Characterization of Patients with Breast Cancer and National Comprehensive Cancer Network Criteria for Performing *BRCA1* and *BRCA2* Genetic Test

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Caracterização de Pacientes com Câncer de Mama e Critérios da National Comprehensive Cancer Network para Realização do Teste Genético BRCA1 e BRCA2

Caracterización de Pacientes con Cáncer de Mama y Criterios de la National Comprehensive Cancer Network para Realizar Prueba Genética de *BRCA1* y *BRCA2*

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ABSTRACT

Introduction: Approximately 10% of breast cancer cases are attibutable to germinative mutations in susceptibility genes, including *BRCA1*, *BRCA2* and others. The National Comprehensive Cancer Network (NCCN) recommends screening women with breast cancer for mutations in *BRCA1/2* in defined scenarios. However, these genetic tests are unavailable at the Brazilian Public Health System (SUS). **Objective:** This study aimed to characterize women with breast cancer and define the criteria for performing *BRCA1/2* test. **Method:** Quantitative, descriptive, analytic, and retrospective study. Medical records of women diagnosed by SUS with breast cancer between January 2016 and December 2018 were analyzed through the software JAMOVI (version 2.3 - 2022). **Results:** A total of 245 women were diagnosed. According to NCCN guidelines, 97 women met the criteria for performing *BRCA1/2* test, with mean age of 47 years old, predominantly white (90,7%), with comorbidities (55.6%), premenopausal (59.8%), diagnosed in early stages 0 - IIb (68.2%) and 48.4% had familial history of breast cancer. Most frequent histology and molecular subtype was invasive ductal carcinoma (87.2%) and luminal type (59.8%). **Conclusion:** A significant number of women diagnosed by SUS had indication for *BRCA1/2* test. These women are younger, had fewer comorbidities, not menopausal, and differ in terms of the molecular subtype when compared with those without indication for performing the test.
Key words: breast neoplasms; ovarian neoplasms; hereditary breast and ovarian cancer syndrome; genes BRCA1.

RESUMO

Introdução: Aproximadamente 10% dos casos de câncer de mama são atribuíveis a mutações germinativas em genes de suscetibilidade, incluindo *BRCA1* e *BRCA2*. A *National Comprehensive Cancer Network* (NCCN) recomenda a triagem de mulheres com câncer de mama para mutações em *BRCA1/2* em cenários definidos. No entanto, esses testes genéticos não estão disponíveis no Sistema Único de Saúde (SUS). **Objetivo:** Caracterizar as mulheres com câncer de mama e definir os critérios para realização do teste *BRCA1/2*. **Método:** Estudo quantitativo, descritivo, analítico e retrospectivo. Foram analisados prontuários de mulheres com diagnóstico de câncer de mama pelo SUS entre janeiro de 2016 e dezembro de 2018, por meio do *software* JAMOVI (versão 2.3 - 2022). **Resultados:** Foram diagnosticadas 245 mulheres. De acordo com as diretrizes da NCCN, 97 mulheres atenderam aos critérios para realizar o teste *BRCA1/2*, com idade média de 47 anos, predominantemente brancas (90,7%), com comorbidades (55,6%), na pré-menopausa (59,8%), diagnosticadas nos estágios iniciais 0 - IIb (68, 2%), e 48,4% tinham histórico familiar de câncer de mama. A histologia e o subtipo molecular mais frequentes foram carcinoma ductal invasivo (87,2%) e tipo luminal (59,8%). **Conclusão:** Considerando os critérios da NCCN, um número significativo de mulheres diagnosticadas pelo SUS teve indicação para realização do teste *BRCA1/2*. Essas mulheres são mais jovens, têm menos comorbidades, estão em período pré-menopausa mais frequentemente e diferem quanto ao subtipo molecular quando comparadas àquelas sem indicação de realização do exame.
Palavras-chave: neoplasias da mama; neoplasias ovarianas; síndrome hereditária de câncer de mama e ovário; genes, BRCA1.

RESUMEN

Introducción: Aproximadamente el 10% de los casos de cáncer de mama son atribuibles a mutaciones germinales en genes de susceptibilidad, incluidos *BRCA1* y *BRCA2*. La *National Comprehensive Cancer Network* (NCCN) recomienda la detección de mutaciones *BRCA1/2* en mujeres con cáncer de mama en entornos definidos. Sin embargo, estas pruebas genéticas no están disponibles en el Sistema Único de Salud (SUS). **Objetivo:** Caracterizar mujeres con cáncer de mama y definir los criterios para la realización de la prueba *BRCA1/2*. **Método:** Estudio cuantitativo, descriptivo, analítico y retrospectivo. Las historias clínicas de las mujeres diagnosticadas con cáncer de mama entre enero de 2016 y diciembre de 2018, usuarias del SUS, fueron analizadas mediante el software JAMOVI (versión 2.3 - 2022). **Resultados:** 245 mujeres fueron diagnosticadas. Según las pautas de NCCN, 97 mujeres cumplieron con los criterios para someterse a la prueba *BRCA1/2*. Las mujeres con indicación para la prueba tenían un promedio de edad de 47 años, eran predominantemente blancas (90,7%), con comorbilidades (55,6%), premenopáusicas (59,8%), diagnosticadas en estadios tempranos 0 - IIb (68,2%) y 48,4% tenía antecedentes familiares de cáncer de mama. Los subtipos histológicos y moleculares más frecuentes fueron el carcinoma ductal invasivo (87,2%) y el tipo luminal (59,8%). **Conclusión:** Considerando los criterios de la NCCN, un número significativo de mujeres, usuarias del SUS, fueron designadas para hacer la prueba *BRCA1/2*. Estas mujeres son más jóvenes, tienen menos comorbilidades, están en el periodo de la premenopausia con mayor frecuencia y difieren en el subtipo molecular en comparación con aquellas sin orden de realizarse la prueba.
Palabras clave: neoplasias de la mama; neoplasias ováricas; síndrome de cáncer de mama y ovario hereditario; genes BRCA1.

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INTRODUCTION

Breast cancer is the second most prevalent neoplasm globally, with approximately 2 million cases annually, and is the leading cause of cancer-related deaths among women[1]. In Brazil, 704,000 new cases of cancer are estimated for each year of the triennium 2023-2025[2]. The majority of breast cancer cases occur sporadically associated with somatic genetic alterations. However, approximately 10% of the cases result from germline mutations, primarily caused by inherited mutations in the *BRCA1* and *BRCA2* genes; less frequently, they may also be associated with other inherited syndromes[3,4].

The *BRCA1* and *BRCA2* genes encode homologous proteins responsible for repairing DNA damage, particularly double-strand breaks. If not repaired properly, these breaks can lead to an accumulation of mutations in the DNA[5] and ultimately contribute to carcinogenesis. Individuals who carry pathogenic variants in the *BRCA1* and *BRCA2* genes have a significantly higher risk of developing new primary tumors compared to those without the variants[6,7]. Additionally, the risk of ovarian cancer is 44% for those with pathogenic variants in *BRCA1* and 17% in *BRCA2*[8].

Prophylactic contralateral mastectomy in patients with pathogenic variants in *BRCA1* and *BRCA2* genes is associated with a reduction of 95% in the incidence of breast cancer[9]. Similarly, prophylactic bilateral salpingoophorectomy in these patients can significantly reduce the risk of developing ovarian cancer[10,11]. Therefore, it is currently recommended that these patients undergo prophylactic contralateral mastectomy and bilateral salpingoophorectomy[12].

Additionally, identifying a carrier of a pathogenic variant in *BRCA1* and *BRCA2* enables the identification of other family members who may also carry the variant, allowing them to be offered appropriate therapies to reduce their risk of developing cancer[13]. The National Comprehensive Cancer Network (NCCN) guidelines recommend screening for *BRCA1* and *BRCA2* genes in specific scenarios for patients diagnosed with breast cancer[12]. According to NCCN criteria, patients from a similar geographic population with indications for *BRCA*1 and *BRCA2* gene testing have a 13.5% and 9.3% chance, respectively, of having a mutation in these genes[14]. In a large patient database from the "*Hospital do Câncer de Barretos*" in Brazil, the probability is 18%[15] .

A recent study has shown that the strategy of testing pathogenic variants in *BRCA1* and *BRCA2* genes and implementing preventive measures, such as prophylactic bilateral mastectomy and salpingoophorectomy, is cost-effective in the context of the Brazilian Public Health System (SUS)[15]. This finding provides strong support for implementing testing strategies for high risk patients, as it not only prevents new cases of cancer but also reduces costs to the healthcare system.

Despite extensive knowledge of the risks of developing cancer in individuals with pathogenic variants in *BRCA1* and *BRCA2* and the benefits of performing prophylactic surgical procedures and the existence of a formal recommendation for testing in well-defined scenarios, the access to testing *BRCA1* and *BRCA2* is non-existent in SUS[16]. To achieve this, it is crucial to understand the epidemiological, clinical, and pathological profile of women diagnosed with breast cancer, as well as the number and characteristics of women who, upon diagnosis, would be eligible for testing for pathogenic variants in the *BRCA1* and *BRCA2* genes.

It is believed that a significant number of women diagnosed with breast cancer meet the criteria for genetic testing for *BRCA1* and *BRCA2*. Therefore, the purpose of this study is to identify and describe the characteristics of women diagnosed with breast cancer who meet the criteria for testing for pathogenic variants in *BRCA1* and *BRCA2* according to NCCN guidelines.

METHOD

Retrospective, quantitative and descriptive analysis of medical records of women diagnosed with histologically confirmed breast cancer (International Classification of Diseases, 10th Revision – ICD10[17] C50) between January 2016 and December 2018, consulted at SUS and at a High Complexity Oncology Unit (UNACON) in a reference hospital located in Vale do Taquari, Rio Grande do Sul, Brazil.

Data on the epidemiological profile (age, place of residence, skin color), clinical characteristics (risk factors, family history of breast cancer and other cancers, presence of comorbidities, menopausal status), and pathological features (histological type, molecular profile, clinical stage at diagnosis) were collected from the electronic medical records of the patients and organized in Excel spreadsheets. Patients who met the criteria for testing pathogenic variants in *BRCA1* and *BRCA2* at the time of diagnosis according to the NCCN - 2020 guidelines were identified.

The data were analyzed using the statistical program JAMOVI (Version 2.3)[18] [Computer Software] (2022). The Kolmogorov-Smirnov test was used to assess the normality of the data. Non-parametric continuous data were analyzed using the Mann-Whitney U-test and presented as mean + standard deviation (SD). The number and percentage were presented as n (%) and nominal and ordinal categorical variables were analyzed using the chi-

square test (x^2) and Fisher's exact test. A p value of < 0.05 was considered statistically significant for the analyses.

The Institutional Review Board of Univates (COEP) approved the study, report number 4,607,477, CAAE (submission for ethical review): 44455721.9.0000.5310, in compliance with Resolution 466/2012[19] of the National Health Council, which waives the informed consent form for retrospective and secondary data based studies.

RESULTS

The medical records of 245 women diagnosed with breast cancer between the years 2016 and 2018 were analyzed. Of these 245 medical records analyzed, 230 women (93.9%) were white and 176 (71.8%) lived in urban areas; at diagnosis, the mean age was 56+12.8 years, mostly menopausal (59.6%), with breast cancer related comorbidities (73.8%), and systemic arterial hypertension (SAH) was the most prevalent comorbidity (46.9%). In addition, 59.6% were postmenopausal at diagnosis, 26.5% were previously screened for breast cancer, and the objective of the diagnosis of breast cancer was to detect symptoms (51.4%). Most women had no personal history of breast cancer (87.3%); 75 (30.6%) women had family history of breast cancer, 48% had first degree family member affected by breast cancer , and 110 (44.9%) had family history of other types of cancer (Table 1).

The most common histological type was invasive ductal carcinoma, present in 215 women (87.7%), followed by lobular carcinoma in 12 (4.9%) women. The most common molecular subtype was luminal tumors, followed by HER2 positive and triple-negative tumors, present in 169 (69%), 45 (18.4%), and 28 (11.4%) patients, respectively (Table 2).

Most women were diagnosed at early stages of the disease according to the 8th edition of the TNM[20] – Classification of Malignant Tumors of the American Joint Committee on Cancer (AJCC) and The Union for International Cancer Control (UICC), with 66 (26.9%) at stage IA, 3 (1.2%) at stage IB, 71 (29%) at stage IIA, and 27 (11%) at stage IIB. Advanced stages were less common, with 19 (7.8%), 21 (8.6%), and 12 (4.9%) patients diagnosed with stage IIIA, IIIB, and IIIC, respectively. Only 10 (4.1%) women were diagnosed with stage IV, and bones were the most common site of metastasis. Additionally, 16 patients (6.5%) were diagnosed with tumors *in situ* (clinical stage 0) (Table 2).

Regarding the pathogenic variants in *BRCA1* and *BRCA2* genes at diagnosis, 97 (39.6%) patients met the criteria according to the NCCN guidelines and 148 (60.4%) did not. The most frequent criteria that would indicate the necessity for further investigation were:

Table 1. Sociodemographic and clinical characteristics of patients diagnosed with breast cancer between 2016 and 2018 (n=245)

Variables	Number of patients (%) 245 (100)
Age at the time of breast cancer diagnosis (years)	56±12.8
Residential area	
Urban	176 (71.8)
Rural	69 (28.2)
Race/ethnicity	
White	230 (93.9)
Black	5 (2)
Brown	9 (3.7)
Asian	1 (0.5)
Other	0 (0)
Comorbidities	
Yes	181 (73.8)
No	62 (25.3)
Not specified	2 (0.9)
Prevalence of comorbities	
Systemic arterial hypertension	115 (46.9)
Mood Disorder	54 (22)
Dyslipidemia	52 (21.2)
Diabetes mellitus	37 (5.1)
Hypothyroidism	19 (10.5)
Obesity	14 (5.7)
Other	52 (21.2)
Menopausal status at the time of diagnosis	
Premenopausal	79 (32.2)
Postmenopausal	146 (59.6)
Not specified	20 (8.2)
Previous breast cancer screening	
Yes	65 (26.5)
No	69 (28.2)
Not specified	111 (45.3)
Method of breast cancer diagnosis	
Screening	76 (31)
Symptoms	126 (51.4)
Not specified	43 (17.6)
Family history of breast cancer	
Yes	75 (30.6)
No	151 (61.6)
Not specified	19 (7.8)

to be continued

Table 1. continuation

Variables	Number of patients (%) 245 (100)
Family member affected by breast cancer	
First degree	36 (48)
Second degree	5 (6.7)
Third degree	25 (33.3)
Fourth degree or +	6 (8)
Not specified	1 (4)
Personal history of breast cancer	
Yes	5 (2.1)
No	214 (87.3)
Not specified	26 (10.6)
Family history of other cancers	
Yes	110 (44.9)
No	96 (39.2)
Not specified	39 (15.9)

diagnosis of breast cancer before 45 years (20%) and diagnosis of breast cancer at any age with 1st, 2nd, or 3rd degree relatives diagnosed with breast cancer before 50 years, or metastatic ovarian, pancreatic, or prostate cancer at any age (8.6%) (Table 3).

Among women with indication for pathogenic variants tests in *BRCA1* and *BRCA2*, 54 (55.6%) had comorbidities at diagnosis, *versus* 127 (85.8%) without any indications ($p < 0.001$). The mean age at diagnosis for women with indication was 47.7+11.6 years, while those without indication, it was 62+11.6 years ($p < 0.001$). In terms of menopausal status, 33 (34%) women with indication were menopausal and 58 (59.8%) were premenopausal, while those without indication, 113 (76.3%) and 21 (14.2%) were menopausal and premenopausal, respectively ($p < 0.001$). There was no statistically significant difference in the skin color of women with and without indication for genetic testing. Previous breast cancer screening was more frequent in women who did not meet the criteria 42 (28.4%) ($p < 0.05$). However, there was no difference in the method of breast cancer diagnosis ($p > 0.05$) (Table 4).

Among women with indication for testing, 47 (48.4%) had family history of breast cancer, while those without indication, only 29 (19.6%) had family history of breast cancer ($p < 0.001$). There was no difference between groups of family members affected by breast cancer ($p > 0.05$). Family history of other types of cancer was present in 44 patients (45.4%) with indication and 66 (44.6%) without indication. There was no difference between

Table 2. Pathological characteristics of women diagnosed with breast cancer between 2016 and 2018 (n=245)

Variables	Number of patients (%) 245 (100)
Histological type	
Ductal	215 (87.2)
Lobular	12 (4.9)
Other	15 (6.1)
Not specified	3 (1.2)
Histological grade	
Grade 1	20 (8.2)
Grade 2	145 (59.2)
Grade 3	46 (18.8)
Not specified	34 (13.9)
Molecular subtype	
Luminal	169 (69)
HER2-positive	45 (18.4)
Triple-negative	28 (11.4)
Not specified	3 (1.2)
Clinical stage	
0	16 (6.5)
IA	66 (26.9)
IB	3 (1.2)
IIA	71 (29)
IIB	27 (11)
IIIA	19 (7.8)
IIIB	21 (8.6)
IIIC	12 (4.9)
IV	10 (4.1)

Source: Brierley JD, Gospodarowicz MK, Wittekind C[20].

women with indication and without indication regarding residential area, comorbidities, and personal history of breast cancer ($p > 0.05$ for all) (Table 4).

Ductal carcinoma and histological grade 2 was the most prevalent histological type among patients with and without indication for *BRCA1* and *BRCA2* genetic testing, however there was no difference between groups ($p > 0.05$). Women with indication for genetic testing were more likely to have luminal tumors, followed by triple-negative and HER2-positive tumors, present in 59.8%, 22.7%, and 16.5% respectively. In contrast, among those without indication, the most common molecular subtype was also luminal tumors, present in 75% of the cases, followed by HER2-positive tumors (19.6%), and less frequently, triple-negative tumors (4.1%) ($p < 0.001$). The clinical stages IIA and IA were the most frequent, however there was no significant difference between groups with and without indication ($p > 0.05$) (Table 5).

Table 3. Eligibility Criteria for *BRCA1* and *BRCA2* genetic testing among women diagnosed with breast cancer between 2016 and 2018 (n=245)

Indication for *BRCA1* and *BRCA2* genetic testing	Number of patients (%)
Not eligible	148 (60.4)
Eligible	97 (39.6)
Criteria for *BRCA1* and *BRCA2* genetic testing (NCCN - 2020)*	
1	49 (20)
2	17 (6.9)
3	16 (6.5)
4	0 (0)
5	21 (8.6)

(*) 1 – Breast cancer diagnosed before age 45; 2 – Breast cancer diagnosed between ages 46 and 50 with: unknown or limited family history; new primary breast cancer diagnosis at any age; ≥1 case of breast, ovarian, pancreatic, or prostate cancer in a 1st, 2nd, or 3rd degree relative diagnosed at any age; 3 – Breast cancer diagnosed at any age in Ashkenasi Jews; 4 – Breast cancer diagnosed at any age in Ashkenasi Jews. Triple-negative breast cancer diagnosed before age 60; 5 – Breast cancer diagnosed at any age with a 1st, 2nd, or 3rd degree relative diagnosed with breast cancer before 50 years, or metastatic ovarian, pancreatic, or prostate cancer at any age[12].

DISCUSSION

This study enabled to determine the number of women diagnosed with breast cancer who met the criteria of the NCCN guidelines for genetic testing of pathogenic variants in *BRCA1* and *BRCA2* in Brazil's southern region; the epidemiological, clinical, and pathological characteristics of these women were analyzed. As expected, a considerable number of women diagnosed with breast cancer in the Vale do Taquari region, located in the state of Rio Grande do Sul met the criteria for genetic testing.

During the years 2016-2018, a total of 245 women were diagnosed with breast cancer and received treatment at the UNACON, with an average age of 56 years at diagnosis and the majority were white (93.9%). This finding aligns with the population demographics of the Vale do Taquari region, where UNACON is located, which has a significant population of German and Italian descent. Furthermore, this result is consistent with data from Population-Based Cancer Registries (RCBP), where

Table 4. Sociodemographic and clinical characteristics of patients diagnosed with breast cancer between 2016 and 2018 that met and did not meet the criteria for *BRCA1* and *BRCA2* genetic testing (n=245)

Variables	Met the criteria Number of patients (%) 97 (100)	Did not meet the criteria Number of patients (%) 148 (100)	*p* value*
Age at the time of breast cancer diagnosis (years) (mean±standard deviation)	47.7±11.6	62±10.2	< 0.001**
Residential area			
Urban	75 (77.3)	101 (68.2)	0.122
Rural	22 (22.7)	47 (31.8)	
Race/ethnicity			
White	88 (90.7)	142 (95.9)	
Black	4 (4.1)	1 (0.7)	
Brown	5 (5.2)	4 (2.7)	0.111
Asian	0 (0)	1 (0.7)	
Other	0 (0)	0	
Presence of comorbidities			
Yes	54 (55.7)	127 (85.8)	< 0.001
No	42 (43.3)	20 (13.5)	
Prevalence of comorbidities			
Systemic arterial hypertension	29.9	58.1	< 0.001
Mood Disorder	19.6	23.6	0.168
Dyslipidemia	15.5	25.7	0.167
Diabetes mellitus	8.2	18.9	0.132
Hypothyroidism	4.1	10.8	0.117
Obesity	6.2	5.4	0.796
Other	27.8	23.6	

to be continued

Table 4. continuation

Variables	Met the criteria Number of patients (%) 97 (100)	Did not meet the criteria Number of patients (%) 148 (100)	*p* value*
Menopausal status at the time of diagnosis			
Premenopausal	58 (59.8)	21 (14.2)	
Postmenopausal	33 (34)	113 (76.3)	< 0.001
Not specified	6 (6.2)	14 (9.5)	
Previous breast cancer screening			
Yes	23 (23.8)	42 (28.4)	
No	37 (38.1)	32 (21.6)	0.034
Not specified	37 (38.1)	74 (50)	
Method of breast cancer diagnosis			
Screening	25 (25.8)	51 (34.5)	
Symptoms	57 (58.8)	69 (46.6)	0.084
Not specified	15 (15.4)	28 (18.9)	
Family history of breast cancer			
Yes	47 (48.5)	29 (19.6)	
No	43 (44.3)	107 (72.3)	<0.001
Not specified	7 (7.2)	12 (8.1)	
Family member affected by breast cancer			
First degree	57.4	65.5	
Second degree	8.5	6.9	
Third degree	51.1	31	
Fourth degree or +	10.6	6.9	
Not specified	2.1	0	
Personal history of breast cancer			
Yes	4 (4.1)	1 (0.7)	
No	84 (86.6)	130 (87.8)	0.06
Not specified	9 (9.3)	17 (11.5)	
Family history of other cancers			
Yes	44 (45.4)	66 (44.6)	
No	35 (36.1)	61 (41.2)	0.602
Not specified	18 (18.5)	21 (14.2)	

(*) Analyzed using the chi-square test (x^2) and Fisher's exact test; $p < 0.05$ was considered statistically significant for all analyses.
(**) Analyzed using the Mann-Whitney U-test.

the median age at breast cancer diagnosis was 56 years in Brazil between 2000 and 2010[21].

The majority of the women (51%) had suspected breast cancer diagnosis due to symptoms or changes found during physical examination, and only 31% were diagnosed as a result of an abnormal screening test. Additionally, only 28.2% of the women were submitted to prior screening before their diagnosis. These findings highlight the necessity to increase adherence to breast cancer screening programs among women in this region through ongoing awareness efforts which are not limited to international awareness campaigns such as "*Outubro Rosa*".

Nevertheless, most women (74.6%) were diagnosed at early stages of breast cancer (stages 0-IIb), the majority (29%) at stage IIa. National data from the Hospital Cancer Registry (RHC) indicate that 65% of the women are diagnosed at early stages[21], which is lower than the findings of this study. The high proportion of white women may have contributed to this difference, as studies have shown that this ethnicity is more likely to be diagnosed with breast cancer at early stages than black women[22,23]. It is

Table 5. Pathological characteristics of patients diagnosed with breast cancer between 2016 and 2018 that met and did not meet the criteria for *BRCA1* and *BRCA2* genetic testing (n=245)

Variables	Met the criteria Number of patients (%) 97 (100)	Did not meet the criteria Number of patients (%) 148 (100)	*p value**
Histological type	84 (86.6)	131 (88.5)	
Ductal	5 (5.2)	7 (4.7)	
Lobular	0 (0)	0 (0)	0.836
Other	7 (7.2)	8 (5.4)	
Not specified	1 (1)	2 (1.4)	
Histological grade			
Grade 1	7 (7.2)	13 (8.8)	
Grade 2	57 (58.8)	88 (59.4)	0.248
Grade 3	24 (24.7)	22 (14.9)	
Not specified	9 (9.3)	25 (16.9)	
Molecular subtype			
Luminal	58 (59.8)	111 (75)	
HER2-positive	16 (16.5)	29 (19.6)	<0.001
Triple-negative	22 (22.7)	6 (4)	
Not specified	1 (1)	2 (1.4)	
Clinical stage			
0	1 (1.1)	15 (10.1)	
IA	25 (25.8)	41 (27.7)	
IB	1 (1.1)	2 (1.4)	
IIA	26 (26.8)	45 (30.4)	
IIB	13 (13.4)	14 (9.5)	0.092
IIIA	11 (11.3)	8 (5.4)	
IIIB	8 (8.2)	13 (8.8)	
IIIC	6 (6.2)	6 (4.1)	
IV	6 (6.2)	4 (2.7)	

Source: Brierley JD, Gospodarowicz MK, Wittekind C[20].
(*) Analyzed using the chi-square test (x^2) and Fisher's exact test; *p* value of < 0.05 was considered statistically significant for all analyses.

noteworthy that, as stated by Amin MB[24], the prognosis for early stages of the disease is favorable, with a 5-year disease-free survival rate of 98-100% for stage I and 85-98% for stage II[24].

Similar to previous studies, the most frequently observed histological subtype was invasive ductal carcinoma (IDC) and the most common molecular subtype was luminal tumors, with IDC representing 87.2% of cases, which is higher than the commonly reported range of 70-80% in the literature[25]. Additionally, the prevalence of other molecular subtypes, such as HER2-positive tumors (23%) and triple-negative subtypes (13%), was consistent with findings reported by Parise et al.[26].

According to UNACON-SUS, 39.7% of the women diagnosed with breast cancer between 2016 and 2018 met the criteria for genetic testing for pathogenic variants in the *BRCA1* and *BRCA2* genes according to the NCCN guidelines from 2020, consistent with previous studies, where approximately 40% of breast cancer patients met these criteria, with range of 35-47.9% reported in the literature[27,28]. The current findings concur with the study by Borges et al[28] which found that the most common criterion for genetic testing was a diagnosis of breast cancer before the age of 45, present in 21% of their sample and 20% of the sample investigated. However, the criterion of a triple-negative tumor subtype diagnosis before the age of 60 was the second most prevalent in their study, present in 12% of patients, while it was the least frequent in only 6% of the patients investigated.

The analysis revealed that women who met the criteria for genetic testing for pathogenic variants in the *BRCA1*

and *BRCA2* genes (with a mean age of 47.7 years) were significantly younger than those without indication for testing (with a mean age of 62 years). Additionally, the majority of these women were premenopausal at diagnosis, with a mean age of menopause of 49 years. This age difference meets the NCCN guidelines of early age at the diagnosis as criterion for genetic testing.

Women who met the criteria for genetic testing for pathogenic variants in the *BRCA1* and *BRCA2* genes were more likely to have a family history of cancer than those who did not meet the criteria; this supports the use of family history as a criterion for genetic testing according to the NCCN guidelines. Specifically, 15.5% of women had an indication for genetic testing based on a family history of cancer. Additionally, a personal history of prior breast cancer was more common among women who met the criteria for genetic testing.

A significant number of women had no documentation of family history of breast cancer in their medical records. This information is crucial not only to determine the indication for genetic testing for pathogenic variants in the *BRCA1* and *BRCA2* genes, but also for recommending earlier initiation of screening tests for family members. However, the lack of such information in medical records is a known limitation of retrospective studies like this one.

Women who met the criteria for genetic testing for pathogenic variants in the *BRCA1* and *BRCA2* genes were less likely to have been submitted to previous screening tests, possibly because these women were significantly younger than those without indication for testing, consistent with the Ministry of Health primary healthcare network recommendations, which advise screening tests only after 50 years of age. This also explains why women with indication were more likely to have been diagnosed through symptoms of the disease rather than through screening tests, in contrast to those without indication for testing.

The prevalence of comorbidities at the time of cancer diagnosis was significantly lower among women who met the criteria for genetic testing for pathogenic variants in the *BRCA1* and *BRCA2* genes when compared to those without indication for testing, particularly concerning systemic arterial hypertension (SAH). This finding concurs with Bluethmann et al[29] which found that the incidence of comorbidities increases with age. This may be explained by the fact that women with indication for genetic testing were diagnosed at an earlier age compared to those without indication.

The study found a statistically significant difference in the molecular subtype of the tumor as assessed by protein expression in immunohistochemistry, similar to the study by Borges et al[27]. Specifically, the diagnosis of triple-negative tumors was more common among women who met the criteria for genetic testing for pathogenic variants in the *BRCA1* and *BRCA2* genes when compared to those without indication for testing, and there were fewer tumors of the luminal subtype (22.7% *versus* 4% and 59.8% *versus* 75%). Subsequently, there was no difference between the groups in terms of histological type and tumor grade ($p = 0.836$ and 0.248, respectively).

Previous studies by Alemar et al[14] and Lourenção et al[15] estimate that 17 to 22 women diagnosed with breast cancer during this period are unaware of their carrier status for germline mutations in the *BRCA1* and *BRCA2* genes because of poor access to genetic testing at SUS. Given the high risk of new primary tumor incidence in both ipsilateral and contralateral breast[6,7] and ovarian tumors[8], knowledge of the carrier status of pathogenic variants in these genes is crucial for the discussion of risk reduction surgeries, such as contralateral mastectomy and bilateral prophylactic salpingoophorectomy, which have been shown to effectively reduce the incidence of new cases of breast cancer (ipsilateral and contralateral) and ovarian cancer in these women[9-12].

Additionally, identifying a patient who carries a pathogenic variant in the *BRCA1* and *BRCA2* genes allows the identification of other family members who also carry the variant and offers them the opportunity for therapies to reduce their risk of developing cancer[13]. A study by Lourenção et al[15] demonstrated that the strategy of genetic testing for pathogenic variants in the *BRCA1* and *BRCA2* genes, followed by preventive strategies such as risk-reducing surgeries (prophylactic bilateral mastectomy and salpingoophorectomy) proved to be cost-effective in the context of SUS, resulting in more quality-adjusted life years (QALYs) and with an incremental cost-effectiveness ratio of R$11,900.31 (U$5,504.31)/QALY.

Based on the NCCN criteria for indication of genetic testing for mutations in the *BRCA1* and *BRCA2* genes, it was found that 40% of patients consulted at a UNACON in a reference hospital in Rio Grande do Sul met the criteria for genetic testing at the time of their breast cancer diagnosis but were unable to access the test because of its unavailability at SUS. It is estimated that a significant number of these patients are carriers of pathogenic variants in the *BRCA1* and *BRCA2* genes without being aware of the condition, and thus they are not offered therapies that could reduce the risk of developing new neoplasms.

CONCLUSION

A significant number of SUS patients consulted at a reference oncology center in the state of Rio Grande do

Sul met the criteria for genetic testing to detect pathogenic variants in the *BRCA1* and *BRCA2* genes per the NCCN guidelines. Given that this testing is a cost-effective strategy for SUS, changes must be made to the current public health policies to ensure that patients diagnosed with breast cancer receive the best possible care.

CONTRIBUTIONS

All the authors contributed substantially to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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