Distribution of Molecular Subtypes of Hereditary Breast Cancer in Brazilian Patients According to Pathogenic or Likely Pathogenic Germline Genetic Variants.

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Introduction

Hereditary breast cancer accounts for approximately 10 to 20% of cases [1-3]. In Brazil, the primary genes involved are BRCA1, BRCA2, and TP53 [2]. Detecting the presence of pathogenic (PV) or likely pathogenic (LPV) germline variants in these patients can alter the approach to surgical and systemic treatments as well as the indication for loco-regional radiotherapy [4-6].

Breast cancer is a heterogeneous disease. The classification of intrinsic molecular subtypes, based on somatic genetic analyses of specific genes, along with their associations with immunohistochemical molecular subtypes, has identified molecular types that impact treatment and prognosis [30] . Somatic presentations of certain subtypes appear to be more closely associated with pathogenic or likely pathogenic variants (PV/LPV) in specific genes, as observed in triple-negative tumors and in PV/LPV in the BRCA1 gene.

In Brazil, few institutions offer services dedicated to high-risk populations for breast cancer and/or hereditary cancer. Additionally, in public institutions, access to germline genetic panels is not available due to lack of coverage by the Unified Health System (SUS), which limits the availability of these tests. Therefore, it is important to evaluate the distribution pattern of breast cancer molecular subtypes according to pathogenic or likely pathogenic variants (PV/LPV), considering the diversity of altered genes and different populations.

Objective

To assess the distribution of molecular subtypes of hereditary breast cancers, according to the presence of pathogenic or likely pathogenic germline genetic variants detected by multigene panel testing.

Methods and Materials

A prospective cohort study was conducted from November 2021 to October 2022, involving women under follow-up at the high-risk outpatient clinic at the University of Campinas (UNICAMP). Patients were required to meet the following criteria: a personal history of luminal or HER2-positive breast cancer diagnosed before age 45, or triple-negative breast cancer diagnosed before age 60, along with at least one first- or second-degree relative with breast, ovarian, and/or prostate cancer, or who met the NCCN high-risk criteria (NCCN version 3.2021). Patients completed a questionnaire, after which they were referred for genetic testing. Following the test results, they received counseling based on the findings.

Results

A total of 184 patients and 198 breasts were studied. Pathogenic variants (PV) or likely pathogenic variants (LPV) were detected in 36% (67/184) of the patients. Approximately 28% (51/184) were under 40 years of age, 30% (74/184) were non-Caucasian, and 49% (90/184) were premenopausal. General Analysis: The molecular subtypes most associated with pathogenic/probably pathogenic variants (PV/LPV) were Luminal B HER2-negative "like" (OR=11.76; CI 4.19-33.01) and triple-negative (OR=8.4; CI 3.45-20.43). These associations remained consistent even when the analysis was restricted to BRCA1 and BRCA2 genes only (OR=9.33; CI 2.00-29.99) (OR=9.03; CI 3.37-24.20) or to non-BRCA genes (OR=7.75; CI 2.96-29.44) (OR=3.48; CI 1.32-9.20) for Luminal B HER2-negative "like" triple-negative subtypes.

Table 1 - Distribution of epidemiological and sociodemographic characteristics (n=184 patients and 198 breasts)

Caracteristics		n (%)
Age	<30	4 (2.17)
	30-39	47 (25.54)
	40-49	85 (46.20)
	50-59	37 (20.11)
	60-69	10 (5.43)
	>=70	1 (0.54)
Self-declared ethnicity	White	110 (59.78)
	Black	20 (10.87)
	Brown	53 (28.80)
	Indigenous	1 (0.54)
BMI	<25	46 (25.00)
	25-29.9	79 (42.93)
	>=30	59 (32.07)
Pregnancy history	No	17 (9.24)
	Yes	167 (90.76)
Menopausal status	Pre-menopause	90 (49.18)
	Post menopause	93 (50.82)
Breast	Bilateral	14 (7.61)
	Right	98 (49.49)
	Left	100 (50.51)

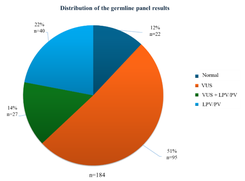


Figure 1. Distribution of the Germline panel results (n=184).

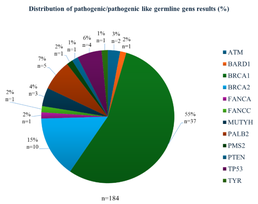


Figure 2. Distribution of pathogenic/pathogenic like germline gens results (n=184).

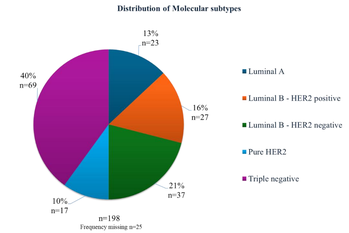


Figure 3. Distribution of molecular subtypes (n=198)

Table 2. Distribution of the anatomopathological characteristics of the tumors (n=198 *breasts*)

Anatomopathological characteristics		n (%)
Clinical Stage T	cTis	4 (2.09)
	cT1	41 (21.47)
	cT2	73 (38.22)
	cT3	35 (18.32)
	cT4	3 (1.57)
	cT4a	1 (0.52)
	cT4b	14 (7.33)
	cT4c	1 (0.52)
	cT4d	19 (9.95)
Clinical Stage N	cN0	74 (38.74)
	cN1	81 (42.41)
	cN2	27 (14.14)
	cN3	9 (4.71)
Histological type	Invasive ductal carcinoma NOS	176 (88.89)
	Invasive lobular carcinoma	11 (0.51)
	Others	21 (10.61)
Histological grade	Grade 1	6 (3.17)
	Grade 2	77 (40.74)
	Grade 3	106 (56.08)
Estrogen receptor	Negative	90 (47.37)
	Positive	100 (52.63)
Progesterone receptor	Negative	100 (52.36)
	Positive	91 (47.64)
Subtype according to immunohistochemical expression/in situ hybridization	Hormone Receptor positive, Her2 negative	63 (35.39)
	Hormone Receptor positive, Her2 positive	26 (14.61)
	Hormone Receptor negative, Her2 positive	17 (9.55)
	Hormone Receptor negative, Her2 negative	69 (38.76)
	Positive Hormone Receptor, Her2 not evaluable	3 (1.69)
Molecular subtype	Luminal A “Like”	23 (13.29)
	Luminal B - HER2 positive “Like”	27 (15.61)
	Luminal B - HER2 negative “Like”	37 (21.39)
	Pure HER2 “Like”	17 (9.83)
	Triple negative	69 (39.88)

Table 3 – Association of molecular subtypes by germline pathogenic/pathogenic like variances (PV/LPV) (n=198)

Molecular subtypes groups by germlines variants	Categories	Without LPV/PV	With lPV/PV	n total	Univariate analysis *		
		n (%)	n (%)	n (%)	O.R.*	CI 95%*	*p value*
Molecular subtype – all variants	Luminal A (ref.)	22 **(95.7)**	1 (4.3)	23 (100%)	1.00	---	---
	Luminal B/HER2+	20 (74)	7 (26)	27 (100%)	2.43	0.82 – 7.15	0.1080
	Luminal B/HER2-	15 (40.5)	22 **(59.5)**	37 (100%)	11.76	4.19 – 33.01	**<0.0001**
	HER Pure	14 (82.4)	3 (17.6)	17 (100%)	2.54	0.87 – 7.44	0.0894
	Triple Negative	35 **(50.7)**	34 **(50.3)**	69 (100%)	8.40	3.45 - 20.43	**<0.0001**
Total				**173****			
Molecular subtype in BRCA1 or BRCA2	Luminal A (ref.)	**22 (95.7)**	1 (4.3)	23 (100%)	1.00	---	---
	Luminal B/HER2+	20 (91)	2 (9)	22 (100%)	1.26	0.42 – 3.80	0.6757
	Luminal B/HER2-	15 (51.7)	14 **(48.3)**	29 (100%)	9.33	2.96 – 29.44	**0.0001**
	HER Pure	14 (87.5)	2 (12.5)	16 (100%)	2.40	0.76 – 7.59	0.1364
	Triple Negative	35 **(54.7)**	29 **(55.3)**	64 (100%)	9.03	3.37 – 24.20	**<0.0001**
Total				**154**			
Molecular subtype in non genes BRCA1 or BRCA2	Luminal A (ref.)	22 **(100)**	0 (0.0)	22 (100%)	1.00	---	---
	Luminal B/HER2+	20 (80)	5 (20)	25 (100%)	2.67	0.75 – 9.46	0.1283
	Luminal B/HER2-	15 (65.2)	8 **(34.8)**	23 (100%)	7.75	2.00 – 29.99	**0.0030**
	HER Pure	14 (93.3)	1 (6.7)	15 (100%)	2.44	0.76 – 7.86	0.1362
	Triple Negative	35 **(87.5)**	5 **(32.5)**	40 (100%)	3.48	1.32 – 9.20	**0.0120**
Total				**125**			

***Análise GEE (Generalized Estimating Equations)**
****Frequency missing n=25**

Discussion

Our analyses revealed that the molecular subtypes Luminal B HER2-negative "like" and triple-negative were associated with the presence of PV/LPV in the genes studied. When we evaluated only BRCA1 and BRCA cases accounting for approximately 70% of our positive test population the associations with these two molecular subtypes, Luminal B HER2- negative "like" and triple-negative, the association remained very expressive. This is likely due to a weak association of these variants with HER2 positive (HER2 +3 / HER2 +2 (ISH positive) and potentially higher Ki67, markers utilized in molecular subtype classification. It is important emphasize that our data allow us to highlight that patients with germline PV or LPV are associated to with Luminal HER2 negative “like” and triple negatives tumors in the same risk proportion using Luminal A “like” tumors, as reference. This analysis, made from the both points of view, is relevant. To women with PV or LPV without breast cancer it could be predict what would be the chance of the tumor subtype, in case of having a breast tumor in the future. As well for breast cancer patients, is very important to estimate the germline PV or LPV related to tumor subtypes for many reasons (cost effectiveness of germline panel tests, new treatments modalities, prevention, etc.). Our findings align with those of the "Breast Cancer Association Consortium" study [7], which investigated these associations in a cohort of 89,067 patients. This large, multicenter study provided the statistical power needed to assess nine genes. In the BRCA1 gene, the most associated subtypes were high-grade triple-negative and high-grade Luminal B HER2-negative (OR=55.3, 95% CI {40.5-75.5}) and (OR=13.50, 95% CI {9.16-19.9}), respectively. For BRCA2, triple-negative (OR=10, 95% CI {7.6- 13.3}) and Luminal B HER2-negative (OR=11.53, 95% CI {8.92-14.9}) were the prominent associations. Paixão D. et al. [8], in a study of 81 Brazilian patients with breast cancer, reported a 25% positivity rate for pathogenic germline variants using a multigene panel. Among triple-negative and HER2-negative luminal tumors, pathogenic variants were identified in 31.7% and 18.7% of cases, respectively.

In comparison, our study observed higher rates, with 36% of PV/LPV in the overall cohort. Specifically, in HER2-negative Luminal B-like and triple-negative tumors, the positivity rates for PV/LPV were 59.5% and 50%, respectively. When analyzing only BRCA1 and BRCA2, the frequencies of PV/LPV in Luminal B-like and triple-negative tumors were 48.3% and 55.3%, respectively.

These differences may be attributed to the higher-risk profile of our study population, which included a younger cohort, with 74% of patients being under 50 years of age. It is crucial to highlight the consistency of these associations, which remained remarkably similar even in a smaller study. Our primary limitation was sample size, which allowed a more robust evaluation primarily of the BRCA1 and BRCA2 genes, given their higher prevalence. In addition, some data loss occurred due to the lack of KI67 assessment, which rendered the classification of molecular subtypes unfeasible in a few cases. However, this is a single-institution study within a public health context, underscoring the value of germline testing as it relates to the somatic molecular behavior of these tumors. These data may help optimize the design of gene panels for use in public health settings and refine the selection criteria for implementation.

Conclusions

Two molecular subtypes were associated with the presence of pathogenic or likely pathogenic variants in genes associated with hereditary breast cancer: Luminal B HER2-negative and triple-negative subtypes.

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