

3 Frequency of Germline Variants in Breast Cancer Predisposing Genes: Genetic Background of Brazilian Women With Breast Cancer

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Background

Five percent to 10% of breast cancer cases present strong hereditary components; to date, several genes have been associated with breast cancer predisposition. The population background has to be considered, combined with other criteria, to assign pathogenicity to germline variants following the American College of Medical Genetics (ACMG) guidelines. However, there is a bias in large databases against underrepresented admixed populations, such as Brazilians, which makes it difficult to accurately interpret the clinical relevance of germline variants. To contribute to the characterization of the genetic background of breast cancer predisposition in the Brazilian population, we evaluate the frequency and spectrum of germline variants of breast cancer susceptibility genes in a cohort of Brazilian patients with breast cancer.

Material and Methods

Two hundred and five unrelated women with breast cancer were tested for germline variants in breast cancer predisposition

genes between 2014 and 2021 in 2 Brazilian centers: the Human Genome and Stem Cell Research Center (n = 150) and the Institute of Fetal Medicine and Human Genetics of São Paulo (n = 55). Of the 205 women, 108 (52.7%) were diagnosed at 45 years or younger; 44.91% had a positive family history, defined as 1 or more first- or second-degree relatives diagnosed with breast or ovarian cancer. Genetic testing was performed using custom panels containing up to 37 breast cancer-predisposing genes. We selected only variants with frequency less than 0.5% in an international (Genome Aggregation Database) and a Brazilian population database (Online Archive of Brazilian Mutations). Filtered variants were classified as pathogenic (P), likely pathogenic (LP), or variant of uncertain significance (VUS) using the ACMG 2015 guidelines.

Results

Thirty-seven patients were found to carry P/LP variants (18.1%), and a VUS was detected in 33 (16.1%). Twenty of the P/LP variants affected the *BRCA1* and *BRCA2* genes, and the remaining 17 patients carry variants mapped to *ATM*, *BRIP1*, *CHEK2*, *FANCD2*, *MUTYH*, *RAD51C*, *RAD51D*, *PALB2*, and *TP53* genes. The *BRCA1* c.5074+2T>C pathogenic variant was identified in 3 patients, which represents 8.1% of the total molecular diagnosis (P/LP). It is interesting to note that this variant is absent from consulted population databases.

Conclusions

Our findings contribute to the characterization of the genetic background of breast cancer predisposition in the highly admixture Brazilian population as a useful resource to discriminate among deleterious variants.

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15 COVID-19 Disease Course in Immunocompetent and Immunocompromised Patients in a Breast Cancer Registry

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The demographics, comorbidities, menopausal status, endocrine therapy, breast cancer morphology, and treatment history of 45 patients with non-stage IV breast cancer and COVID-19 were analyzed. Immune status at COVID-19 diagnosis,

COVID-19 disease severity and treatment, complete blood count (CBC) with differentials at and within 2 weeks of COVID-19 diagnosis, hospital/intensive care unit admission, and mortality were explored in relation to the influence of SARS-CoV-2 on the mononuclear phagocyte system (via M1/M2 macrophages) and the multimodal influences of menopause, estrogen, immunomodulatory drugs, and endocrine therapy on the immune system as well as gene expression of *ACE2*, *NRP1*, and *TMPRSS2*. Within each ethnicity group, percentages by number of comorbidities and body mass index ranges were correlated with disease severity and mortality. In the second analysis, COVID-19 outcomes were then examined, taking note of menopausal status, endocrine therapy, and receptor positivity.

Hispanic individuals had a similar percentage of obese patients as African Americans, the highest percentage of class III obesity (16.67%), and the highest percentage of severe COVID-19 disease (10.57%). Recent studies report reliable laboratory markers such as neutrophil-to-lymphocyte ratio in a COVID-19 hematocytometric index for severity and mortality. No appreciable changes in CBC differentials were noted due to limited serial CBCs. All immunocompetent patients with breast cancer hospitalized for hypoxia or acute hypoxic respiratory failure had a mild COVID-19 disease course and

the vast majority displayed eosinopenia; aromatase inhibitors were the known form of endocrine therapy in usage. There was a significantly greater number of postmenopausal patients infected irrespective of immune status. Recording of periodic CBC differentials, immunomodulatory drugs, endocrine therapy, and menopausal status can determine priority groups of care for non-stage IV breast cancer during the COVID-19 pandemic. Further investigation of the protective roles of selective estrogen receptor modulators and other forms of endocrine therapy against SARS-CoV-2 is warranted.

18 Psychosocial Wellbeing and Health Care Resource Utilization Among Patients With Breast Cancer During COVID-19

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Background

Global efforts are underway to assess the impact of COVID-19 on patients with cancer; data on outcomes from the perspective of patients with breast cancer (BC) are limited. This study described psychosocial well-being and health care resource utilization (HCRU) among patients with BC during the pandemic.

Materials and Methods

From March 30 to July 6, 2021, 669 patients with BC 18 years or older from Ciitizen, a patient-mediated health records and real-world evidence platform, and patient advocacy groups participated in an online survey. Sociodemographic and health characteristics, HCRU in the past 3 months, and psychosocial well-being were assessed via descriptive analysis.

Results

Of 669 patients, median age was 52 years (range, 28-82), 83.9% were White, and 51.4% had metastatic BC. More than half (58.7%) were currently being treated with hormone therapy. A total of 62 (9.3%; 95% CI, 7.3%-11.7%) reported ever being diagnosed with COVID-19. Patients had a median of 9 (interquartile range [IQR], 5-15) health care provider (HCP) visits in the past 3 months, of which a median of 6 (IQR, 3-12) were BC related. Of the 12.9% with ≥ 1 emergency

department visits in the past 3 months, a median of 1 (IQR, 0-1) was BC related; of the 9.1% with ≥ 1 hospitalizations in the past 3 months, a median of 2 (IQR, 1-3) were BC related. The prevalence of depressive symptoms in the past 2 weeks was 31.1% (95% CI, 27.7%-34.7%). The lowest Functional Assessment of Cancer Therapy subscale scores were observed for emotional and functional well-being; of those Psychological Impact of Cancer subscales that measure negative coping responses, scores were highest on emotional distress (**Table**).

TABLE. Psychosocial Well-being

Scale	Mean	SD
PIC		
Cognitive distress	5.4	2.0
Cognitive avoidance	7.3	2.2
Emotional distress	9.1	1.8
Fighting spirit	10.0	1.6
FACT		
BC subscale	22.8	6.8
Physical well-being	18.5	6.3
Social well-being	17.4	6.0
Emotional well-being	15.4	4.8
Functional well-being	16.3	6.1
FACT-general	67.6	17.9
FACT-BC	90.4	22.5

BC, breast cancer; FACT, Functional Assessment of Cancer Therapy; PIC, Psychological Impact of Cancer.

Conclusions

The prevalence of COVID-19 diagnosis among patients with BC was high. HCRU in the past 3 months was primarily driven by HCP visits, both all-cause and due to BC. Results also suggest impairments to psychosocial well-being, particularly aspects of mental health and emotional functioning. These findings underscore the unique vulnerability, burden, and unmet needs among patients with BC during the COVID-19 pandemic.

37 The Routine Use of Bioimpedance Spectroscopy Measurements in the Clinic as a Surrogate for Bone Mineral Content in Oncology Patients: Practical Application of the SOZO Device

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Background

Many patients with cancer, particularly those with breast or prostate cancer, receive hormonal manipulation therapies that can significantly impact their bone mineral content (BMC), potentially leading to life-threatening fractures, especially given the often advanced age of patients with these malignancies. Bioimpedance spectroscopy (BIS) is a noninvasive tool that measures fluid and body composition values including skeletal muscle mass (SMM) and fat-free mass (FFM). ImpediMed's SOZO BIS device can be used easily and quickly at point-of-care as the patient stands on the device, placing their hands and feet on metal electrodes. Multiple studies have shown a strong correlation between SMM and bone, suggesting that a SOZO reading can provide a reproducible, simple, and quick estimate of BMC. To that end, we present initial findings correlating SOZO BIS readings with dual x-ray absorptiometry (DXA) to determine if BIS readings can be applied as an accurate surrogate measure of BMC.

Materials and Methods

Concurrent BIS measures and DXA scans were performed in 75 healthy patients and in 76 with cancer (during and after cancer treatment), including: Group 1 (75 healthy cases [32 male, 43 female]; mean age, 27.4 years [range, 18-66]); Group 2 (35 patients undergoing cancer treatment [8 male, 27 female]; 13 breast, 5 lung, 4 endometrial, 4 colorectal, 3 prostate, 6 other cancers; mean age, 60.4 years [range, 39-79]); and Group 3 (41 patients participating in a 12-week exercise program after cancer treatment [11 males, 30 females]; 20 breast, 5 prostate, 3 colorectal, 3 endometrial, 10 other cancers; mean age, 58.4 years [range, 20-79]).

Results

The Pearson correlation coefficient (*R*) for DXA BMC and SOZO SMM were strong for all 3 groups (*R* = 0.92, 0.86, and 0.78 for groups 1, 2, and 3, respectively). Stepwise multiple linear regression for BMC was performed. For group 1, age, FFM, and height resulted in a multiple correlation coefficient of 0.94 (*P* < .001); for groups 2 and 3 combined, BMC was dependent on height (*P* = .03) and SMM (*P* < .0001) for a multiple correlation coefficient of 0.815 (*P* < .001).

Conclusions

Concurrent measures of SOZO SMM correlated strongly with DXA BMC, demonstrating that SOZO SMM may be a useful surrogate in the clinic to provide a quick, easy, and reproducible indicator of change in BMC, particularly for those patients undergoing treatments that may affect BMC. Tracking SMM during or after cancer treatment with SOZO may provide an estimate of changes in BMC, allowing clinicians to obtain additional diagnostic testing and/or consider treatment modifications.

43 Early Detection of Breast Cancer-Related Lymphedema: Accuracy of Indocyanine Green Lymphography Compared With Bioimpedance Spectroscopy and Symptoms

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Background

The incidence of breast cancer-related lymphedema (BCRL) is highly variable within an average of 25% to 40% occurrence among different studies. Although the extent and modality of breast cancer therapies, the timeliness of referrals for evaluation, and the duration of follow-up all have major impacts on BCRL incidence, high variability among studies is also a result of the different diagnostic techniques used and the lack of a standardized definition. The objective superiority of indocyanine green lymphography (ICG-L) for detection of BCRL is in its ability to provide not only an accurate diagnosis but also a chance to intervene and prevent progression. In this study, we aimed to compare

Multidisciplinary

sensitivity and specificity of ICG-L with lymphedema (LE) symptoms and bioimpedance spectroscopy (BIS) to detect LE in patients with no clinically detectable swelling.

Methods

Patients who underwent axillary lymph node dissection (ALND) or had greater than 5 sentinel lymph nodes (SLNB) removed, regardless of their LE symptoms, were included in a prospectively maintained registry. All patients had bilateral arm circumferential tape measurements immediately after surgery and were monitored every 3 to 6 months. All patients had no detectable signs of clinical LE. Clinical LE was defined as having any girth difference of 2.0 cm or more in the involved limb as compared with the uninvolved limb. LE symptoms were defined as heaviness, fullness, and/or swelling. The L-Dex U400 or SOZO (ImpediMed limited and Impedi Med Inc) was used for BIS measurements. Subclinical LE was defined as either L-Dex values that lie outside the normal range (between -7 and +7 units) or a 7-unit change between 2 measurements. ICG-L was performed once anytime postoperatively. The near infrared camera system (PDE; Hamamatsu Photonics K.K.) was used for this study. ICG injection USP (25 mg; Patheon Italia S.p.A) was mixed with 10 mL of saline. ICG injections were in the distal aspect of the upper limb on the affected side including the first and fourth web spaces, and if necessary, additional wrist or elbow regions. If there were detectable changes in the lymphatic system after the ICG-L, patients were treated accordingly and are now being followed up for the development of clinical signs of LE.

Results

We enrolled 123 patients, which accounted for 133 arm ICG-L and BIS measurements. The mean age was 54 ± 12 years. Surgical procedures included 46 segmental mastectomies (34.6%), 86 total mastectomies (64.7%), and 1 other surgery in 1 patient (0.8%). SLNB was performed in 57 cases (42.9%) and ALND in 74 cases (55.5%). Based on BIS measurements, 43 arms (32.3%) had values outside the normal range. ICG-L detected lymphatic flow disruption in 63 (47.4%) arms. When compared with ICG-L, BIS had 51% positive predictive value (PPV), 54% negative predictive value (NPV), and 53% accuracy ($R = .053$; $P = .545$; $AUC = 0.54$). When comparing LE symptoms with ICG-L, the PPV of symptoms was 58%, NPV was 66%, and accuracy was 60% ($R = .0231$; $P = .01$; $AUC = 0.62$). Both L-Dex (BIS) and LE symptoms have less than 0.70 AUC-ROC curve; this shows that L-Dex and LE symptoms are not good tools for distinguishing between positive and negative LE in patients who had not presented with swelling.

Conclusions

Minimally invasive ICG-L appears to be the most reliable diagnostic tool available for identifying subclinical LE. ICG-L was able to accurately detect lymphatic flow disruption in patients following axillary surgery, even before clinical signs were present. Adapting ICG-L to the subclinical LE diagnosis protocol provides a great opportunity for earlier identification of problematic areas in lymphatic flow, which can lead to a more personalized plan of care and implementation of appropriate treatment accordingly.

46 Racial/Ethnic Groups Have Different Clustering of Variants of Uncertain Significance

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Background

Racial/ethnic disparities in access to genetic testing have been well established. This lack of testing not only leads to missing potentially lifesaving identification of pathogenic

variants but may lead to more variants of unknown significance due to lack of broad population-based adjudication of these variants.

Methods

Patient data were obtained from the Informed Genetics Annotated Patient (iGAP) Registry, an institutional review board-approved, multicenter, longitudinal, observational study designed to capture genetic and genomic test results and their utilization and impact on treatment practices and outcomes. Patients self-declare race/ethnicity for the iGAP Registry. Choice of multigene panel testing lab is physician directed. Variant classification is determined by the performing genetic testing lab and reported as negative, variant of uncertain significance (VUS), or pathogenic/likely pathogenic. Descriptive statistics were used to assess and compare data of these populations and germline genetic testing results indicating variant of uncertain significance.

Results

Number of VUS/total tests were as follows: White, 886/1406 (63.1%); Hispanic, 117/156 (75.0%); Black, 116/124 (93.5%); Asian, 95/106 (89.6%). Average number of VUS per patient were as follows: White, 6.3; Hispanic, 7.5; Black, 9.4; Asian, 9.0. Examples of VUS rates (VUS/total tested) in *BRCA1/2* were as follows: White, 2.1%; Hispanic, 2.6%; Black, 3.2%; Asian, 7.6%. VUS rates in *ATM* were as follows: White, 3.0%; Hispanic, 5.8%; Black, 8.1%; Asian, 4.7%.

Conclusions

Hispanic, Black, and Asian patients had a higher proportion of subjects with a VUS and had a greater number of VUS genes per subject compared with White patients for all cancer genes examined. Variant adjudication has disproportionately sorted out more uncertain results in White patients than in Hispanic, Black, and Asian patients. This leads to greater uncertainty in posttest counseling for these groups as well as attenuated overall benefit from appropriate testing. Variant adjudication in minority groups should be a focus for lab testing companies going forward.

47 Breast Cancer Categorized as Having High Risk of Recurrence and/or Basal-Type or Luminal B Molecular Subtype by MammaPrint and Blueprint, Respectively, Should Universally Undergo Germline Genetic Testing

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Background

With the rise of somatic testing, more clinicians are using panels to understand the genetic profile of breast cancer to help aid in clinical management. However, little is known about the relationship between the results of somatic tests and the likelihood of identifying an underlying germline variant.

Methods

Data were obtained from the Informed Genetics Annotated Patient (iGAP) Registry, an institutional review board-approved, multicenter, longitudinal registry designed to capture biomarker test results and their impact on treatment practices and outcomes. Two somatic tests were studied: MammaPrint and Blueprint. Of the 2765 subjects currently enrolled in the registry, 1526 have been diagnosed with breast cancer (55.19%). All subjects underwent germline genetic testing, with 403 and 226 individuals undergoing tumor profiling through MammaPrint and Blueprint,

respectively; 222 individuals underwent both MammaPrint and Blueprint.

Results

Results indicate that of the individuals who were tested through MammaPrint (n = 403) and/or Blueprint (n = 226) panels and underwent germline genetic testing, 176 (43.67%) were classified as being at high risk for recurrence on MammaPrint, 218 (54.09%) were identified as being at low risk for recurrence, and 9 were identified as having ultralow risk of recurrence (2.23%). Individuals with a high risk of recurrence had a 17.61% positive germline variant rate compared with a positive rate of 11.01% in the low-risk group (ultralow, 11.11%; not significant [NS]). Of the 127 individuals categorized through the Blueprint panel, 22 were classified as basal type, 7 as HER2-type, 124 as luminal A type, and 73 as luminal B type. Basal and luminal B types had the highest positive germline rates of 18.18% and 17.81%, respectively, compared with HER2-type (14.29%) and luminal A (10.48%) types (all NS).

Conclusions

The iGAP real-world evidence revealed that individuals categorized as having a high risk of breast cancer recurrence through MammaPrint somatic testing were identified to harbor a pathogenic or likely pathogenic germline variant 17.61% of the time. A similarly high likelihood (18.18% and 17.81%) was seen in Blueprint-tested individuals with basal and luminal B unspecified molecular subtypes, respectively, with comparatively lower likelihood in HER2-positive (14.29%) and especially lower in luminal A (10.48%) types. These data argue that germline genetic testing should be offered to every individual, regardless of age, identified as having a high risk of breast cancer recurrence and/or basal or luminal B molecular subtype on MammaPrint and Blueprint tests.

48 A Comparison of Race and Ethnicity and Germline Results in ASBrS vs NCCN Guidelines

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Background

National and society guidelines play a critical role in qualifying patients for germline genetic testing. These guidelines' purpose is to identify individuals who are at risk for carrying germline genetic variants responsible for cancer predisposition and to enable health care providers to intervene.

Methods

Data were obtained from the Informed Genetics Annotated Patient (iGAP) Registry, an institutional review board-approved, patient-consented, multicenter prospective registry that includes patients with cancer who are undergoing genetic testing as well as unaffected patients with pathogenic mutations. In total, 1815 subjects were assessed with the National Comprehensive Cancer Network High Risk Assessment for Breast, Ovarian, and Pancreatic Hereditary Genetic Testing Guidelines (NCCN BOP) and the American Society of Breast Surgeons (ASBrS) Guidelines for Genetic Testing for Hereditary Breast Cancer (version up to date at time of screening, from 2019-2022).

Results

In total, 1815 subjects were risk assessed and completed a germline genetic test. Of these subjects, 849 met NCCN BOP criteria (46.78%) and 1491 (82.15%) met ASBrS Guidelines for Genetic Testing. Of the subjects who met NCCN BOP vs ASBrS Guidelines, the average age was 55.87 vs 60.47 years, respectively. Subjects with personal history of cancer accounted for 80.92% (687/849) vs 91.15% (1359/1491), respectively; those with a family history of cancer accounted for 85.04% (722/849) vs 42.59% (1017/1491). Proportionally more subjects who met the NCCN BOP criteria had a positive variant, with 23.67% (201/849), compared with 18.71% (279/1491) who met ASBrS criteria. Racial/ethnic categories were also examined in the 2 different guideline groups, with 36.25% more White patients (1096 vs 611) meeting ASBrS guidelines over NCCN; 25.20% (111 vs 79) more Hispanic patients; 53.77% (94 vs 37) more Asian patients; 33.33% (84 vs 52) more African/Black patients; and 3.57% (25 vs 26) fewer Ashkenazi patients (**Table**).

Conclusions

Germline genetic testing impacts patient care. Current national guidelines may miss a significant number of patients with germline mutations and variants of unknown significance. More studies are needed to evaluate the current underutilization of germline genetic testing.

TABLE. Guideline Criteria Match by Racial/Ethnic Category

RE by guideline (%)	White	Hispanic	Asian	African/Black	Ashkenazi	Multiple	Other	Unknown
Meets NCCN	45.67%	62.20%	34.91%	54.17%	92.86%	33.33%	40.00%	35.63%
Meets ASBrS	81.91%	87.40%	88.68%	87.50%	89.29%	100.00%	83.33%	35.63%
Total subjects (n)	1338	111	106	96	28	3	30	87
Meets ASBrS, not NCCN	36.25%	25.20%	53.77%	33.33%	-3.57%	66.67%	43.33%	0.00%

ASBrS, American Society of Breast Surgeons; NCCN, National Comprehensive Cancer Network; RE, race/ethnicity.

49 Racial/Ethnic Groups Have Different Clustering of Common Cancer Genes

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Background

Racial/ethnic disparities have been well documented in terms of access to cancer screening and treatment, as well as treatment outcomes. Less is known regarding the proportion of higher- and lower-penetrance genetic pathogenic variants in these populations.

Methods

Patient data were obtained from the Informed Genetics Annotated Patient (iGAP) Registry, an institutional review board-approved, multicenter, longitudinal, observational study designed to capture genetic and genomic test results and their utilization and impact on treatment practices and outcomes. Patients self-declare race/ethnicity for iGAP. Choice of multigene panel testing lab is physician directed. Variant classification is determined by the lab that performs the genetic testing, and the variants are reported as negative, variant of uncertain significance, or pathogenic/likely pathogenic. Descriptive statistics were used to assess and compare data from these populations, and the results of germline genetic testing included higher- and lower-penetrance pathogenic variants.

Results

BRCA1/2 pathogenic variant/total number of subjects tested rates were as follows: White, 16/1406 (1.14%); Hispanic, 20/156 (12.82%); Black, 8/124 (6.45%). Pathogenic variants of non-*BRCA* genes/total number of pathogenic variants rates were as follows: White, 289/305 (95%); Hispanic, 27/47 (57%); Black, 8/16 (50%). The Hispanic group has a considerably higher percentage of *BRCA1/2* pathogenic variants compared with Black and White patients. However, White patients have considerably more pathogenic variants in lower-penetrance genes than other racial/ethnic groups.

Conclusions

Racial/ethnic groups varied by proportion of both *BRCA1/2* and lower-penetrance pathogenic variants. The higher percentage of *BRCA1/2* pathogenic variants in our Hispanic group could be due to the greater representation of Hispanics from New Mexico in the iGAP Registry, who may harbor Ashkenazi ethnicity. Further studies are needed to understand whether these differences are a result of disparate access to testing, true population differences, or other factors.