37.7%), and Ki-67 < 25% (48.1%) (►Table 2).

There was a significant difference between the groups regarding staging, tumor size, histological grade, and Ki-67 index. Women at increased risk had higher percentages of diagnosed disease at an advanced stage (32.3%), with tumors > 2 cm (63.0%), and an increased prevalence (~1.4 times) for both characteristics, when compared with those at usual risk.

Also in women at increased risk, higher percentages of HG3 (43.3%) and Ki-67 > 25% (64.6%) were found, with a prevalence about twice as high in this group (PR = 2.64 and 2.03, respectively). On the other hand, in women at usual risk, higher percentage of more differentiated tumors was identified, with HG2 (38.0%) and Ki-67 < 25% being intermediate or low (54.8%).

There was no significant difference in the distribution of histological types between groups. The lymph node involvement was 56.0% in women at increased risk, and 46.2% in women at usual risk, although it was also statistically insignificant (►Table 2).

Regarding estrogen and/or progesterone hormone receptors (HR), an absence of HR expression was found in 30.0% of the women at increased risk, compared with 11.0% of women at usual risk (p < 0.01), with a prevalence about two times higher in the increased risk group. Higher percentages of HER-2 expression negativity were also observed in both groups (increased risk: 81.8% vs. usual risk: 80.9%), with no significant difference between groups (►Table 2).

The biomarkers (HR and/or HER-2) used to classify breast cancer subtypes through the immunohistochemical technique had a percentage of 88.4 in the study population. However, its distribution was significantly different between the groups, with an absence of expression of biomarkers, that is, triple-negative tumors in 25.2% of women at increased risk, and 6.0% in women at usual risk, with a prevalence of absence of biomarkers 2.5 times higher among women in the increased risk group.

The other variables related to tumor characteristics did not show a significant difference in distribution according to the groups considered (►Table 2).
Table 2. Histological and immunohistochemical characteristics of the breast tumor, according to the risk of predisposition for Hereditary Breast-Ovarian Cancer Syndrome (HBOC) in women treated.

| Variables                                  | Usual risk | Increased risk | P \( ^* \) | PR \( ^b \) (95% CI) |
|--------------------------------------------|------------|---------------|------------|----------------------|
| Stage at diagnosis\(^a\)                  |            |               |            |                      |
| Early stage/intermediate                   | 320        | 74.4          | 234        | 77.2                 | 86       | 67.7       | 0.04       | 1.00     |
| Advanced                                   | 110        | 25.6          | 69         | 22.8                 | 41       | 32.3       | 1.39       | (1.02–1.88) |
| Histological type                          |            |               |            |                      |
| Invasive lobular                           | 34         | 7.9           | 27         | 9.0                  | 7        | 5.5        | 0.51       | 1.00     |
| Others                                     | 40         | 9.3           | 28         | 9.2                  | 12       | 9.5        | 1.46       | (0.65–3.28) |
| Invasive ductal                            | 354        | 82.3          | 246        | 81.2                 | 108      | 85.0       | 1.48       | (0.75–2.92) |
| Tumor size \( ^c \)                        |            |               |            |                      |
| \( \leq 2cm \)                             | 195        | 45.3          | 148        | 48.8                 | 47       | 37.0       | 0.04       | 1.00     |
| \( > 2cm \)                                | 233        | 54.2          | 153        | 50.5                 | 80       | 63.0       | 1.42       | (1.05–1.93) |
| Compromised lymph nodes \( ^d \)            |            |               |            |                      |
| No                                        | 219        | 50.9          | 163        | 53.8                 | 56       | 44.0       | 0.07       | 1.00     |
| Yes                                       | 211        | 49.1          | 140        | 46.2                 | 71       | 56.0       | 1.32       | (0.98–1.77) |
| Histological grade (HG)\(^e\)              |            |               |            |                      |
| HG 1                                       | 90         | 20.9          | 75         | 24.8                 | 15       | 11.8       | \(< 0.01\) | 1.00     |
| HG 2                                       | 162        | 37.7          | 115        | 38.0                 | 47       | 37.0       | 1.74       | (1.03–2.93) |
| HG 3                                       | 125        | 29.1          | 70         | 23.0                 | 55       | 43.3       | 2.64       | (1.60–4.36) |
| Ki67                                       |            |               |            |                      |
| \( \leq 25\% \)                            | 207        | 48.1          | 166        | 54.8                 | 41       | 32.3       | \(< 0.01\) | 1.00     |
| \( > 25\% \)                              | 204        | 47.5          | 122        | 40.3                 | 82       | 64.6       | 2.03       | (1.47–2.80) |
| Perineural invasion                        |            |               |            |                      |
| Absent                                    | 388        | 90.2          | 271        | 89.4                 | 117      | 92.0       | 0.39       | 1.00     |
| Present                                   | 42         | 9.8           | 32         | 10.6                 | 10       | 8.0        | 0.79       | (0.45–1.38) |
| Vascular invasion                         |            |               |            |                      |
| Absent                                    | 334        | 77.7          | 234        | 77.2                 | 100      | 78.7       | 0.73       | 1.00     |
| Present                                   | 96         | 22.3          | 69         | 22.8                 | 27       | 21.3       | 0.94       | (0.66–1.35) |
| Inflammatory infiltrate \( ^f \)            |            |               |            |                      |
| Absent                                    | 319        | 74.2          | 229        | 75.6                 | 90       | 71.0       | 0.31       | 1.00     |
| Present                                   | 111        | 25.8          | 74         | 24.4                 | 37       | 29.0       | 1.18       | (0.86–1.62) |
| Multifocality                              |            |               |            |                      |
| Absent                                    | 387        | 90.0          | 276        | 91.1                 | 111      | 87.4       | 0.25       | 1.00     |
| Present                                   | 43         | 10.0          | 27         | 8.9                  | 16       | 12.6       | 1.30       | (0.85–1.97) |
| Multicentricity                           |            |               |            |                      |
| Absent                                    | 416        | 96.7          | 295        | 97.4                 | 121      | 95.3       | 0.27       | 1.00     |
| Present                                   | 14         | 3.3           | 8          | 2.6                  | 6        | 4.7        | 1.47       | (0.79–2.75) |
| Intraductal component \( ^g \)             |            |               |            |                      |
| Absent                                    | 320        | 74.4          | 228        | 75.2                 | 92       | 72.4       | 0.54       | 1.00     |
| Present                                   | 110        | 25.6          | 75         | 24.8                 | 35       | 27.6       | 1.11       | (0.80–1.53) |
| Hormone receptors                         |            |               |            |                      |
| Present                                   | 357        | 83.0          | 268        | 88.4                 | 89       | 70.0       | \(< 0.01\) | 1.00     |
| Absent                                    | 71         | 16.5          | 33         | 11.0                 | 38       | 30.0       | 2.15       | (1.62–2.85) |
| HER-2                                     |            |               |            |                      |
| Present                                   | 74         | 17.2          | 51         | 16.8                 | 23       | 18.1       | 0.55       | 1.00     |
| Absent                                    | 348        | 80.9          | 245        | 80.9                 | 103      | 81.1       | 1.05       | (0.7–1.53) |
| Biomarkers\(^h\)                          |            |               |            |                      |
| Present                                   | 380        | 88.4          | 285        | 94.0                 | 95       | 74.8       | \(< 0.01\) | 1.00     |
| Absent                                    | 50         | 11.6          | 18         | 6.0                  | 32       | 25.2       | 2.56       | (1.95–3.36) |

Abbreviations: 95% CI, 95% confidence interval; PR, prevalence ratios. Notes:
\(^a\)chi-square (X²) test, \( p < 0.05 \).
\(^b\)Prevalence ratio calculated only for valid data.
\(^c\)Stage at diagnosis: early stage (I); intermediate (II); advanced (III and IV).
\(^d\)Histological grade: HG1: well differentiated; HG2: moderately differentiated; HG3: poorly differentiated.
\(^e\)Present biomarkers: HR⁺ and HER-2⁺ or HR⁻ and HER-2-; absent biomarkers: HR- and HER-2- (triple negative).
\(^f\)The difference in totals (N) is due to incompleteness of information.
Hereditary Breast Cancer Risk in a Cohort of Brazilian Women

Freitas et al.

Discussion

Women in the increased risk for hereditary breast cancer group represented 29.5% of the study population and had a mean age of 42 years at diagnosis, which is far below the mean age of the group considered as usual risk (62 years), according to the results found in other studies.15

Between 10 to 25% of breast and ovarian neoplasms are considered hereditary and will manifest earlier in women with some risk factors related to this heredity, that is, history cases of breast, ovarian, and male breast cancers due to the detection of some genetic alteration, especially in the BRCA1 and BRCA2 genes, which reinforces the benefit that these women would have when performing an improved screening.5,7,10

In our study, the frequency of women at increased risk for clinical criteria for HBOC syndrome was higher than reported in the literature, which generally addresses Caucasian populations from Europe and the United States. Moreover, it should be noted that divergence of some criteria and guidelines between referral institutions can make it difficult to reach a consensus on the identification of eligible patients for investigation of hereditary cancer.10

In Brazil, access to risk evaluation for hereditary cancers and genetic screenings is limited. Brazilian experts propose recommendations to expand early diagnosis, risk management, and treatment of hereditary breast cancer, as well as provide epidemiological information about the Brazilian population. The identification of women at increased risk for hereditary breast cancer allows patients and their physicians to assess the available options to mitigate the risk of developing breast cancer, including more frequent screening, chemoprophylaxis, and even prophylactic mastectomy.6

For hereditary breast cancer, family history is the most accepted risk factor among the scientific community, with a risk increase of 2 to 4 times in the presence of family members affected by breast cancer, especially if they have been diagnosed at an early age.7,10,16 In this study, family history—specifically the presence of affected first-degree relatives—was evaluated, observing a higher prevalence of these conditions in the group of women at increased risk. When genetic inheritance is strongly transferred between first-degree relatives, the relative risk of developing breast cancer in pre-climacteric women becomes higher.16

Regarding sociodemographic characteristics, white skin color was the most prevalent among the women evaluated. However, there was a higher number of non-white women in the increased risk for hereditary breast cancer group. It is noteworthy that the worst prognostic features for breast cancer, such as younger age, late diagnosis, and triple-negative tumors, are more frequent in black women.17

Nevertheless, the study performed by Fejerman et al. (2009)18 showed that for every 25% increase in European ancestry, there was a 20% increase in the risk of breast cancer. It is known that the Brazilian population is mainly composed of European, African, and Amerindian ancestral roots, among others, presenting a high genomic diversity.19 However, little is known about the profile of genetic ancestry in the Brazilian population related to breast cancer. In the only study with this approach in a Brazilian population identified in our literature review, Fernandes et al. (2016),12 observed some trends or associations related to genetic ancestry with more aggressive cancer behavior, including higher histological grade in patients whose African component was greater. Nonetheless, this investigation was performed in a cohort that may not represent the diversity of the Brazilian population.

The higher education level predominant in the group of women at increased risk (p = 0.05) may highlight the relationship between educational level and socioeconomic status—which also interferes with greater access to information about the risk factors that permeate the development of cancer—and access to preventive measures, particularly important in women with hereditary predisposition to breast cancer.19,20

In addition to a family history of cancer, tumor characteristics can be of considerable importance in women at increased risk for hereditary breast cancer, where histopathological findings can be potentially useful in predicting the presence of germline mutation, along with the already mentioned criteria for predisposition to HBOC syndrome.21 Furthermore, some characteristics of breast cancer are considered prognostic factors of the disease, including the histological type, tumor size, lymph node involvement, and histological grade.4 They may also present histological and molecular differences that are related to sporadic and hereditary cancers, helping define characteristics that are more prevalent in women at risk for HBOC syndrome.22–24

![Fig. 1](image-url) K_67 > 25\% with absent biomarkers (Column 1); and K_67 > 25\% and absent HR (Column 2) with simultaneous occurrence for each considered group.
Studies show that tumors related to HBOC syndrome are often larger, less poorly differentiated, with high cell proliferation markers, predominance of the invasive ductal histological type, and triple-negative subtype, leading to a more aggressive form of the disease.\textsuperscript{22–26} This study corroborates these results, as there was a higher prevalence of advanced ductal carcinomas, tumor size greater than 2 cm, lymph nodes involvement, poorly differentiated tumors, K\textsubscript{r}67 ≥ 25%, and triple-negative subtype in the increased risk group.

It is known that advanced stages influence the therapeutic options and prognosis of patients, and among the histological types, invasive ductal carcinoma is the most common, accounting for approximately 70% of all prevalent cases of breast cancer.\textsuperscript{20} In this study, a higher prevalence of the invasive ductal histological type was also observed in both the increased risk and usual risk groups (85.0%; 81.2%, respectively). In general, women affected by invasive ductal carcinoma have greater lymphatic involvement, which was also observed in the study population in general.\textsuperscript{21–27} However, there was no data regarding when the study population was stratified by risk of hereditary cancer.

The histological grade (HG) of the invasive carcinomas is an important feature and must be evaluated to guide the therapeutic approach and predict the prognosis.\textsuperscript{28} In the increased risk group, the frequency of HG3 was higher (p < 0.01), as well as K\textsubscript{r}67 ≥ 25% (p < 0.01), compared with the usual risk group. The literature points to higher HG and K\textsubscript{r}67 values in women with hereditary predisposition.\textsuperscript{5,29,30}

In the study of Mavaddat et al. (2012),\textsuperscript{21} performed by the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA), HG3 tumors were identified in 77.0% and 50.0% of women with mutations in the BRCA1 and BRCA2 genes, respectively.

Newman (2015)\textsuperscript{31} suggests an inverse correlation between low incidence and higher breast cancer mortality rates in African American women compared with white women, with a 67% higher risk of death due to breast cancer among African American women.

Regarding hormone receptors (HR), the higher frequency of cases with absence HR was observed in the increased risk for hereditary breast cancer group, compared with the usual risk group (p < 0.01), which reinforces the premise that women at risk for hereditary predisposition are more prone to estrogen receptor negativity.\textsuperscript{30} The presence of hormone receptors in tumor tissue is related to indicators of good prognosis, with a lower histological grade and lower rates of cell proliferation.\textsuperscript{3,4,18}

The higher prevalence of triple-negative subtypes tumors, characterized by the absence of hormone receptors and HER2, in women at increased risk (PR = 2.56; 95% CI: 1.95–3.36) also corroborates findings in the scientific literature. In the meta-analysis performed by Tun et al. (2014),\textsuperscript{32} it was observed that in a population with increased risk characteristics, women with triple-negative breast cancer are 5.7 times more likely to have a hereditary predisposition compared with the non-triple-negative immunophenotype. Fernandes et al. (2019)\textsuperscript{33} performed the same analysis, and their results showed the presence of tumors with HG3 in 56.5% and 25.0% of women with mutations in the BRCA1 and BRCA2 genes, respectively, thus corroborating the higher frequency of this finding in women at risk of HBOC syndrome.

As observed in the study by Fernandes et al. (2019),\textsuperscript{33} most cases of triple-negativity occur in women with hereditary mutations in the BRCA1 and BRCA2 genes (51.1%). Moreover, according to data presented by Young et al. (2009),\textsuperscript{34} women with this subtype of breast cancer diagnosed in pre-climacteric age should be candidates of a risk assessment test for HBOC, even in the absence of a family history of breast and ovary cancer. Therefore, the NCCN guidelines recommend a genetic investigation for all triple-negative breast cancer aged ≤ 60 years.\textsuperscript{9}

When evaluating the simultaneous occurrence of some characteristics in the categorized groups, we sought to verify that the information routinely collected at the time of diagnosis could favor the identification of women at increased risk for HBOC. Higher percentages were observed in the increased risk group, when compared with those of the usual risk group, regarding the presence of K\textsubscript{r}67 ≥ 25% in triple-negative tumors (83.3% vs. 16.7%), K\textsubscript{r}67 ≥ 25% and absence of hormone receptors (66.7% vs. 33.3%). The data presented suggests that a high K\textsubscript{r}67 proliferation index with the absence of expression of biomarkers could be clinical indicators of increased risk for HBOC.

In a retrospective analysis performed by Liang et al. (2020),\textsuperscript{35} the authors evaluated the interaction between K\textsubscript{r}67 and HG in the prognostic of different subtypes of breast cancer. The results indicated that K\textsubscript{r}67 expression was significantly associated with HG in all breast cancer patients, and that patients with increased K\textsubscript{r}67 or HG3 had reduced recurrence-free survival and a worse prognosis.\textsuperscript{5,13,35}

It is important to highlight that these characteristics alone provide relevant information at the time of the diagnosis. This was demonstrated in the study performed by Pérez-López et al. (2016),\textsuperscript{36} when considering tumor size, lymph node involvement HG3, and independent prognostic factors. In the same study, the high K\textsubscript{r}67 score increased the risk of breast cancer mortality by 2.7 times.\textsuperscript{35}

Most of the Brazilian studies published so far regarding HBOC syndrome have been performed with specific populations, that is, with young women diagnosed with breast cancer and/or with an investigation of specific gene regions.\textsuperscript{37,38} Therefore, there is a need to obtain more consistent data related to HBOC syndrome from patients and their families in Brazil.

The identification of patients and family members at risk for hereditary cancer is essential, as the cumulative vital risk is much higher in affected people. This identification makes it possible to know the risk that family members are exposed to, through screening measures that allow for an early diagnosis and the implementation of appropriate follow-up and treatment protocols, which can improve the outcome of the disease in patients and their families.\textsuperscript{39}

A study conducted in the United States found that, in one year, only 8% of 603 women referred for genetic counseling,
according to the NCCN criteria, attended the exam. This exemplifies how genetic counseling is still underused, even in developed countries. Studies highlight the importance of providing patients better information about the genetics of cancer and the risk of hereditary cancer, as well as the role of the genetic counseling service, more specifically disease management, and therapeutic approaches that could implement greater demand for these services. In studies on the assistance of specialized genetic services in Brazil, Llerena (2002) and Horovitz et al. (2012), highlighted the inadequate number of geneticists doctors available, the centralization of services in the private system, usually located in urban centers, and the scarcity of geneticists in the public health system, being available only in some research institutions and universities. Furthermore, the profession of genetic counselor is still not recognized in Brazil, despite the involvement of many health professionals with specialty in genetics.

As a limitation of the study, we emphasize that genetic screening was not performed in the investigated population, particularly in relation to the BRCA genes, which would enable a better characterization of the increased risk for hereditary breast cancer, and the associations raised. It is worth mention the high cost of the test to assess pathogenic mutations in the BRCA1 and BRCA2 genes, which makes its use very restricted in countries with limited sources, such as Brazil.

In this regard, information on tumor histopathology, routinely collected at the time of diagnoses, such as histological grade, the status of estrogen, progesterone, or HER-2, as well as identification of cell proliferation markers, can be incorporated into the criteria already recommended for investigation of the risk of hereditary breast and ovarian cancer, aiming to strengthen and expand the adoption of a practical strategy for genetic evaluation in patients with breast cancer. This becomes particularly important for countries in which specialized genetic services are scarce, financial resources for health are limited and concentrated in more developed regions, and where public and private health systems have major restrictions on coverage of such molecular analyzes, such as in Brazil and other Latin American countries.

Conclusion
The results of this study allow the characterization of the clinical, histological, and immunohistochemical profile of women with breast cancer in a Brazilian hospital-based cohort, according to the risk of hereditary breast cancer. The findings show the possibility of considering, even if only in a complementary way, the frequency of some of these characteristics to help identify and manage women with clinical suspicion of hereditary breast cancer. In this regard, there is a higher frequency of tumors with HG3, K-67 ≥ 25%, absence of hormone receptors, and HER-2, and family history of breast cancer in women classified in this study as at increased risk for HBOC syndrome. Based on the clinical criteria routinely used in the diagnosis of breast cancer, this study collaborated to guide the care practice of genetic counseling for patients at increased risk of hereditary breast cancer in contexts such as in Brazil. Therefore, it guides the indication of women to undergo genetic evaluation and who, consequently, could benefit from these more specific therapies. It also contributes to the risk management of their families, enabling the application of specific preventive measures.

Contributions
Freitas analyzed the data, and promoted the conception and design of the article. Guerra helped in the analysis and writing of the article. Fayer and Campos participated in data collection. Cintra contributed to the screening of patients in the cohort and the collection of clinical information. Warren contributed substantially to the interpretation of the data and performed a critical review of its intellectual content. Ervilhã participated in the data collection and writing of the article. De Paula acted in the graphic presentation of the results, and Teixeira performed a relevant critical review of the intellectual content presented with approval of the final version to be published.

Conflict of Interests
The authors have no conflict of interests to declare.

Acknowledgments
Our sincere acknowledgment to Dr. Fernando Regla Vargas, from the Epidemiology of Congenital Malformations Laboratory of the Oswaldo Cruz Foundation (FIOCRUZ), to all professionals at the 9 de Julho Hospital/Oncological Institute of Juiz de Fora, Minas Gerais, Brazil, and to the CAPES/PNPD Agency for the Postdoctoral Research Funding (Number Process: 88882.316108/2019–01).

References
1 Pollán M. Epidemiology of breast cancer in young women. Breast Cancer Res Treat. 2010;123(Suppl 1):3–6. doi: 10.1007/s10549-010-1098-2
2 Gobbi H. Classificação dos tumores da mama: atualização baseada na nova classificação da Organização Mundial da Saúde de 2012. J Bras Patol Med Lab. 2012;48(06):463–474. doi: 10.1590/S1676-24442012000600013
3 Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000; 406(6797):747–752. doi: 10.1038/35021093
4 Aquino RG, Vasques PH, Cavalcante DI, Oliveira AL, Oliveira BM, Pinheiro LG. Carcinoma ductal invasor: relação de características anatomopatológicas com a presença de metástases axilares em 220 casos. Rev Col Bras Cir. 2017;44(02):163–170. doi: 10.1590/0100-69912017002010
5 Gong P, Wang Y, Liu G, Zhang J, Wang Z. New insight into Ki67 expression at the invasive front in breast cancer. PLoS One. 2013;8(01):e54912. doi: 10.1371/journal.pone.0054912
6 Achatz MI, Caleffi M, Guindalini R, Marques RM, Nogueira-Rodrigues A, Ashton-Prolla P. Recommendations for advancing the diagnosis and management of hereditary breast and ovarian cancer in Brazil. JCO Glob Oncol. 2020;6:439–452. doi: 10.1200/JGO.19.00170
Hereditary Breast Cancer Risk in a Cohort of Brazilian Women

Heisey R, Carroll JC. Identification and management of women with a family history of breast cancer: Practical guide for clinicians. Can Fam Physician. 2016;62(10):799–803

Lee TC, Reyna C, Shaughnessy E, Lewis JD. Screening of populations at high risk for breast cancer. J Surg Oncol. 2019;120(05):820–830. DOI: 10.1002/jso.25611

Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(01):77–102. DOI: 10.6004/jnccn.2021.0001

Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Mangia A, Malfette A, Simone G, Darvishian F. Old and new concepts in histopathological characterization of familial breast cancer. Ann Oncol. 2011;22(05):i24–i30. DOI: 10.1093/annonc/mdq662

Fernandes GC, Michelli RA, Galvão HC, Paula AE, Pereira R, Andrade CE, et al. Prevalence of BRCA1/BRCA2 mutations in a Brazilian population sample at-risk for hereditary breast cancer and characterization of its genetic ancestry. Oncogarger. 2016;7(09):80465–80481. DOI: 10.18632/oncotarget.12610

Delpech Y, Wu Y, Hess KR, Hsu L, Ayers M, Natowicz R, et al. Ki67 expression in the primary tumor predicts for clinical benefit and time to progression on first-line endocrine therapy in estrogen receptor-positive metastatic breast cancer. Breast Cancer Res Treat. 2012;135(02):619–627. DOI: 10.1007/s10549-012-1914-2

Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JM, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/Cologne of American Pathologists Clinical Practice Guideline focused update. Arch Pathol Lab Med. 2018;142(11):1364–1382. DOI: 10.5858/arpa.2018-0902-SA

Flória-Santos M, Lopes-Júnior LC, Alvarenga LdeM, Ribeiro MS, Ferraz VE, Nascimento LC, et al. Self-reported cancer family history is a useful tool for identification of individuals at risk of hereditary cancer predisposition syndrome at primary care centers in middle-income settings: a longitudinal study. Genet Mol. Biol. 2016;39(02):178–183. DOI: 10.1590/1678-4685-GMB-2014-0362

Nelson HD, Zakhir B, Cantor A, Fu R, Griffin J, O’Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med. 2012;156(09):635–648. DOI: 10.7326/0003-4819-151-9-201906010-00006

Scott LC, Mobley LR, Kuo TM, Illyasova D. Update on triple-negative breast cancer disparities for the United States: A population-based study from the United States Cancer Statistics database, 2010 through 2014. Cancer. 2019;125(19):3412–3417. DOI: 10.1002/cncr.32207

Fejerman L, Haiman CA, Reich D, Tandon A, Deo RC, John EM, et al. An admixture scan in 1,484 African American women with breast cancer. Cancer Epidemiol Biomarkers Prev. 2009;18(11):3110–3117. DOI: 10.1159/000305965.EPI-09-0446

Suarez-Kurtz G, Pena SD, Struchiner CJ, Hutz MH. Pharmacogenomic diversity among Brazilians: influence of ancestry, self-reported color, and geographical origin. Front Pharmacol. 2012;3:191. DOI: 10.3389/fphar.2012.00191

Dos-Santos-Silva I, De Stavola BL, Renna NL, Junior, Nogueira MC, Aquino EM, Bustamante-Teixeira MT, et al. Ethnoracial and social trends in breast cancer staging at diagnosis in Brazil, 2001-14: a case only analysis. Lancet Glob Health. 2019;7(06):e784–e797. DOI: 10.1016/S2214-109X(19)30151-2

Mavaddat N, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, et al.; HERBON EMBRACE GEMO Study Colaborators kConFab Investigators SWE-BRCA Collaborators Consortium of Investigators of Modifiers of BRCA1/2. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomarkers Prev. 2012;21(01):134–147. DOI: 10.1158/1055-9965.EPI-11-0775

Amendola LC, Vieira A. A contribuição dos genes BRCA na predisposição hereditária ao câncer de mama. Rev Bras Cancerol. 2005;51(04):325–330

Spurdle AB, Couch FJ, Parsons MT, McGuffog L, Barrowdale D, Bolt A, et al. ABCTB Investigators EMBRACE Group GENICA Network HEBO Group kConFab Investigators. Refined histopathological predictors of BRCA1 and BRCA2 mutation status: a large-scale analysis of breast cancer characteristics from the BCAC, CIMBA, and ENIGMA consortia. Breast Cancer Res. 2014;16(06):3419. DOI: 10.1186/1305-0414-16-9

Mangia A, Malfetone A, Simone G, Darvishian F. Old and new concepts in histopathological characterization of familial breast cancer. Ann Oncol. 2011;22(05):i24–i30. DOI: 10.1093/annonc/mdq662

De Lima Vazquez F, Silva TB, Da Costa Vieira RA, Da Costa AM, Scapulatempo C, Fregnan JH, et al. Retrospective analysis of breast cancer prognosis among young and older women in a Brazilian cohort of 738 patients, 1985–2002. Oncol Lett. 2016;12(06):4911–4924. DOI: 10.3892/ol.2016.5360

Costa NCD, Morsch DM, Opperman CP, Spritzer PM, Rosa DD. Biological features of breast cancer according to age at diagnosis in southern Brazil: An analysis of retrospective data of 1128 women. Breast. 2019;25(04):760–762. DOI: 10.1111/bbj.13327

Buitrago F, Uemura G, Sema MC. Fatores prognósticos em câncer de mama. Comun Ciênc Saúde...;2011;22(05):569–581

Sarioglu S. Tumor deposits in breast carcinomas. In: Sarioglu S. Tumor deposits in breast carcinomas...;2011:139. DOI: 10.1111/j.1863-2348.2010.00430.x

Gnant M, Harbeck N, Thomssen C. St. Gallen 2011: summary of the consensus discussion. Breast Care (Basel). 2011;6(02):136–141. DOI: 10.1115/000328050

Foulkes WD, Metcalfe K, Sun P, Hanna WM, Lynch HT, Ghadirian P, et al. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res. 2004;10(06):2029–2034. DOI: 10.1158/1078-0432.ccr-03-1061

Newman LA. Disparities in breast cancer and african ancestry: a global perspective. Breast J. 2015;21(02):133–139. DOI: 10.1111/tbj.12369

Tun NM, Villani G, Ong K, Yoe L, Bo ZM. Risk of having BRCA1 mutation in high-risk women with triple-negative breast cancer: a meta-analysis. Clin Genet. 2014;85(01):43–48. DOI: 10.1111/cge.12270

Fernandes GC, Felicio PS, Michelli RAD, Coelho AS, Scapulatempo C, Palmero EI. Biological features of breast cancer according to age at diagnosis in southern Brazil: An analysis of retrospective data of 1128 women. Breast. 2019;25(04):760–762. DOI: 10.1111/bbj.13327

Sarioglu S. Tumor deposits in breast carcinomas. In: Sarioglu S. Tumor deposits in breast carcinomas...;2011:139. DOI: 10.1111/j.1863-2348.2010.00430.x

Gnant M, Harbeck N, Thomssen C. St. Gallen 2011: summary of the consensus discussion. Breast Care (Basel). 2011;6(02):136–141. DOI: 10.1115/000328050

Foulkes WD, Metcalfe K, Sun P, Hanna WM, Lynch HT, Ghadirian P, et al. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res. 2004;10(06):2029–2034. DOI: 10.1158/1078-0432.ccr-03-1061

Newman LA. Disparities in breast cancer and african ancestry: a global perspective. Breast J. 2015;21(02):133–139. DOI: 10.1111/tbj.12369
Germline mutations in BRCA1, BRCA2, CHEK2 and TP53 in patients at high-risk for HBOC: characterizing a Northeast Brazilian Population. Hum Genome Var. 2014;1:14012. Doi: 10.1038/hgv.2014.12

The rate of recurrent BRCA1, BRCA2, and TP53 mutations in the general population, and unselected ovarian cancer cases, in Belo Horizonte, Brazil. Cancer Genet. 2016;209(1-2):50–52. Doi: 10.1016/j.cancergen.2015.11.003

Genetic services and testing in Brazil, J Community Genet. 2013;4(03):355–375. Doi: 10.1007/s12687-012-0096-y

Genética médica, Sistema Único de Saúde brasileiro (SUS) e integralidade na atenção e no cuidado à saúde. Cien Saude Colet. 2002;7(01):21–25