EPIEMIOLOGY

Mutational spectrum of breast cancer susceptibility genes among women ascertained in a cancer risk clinic in Northeast Brazil

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Abstract

Purpose There is a paucity of data on the spectrum and prevalence of pathogenic variants among women of African ancestry in the Northeast region of Brazil.

Methods We performed BROCA panel sequencing to identify inherited loss-of-function variants in breast cancer susceptibility genes among 292 Brazilian women referred to a single institution cancer risk assessment program.

Results The study included a convenient cohort of 173 women with invasive breast cancer (cases) and 119 women who were cancer-free at the time of ascertainment. The majority of the women self-reported as African-descended (67% for cases and 90.8% for unaffected volunteers). Thirty-seven pathogenic variants were found in 36 (20.8%) patients. While the spectrum of pathogenic variants was heterogeneous, the majority (70.3%) of the pathogenic variants were detected in high-risk genes BRCA1, BRCA2, PALB2, and TP53. Pathogenic variants were also found in the ATM, BARD1, BRIP1, FAM175A, FANCM, NBN, and SLX4 genes in 6.4% of the affected women. Four recurrent pathogenic variants were detected in 11 patients of African ancestry. Only one unaffected woman had a pathogenic variant in the RAD51C gene. Different risk assessment models examined performed well in predicting risk of carrying germline loss-of-function variants in BRCA1 and/or BRCA2 in breast cancer cases.

Conclusion The high prevalence and heterogeneous spectrum of pathogenic variants identified among self-reported African descendants in Northeast Brazil is consistent with studies in other African ancestry populations with a high burden of aggressive young onset breast cancer. It underscores the need to integrate comprehensive cancer risk assessment and genomic testing in the management of newly diagnosed Black women with breast cancer across the African Diaspora, enabling improved cancer control in admixed underserved and understudied populations.

Keywords Breast cancer · Brazilians · BROCA panel · Genetic testing

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide [1]. This non-communicable disease is the leading cause of female deaths in many countries, with widening disparities in outcomes among developed and developing countries. Geographic differences in incidence and mortality are due to many intrinsic (e.g., genetic) and extrinsic (e.g., environment, lifestyle) factors [2]. Despite notable differences, “one-size-fits-all” cancer control strategies are usually applied in screening and treatment within and across countries, which have led to widening disparities in breast cancer mortality and morbidity among different racial/ethnic groups [3].

This rising global burden of breast cancer in low- to middle-income countries demands innovative interventions to accelerate progress in cancer control and prevention. Through genomic analysis of breast cancer predisposition genes, the burden of inherited susceptibility to breast cancer in diverse populations can be better estimated, allowing
clinical management and treatment recommendations to be tailored to the needs of high-risk women and their families [4]. With advances in high-throughput sequencing technologies, it is now possible to analyze numerous genomic regions simultaneously at greatly reduced cost. Many multi-gene panels such as the BROCA panel have been developed and applied successfully in large genetic testing studies in the United States and Europe [5, 6]. We previously reported the high prevalence of highly penetrant pathogenic variants in BRCA1, BRCA2, PALB2, and TP53 genes in consecutive women presenting with advanced breast cancer at tertiary hospitals in Nigeria, Cameroon, and Uganda [7, 8].

Black women across the African Diaspora have the worst outcomes from breast cancer of all ethnic/racial groups. Given the reported high prevalence of aggressive breast cancer in young Brazilian women [9], we sought to examine the burden of inherited breast cancer in a convenient sample of consecutive women with breast cancer ascertained in a cancer risk clinic in the State of Bahia in the Northeast region of Brazil. This region has a large population of African descendants as it remains segregated and is primarily inhabited by former descendants of slaves. The African ancestral proportion revealed through genomic admixture studies is the highest in this region in comparison with other regions of Brazil [10].

Methods

Study population and eligibility

Between 2008 and 2015, we recruited women with breast cancer referred by their primary care physicians to the Cancer Risk Assessment Program of the Serviço de Oncogenética of Laboratório de Imunologia e Biologia Molecular (ICS-UFBA). This public laboratory service is part of the Brazilian National Network of Hereditary Cancer. Women with breast cancer are usually referred to this service from private and public clinics and hospitals. Since this service is provided by a public entity, counseling was free of charge and more than 90% of patients were willing to participate in the research. To develop a reference control panel to improve interpretation of our findings, we recruited a cohort of cancer-free women who are not the relatives of the cases but were undergoing routine laboratory tests (for regular clinical checkups or for an evaluation of other diseases) in the same laboratory between 2014 and 2015.

All participants signed informed consents, and data regarding their epidemiological and clinical profiles were collected along with questionnaires administered by a research coordinator. The research protocol #1.383.884 was approved by the Brazilian National Committee of Ethics in Research (CONEP, Comissão Nacional de Ética em Pesquisa), the University of Chicago, and the University of Washington, where the sequencing was performed.

Next-generation sequencing and genomic analysis

The genomic DNA was extracted from peripheral blood using a commercial kit, the DNeasy® blood and tissue kit (QIAGEN, German). The quality and quantity of the genomic DNA was assessed with 2% agarose gel electrophoresis analysis and the Quant-iT™ PicoGreen™ dsDNA Assay Kit (Invitrogen, Thermo Scientific, USA). A total of 28 susceptibility genes were analyzed in the BROCA panel. Genes sequenced included established breast cancer genes of both high and moderate penetrance, and genes that have been suggested as candidate breast cancer genes, with varying levels of evidence: ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIPl, CDH1, CHEK1, CHEK2, CTNNA1, FAM175A, FANCM, GEN1, MRE11A, NBN, PALB2, PPM1D, PTEN, RAD51B, RAD51C, RAD51D, RECQL, RINT1, SLX4, STK11, TP53, and XRCC2.

Paired-end reads were mapped to the human genome reference hg19. Subsequently, single-nucleotide variants and small insertions and deletions were called as previously described in detail [5, 11], and copy number variants were detected as well [12]. Only variants that led to a loss of gene function or were experimentally demonstrated to damage gene function were included in further analyses. Interpretations of possible splice variants were based on in silico algorithms or on experimental results from our own work or that of others.

Statistical analysis

Descriptive analysis was performed using Epi Info™ software (CDC, Atlanta, GA, USA) and SPSS® (SPSS Inc. Chicago, IL, USA). Given the limited sample size of the study, we performed an exploratory analysis to estimate performance of different breast cancer risk assessment tools using online calculators: the Myriad Risk calculator [13], the PENN II Risk Model [14], and BRACAPRO [15], based on the BRCA1 and BRCA2 mutational profiles and clinical and epidemiological data.

Results

Clinical characteristics

Over 90% of the study participants were from the Northeast region of Brazil, particularly from the State of Bahia. About 67.0% of the breast cancer cases self-reported as...
African-descended (Black), with enriched family history of cancer, including breast cancer (~65%) (Table 1). The mean age at breast cancer diagnosis among the cases was 44.1 ± 11.3 years while unaffected women were older, with a mean age at interview of 52.2 ± 13.6 years. The breast cancer patients were predominantly diagnosed with breast cancer only (96.5%), followed by breast and ovarian (2.3%) (Table 1). Invasive ductal carcinoma was the most common diagnosis in breast cancer patients of both African and non-African ancestry, 81.9% and 79%, respectively. The tumor subtypes were classified by immunohistochemistry for expression of hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 (HER2) (Table 2). If HER2 was classified as 2+ by immunohistochemistry, additional analysis was performed by using fluorescent in situ hybridization. The ER+/PR+/HER2- was the most common classification, followed by ER+/PR-/HER2-, triple-negative and HER2+ (41.6%, 16.2%, 15.5%, and 10.4%, respectively).

Spectrum of pathogenic variants in breast cancer susceptibility genes

Thirty-seven loss-of-function variants (30 distinct variants) were found in 36 breast cancer patients, one of whom carried both BARD1: c.1921C>T and BRCA2: c.3860delA (Fig. 1, Table 2 and Supplementary Table 1). In the cohort of cancer-free women, only one individual carried a pathogenic variant, RAD51C: c.264_265insA. Among self-reported African-descended breast cancer patients, 24.1% (28 of 116) carried 29 pathogenic variants in ATM, BARD1, BRCA1, BRCA2, BRIP1, FAM175A, FANCM, PALB2 and TP53 genes. The majority of pathogenic variants were found in BRCA1 and BRCA2 (65.5%, 19 of 29). Four recurrent loss-of-function variants were detected in 11 African-descended breast cancer cases, BRCA1: c.3331_3334delCAAG, BRCA1: c.211A>G, BRCA2: c.1389_1390delAG and PALB2: c.1671_1674delTATT (Table 2). Pathogenic variants were found in BRCA1, BRIP1, NBN, PALB2, and SLX4 genes among eight cases of non-African ancestry (14.0%, 8 of 57), with BRCA1 and BRIP1 being the most commonly mutated genes (50%, 4 of 8) (Table 2).

Congruous with previously published annotations, we did not observe any African-specific pathogenic variants, and the majority of tumors arising in BRCA1 and BRCA2 carriers were HR- and HR+, respectively [16] (Supplementary Fig. 1). In Supplementary Fig. 2, we describe in detail the BRCA1 and BRCA2 mutational spectrum of the study population compared with other Black women across the African Diaspora and White women in the literature [17–22].

Using different risk models for pathogenic BRCA1 and BRCA2, we observed that the predicted risk was higher in breast cancer cases carrying germline loss-of-function variants in BRCA1 and/or BRCA2 than in other breast cancer genes, or those carrying wild-type genes (Supplementary Table 2). The data revealed that these risk models can discriminate high-risk from low-risk women (Supplementary Fig. 3), supporting the use of these models in this population.

Discussion

Little is known about the genetic susceptibility to breast cancer of African-descended Brazilian women, an understudied population. As there is a high degree of genetic admixture among Brazilian populations [23–25], we sought to study the genetic susceptibility to breast cancer in one of the largest African-descended populations in Latin America, the

| Characteristic               | Cases (n = 173) | Unaffected volunteers (n = 119) |
|-----------------------------|----------------|-------------------------------|
|                            | N (%)          | N (%)                         |
| Age (years)                 |                |                               |
| ≤ 50                        | 131 (79.3%)    | 50 (42.01%)                   |
| > 50                        | 42 (20.7%)     | 69 (57.9%)                    |
| Mean ± SD                   | 44.1 ± 11.3    | 52.2 ± 13.6                   |
| Type of cancer              |                |                               |
| Breast only                 | 167 (96.5%)    | –                             |
| Breast and ovarian          | 4 (2.3%)       | –                             |
| Other                       | 2 (1.2%)       | –                             |
| Self-reported ancestry      |                |                               |
| White                       | 45 (26%)       | 10 (8.4%)                     |
| African-descended           | 116 (67%)      | 108 (90.8%)                   |
| Other                       | 12 (6.9%)      | 1 (0.8%)                      |
| Family history of cancer    |                |                               |
| Yes                         | 111 (64.2%)    | 47 (39.5%)                    |
| No                          | 62 (35.8%)     | 72 (60.5%)                    |
Table 2  Spectrum of pathogenic variants in breast cancer susceptibility genes among Brazilian cases

| ID    | Variant            | Type of cancer | Age at diagnosis | Self-reported ancestry | Family history of cancer | Histology | Tumor grade | Tumor stage | ER | PR | HER2 |
|-------|--------------------|----------------|------------------|------------------------|--------------------------|-----------|-------------|-------------|----|----|------|
| ACMO76 | NBN c.156_157delTT | Breast         | 56               | Other                  | No                       | IDC       | –           | T4cN3M1     | Pos| Pos| Pos  |
| ACMO88 | BRIP1 c.1741C>T    | Breast         | 40               | White                  | No                       | IDC       | IV          | T2N1M0      | Pos| Pos| –    |
| CM003  | BRCA2 c.2111delIC  | Breast         | 42               | Other                  | Yes                      | IDC       | III         | T2N0M0      | Pos| Neg| Neg  |
| CM023  | BRCA1 c.3331_3334delCAAG | Breast         | 36               | African-descended      | Yes                      | IDC       | I           | T1N0M0      | Pos| Pos| Neg  |
| CM033  | BRCA1 c.1115G>A    | Breast and Ovarian | 36          | African-descended      | Yes                      | IDC+Lobular carcinoma (Breast); Serous adenocarcinoma (Ovarian) | IIB        | T2N1M0      | Pos| Pos| Neg  |
| CM048  | BRCA1 c.211A>G     | Breast         | 39               | African-descended      | Yes                      | Medullary carcinoma of the breast | –          | –           | Neg| Neg| Pos  |
| CM130  | BRCA1 c.815_824dupAGCCATGTGG | Breast and Thyroid | 64               | White                  | Yes                      | IDC       | –           | –           | Neg| Neg| Neg  |
| CM179  | BRIP1 c.2392C>T    | Breast and Ovarian | 42          | African-descended      | Yes                      | Lobular carcinoma | –          | –           | Pos| Pos| Neg  |
| CM211  | SLX4 c.4828delTT   | Breast         | 28               | White                  | Yes                      | DCIS      | III         | TisN0M0     | Neg| Neg| Pos  |
| CM223  | BRCA1 c.3331_3334delCAAG | Breast         | 28               | African-descended      | Yes                      | IDC       | III         | T2N0M1      | Neg| Neg| Neg  |
| CM242  | BRCA1 c.211A>G     | Breast         | 41               | African-descended      | Yes                      | Medullary carcinoma of the breast | –          | –           | Neg| Neg| Neg  |
| CM247  | BRCA2 c.5904_5907delAGTC | Breast         | 34               | African-descended      | Yes                      | IDC       | II          | T2N1M0      | Pos| Neg| Neg  |
| CM252  | BRCA1 c.211A>G     | Breast         | 52               | African-descended      | Yes                      | IDC       | IIa         | T2N0M0      | Neg| Neg| Neg  |
| CM266  | PALB2 c.1671_1674delTATT | Breast         | 35               | African-descended      | Yes                      | IDC       | –           | –           | Pos| Pos| Neg  |
| CM277  | PALB2 c.1671_1674delTATT | Breast         | 49               | African-descended      | No                       | IDC       | II          | –           | Pos| Pos| Neg  |
| CM278  | BRIP1 c.2097+1G>C  | Breast         | 52               | White                  | Yes                      | IDC       | II          | pT2pN0pMx   | Neg| Neg| Pos  |
| CM293  | PALB2 c.355delIC   | Breast         | 49               | White                  | Yes                      | IDC       | –           | –           | Pos| Pos| –    |
| CM297  | ATM c.3801delG     | Breast         | 38               | African-descended      | Yes                      | IDC       | –           | –           | Pos| Pos| Pos  |
| CM309  | FANCM c.5766_5769delGACT | Breast         | 38               | African-descended      | Yes                      | IDC       | –           | –           | Pos| Pos| Pos  |
| CM318  | BRCA2 c.7672G>T    | Breast         | 27               | African-descended      | Yes                      | DCIS      | IV          | T3N2M1      | Pos| Pos| –    |
| CM322  | FAM175A c.1011delA | Breast         | 43               | African-descended      | No                       | IDC       | III         | pT4pN3      | Pos| Neg| Pos  |
| CM362  | BRCA2 c.1389_1390delAG | Breast         | 47               | African-descended      | No                       | IDC       | II          | –           | Pos| Pos| Pos  |
| CM385  | TP53 c.1010G>A     | Breast         | 28               | African-descended      | Yes                      | IDC       | II          | T1N1M0      | Pos| Pos| Neg  |
| CM389  | BRCA1 c.1327A>T    | Breast         | 34               | African-descended      | Yes                      | IDC       | –           | –           | Neg| Neg| Neg  |
| ID     | Variant          | Type of cancer | Age at diagnosis | Self-reported ancestry | Family history of cancer | Histology | Tumor grade | Tumor stage | ER   | PR   | HER2 |
|--------|------------------|----------------|------------------|------------------------|--------------------------|-----------|-------------|-------------|------|------|------|
| CM403  | BRCA2 c.8488-1G>A| Breast         | 34               | African-descended      | Yes                      | IDC       | II          | T1N0M0      | Pos  | Neg | Neg |
| CM420  | BRCA1 c.3331_3334delCAAG| Breast | 38               | African-descended      | Yes                      | IDC       | II          | T2N0M0      | –    | –    | –    |
| CM440  | BRCA2 c.736delT  | Breast         | 42               | African-descended      | Yes                      | IDC       | IV          | T4cN2MX     | Pos  | Pos | Pos |
| CM512  | ATM c.7913G>A    | Breast         | 38               | African-descended      | Yes                      | IDC       | II          | T1N1M0      | Pos  | Pos | Neg |
| CM243  | BRCA1 c.470_471delCT| Breast | 60               | White                  | Yes                      | IDC       | –           | –           | –    | –    | –    |
| CM536  | BRCA2 c.1389_1390delAG| Breast | 46               | African-descended      | Yes                      | IDC       | II          | T1N0M0      | Neg  | Pos | Neg |
| CM550  | BRCA1 c.3331_3334delCAAG| Breast | 26               | African-descended      | No                       | IDC       | II          | pT3pN3a     | Neg  | Neg | Pos |
| CM564  | BRCA1 c.5251C>T  | Breast         | 40               | African-descended      | No                       | IDC       | II          | –           | Neg  | Neg | Neg |
| CM575  | BRCA2 c.3860delA, BARD1 c.1921C>T| Breast | 41               | African-descended      | Yes                      | IDC       | –           | –           | –    | –    | –    |
| CM581  | BRCA2 c.6938-1G>C| Breast         | 43               | African-descended      | Yes                      | IDC (Breast) and Serous papillary cystadenocarcinoma (Ovarian) | II          | T2N0M0      | Pos  | Pos | Neg |
| CM582  | BRCA2 c.2T>G     | Breast and Ovarian | 49               | African-descended      | No                       | IDC (Breast) and Serous papillary cystadenocarcinoma (Ovarian) | – (breast) / III (ovarian) | T2N0M0      | –    | –    | –    |
| CM590  | ATM c.8264_8268delATAAG| Breast | 41               | African-descended      | Yes                      | –          | –           | –           | –    | –    | –    |

ER: estrogen receptor, DCIS: ductal carcinoma in situ, IDC: invasive ductal carcinoma, HER2: human epidermal growth factor receptor 2, Pos: positive, PR: progesterone receptor, Neg: negative
inhabitants of the State of Bahia in the Northeast region of Brazil.

Using the validated BROCA panel, we identified 36 distinct pathogenic variants in 30 patients with breast cancer cases and only one pathogenic variant in cancer-free women. As observed in previous studies worldwide [4, 22, 26], BRCA1 and BRCA2 were the most frequently mutated genes in breast cancer patients, and their mutation frequencies in women from the Northeast region of Brazil are closer to that in Africans than the reported frequencies in African-Americans and women of European ancestry (Table 3). We compared our results with the BRCA1 and BRCA2 mutational spectrum reported by the Brazilian Consortium of Hereditary Cancer [18], as well as other studies [17, 19–22].

Among sixteen BRCA1 and BRCA2 pathogenic variants detected in African-descended breast cancer patients in this study, twelve were documented globally, five were found in self-reported African ancestry individuals in non-African countries/regions, one was found in self-reported African ancestry individuals in African countries, eight were previously reported among Brazilians, and one was newly identified (Supplementary Fig. 2). Our observation that the BRCA1/2 pathogenic variants found in Blacks in Northern Brazil were not unique to the population agrees with the finding of a previous study by Friebel et al. [21]. BRCA1/2 pathogenic variants in Africans are allelic heterogeneous with low frequencies [7, 8, 27]; however, the Friebel et al. study showed that variants identified in Africans were also reported in non-African populations [21]. The possible explanations could be: (1) to date, breast cancer mutation surveys have been done primarily in individuals of European ancestry, which increases the probability of detecting variants also found in African populations; (2) the “out of Africa” theory of early human migrations and the diversity in the African Diaspora [27] suggest that some variants found in non-African populations could be of African origin; and (3) some African-specific variants in highly admixed populations like Brazilians might not be captured due to the limited sample size of the present study.

In this study, other genes frequently mutated were the high-risk gene PALB2, as well as ATM and BRIP1, each found in 1.7% of the cases. Although the prevalence of pathogenic variants in these genes varies in breast cancer patients of African ancestry [6, 7], it confirms that genes involved in DNA repair pathways are the major contributors to inherited breast cancer. Thus, their critical role in
understudied populations with high burden of young onset breast cancer deserves further examination. In the South and Southeast regions of Brazil, TP53 is the third gene most frequently mutated among breast cancer patients. Among these patients, most carry TP53:c.1010G>A, which has a known founder effect in those regions of Brazil. However, this pathogenic variant was quite rare (0.6%, 1 of 173) among the breast cancer cases from the Northeast region of Brazil in our study (Fig. 1 and Table 2).

The spectrum of founder mutations found in our cohort reflects the degree of ancestral admixture within the State of Bahia, where there is a significant history of immigration from Spain, Central Europe, and West Africa [23, 28, 29]. Four recurrent variants were discovered among unrelated African-descended breast cancer patients: BRCA1:c.3331_3334delCAAG, BRCA1:c.211A>G, BRCA2:c.1389_1390delAG, and PALB2:c.1671_1674delTATT. The first two were previously described in Spanish descendants [30, 31] and in the Northeast Brazilian population [29]. BRCA2:c.1389_1390delAG was described in diverse populations in Central Europe [32–34], while PALB2:c.1671_1674delTATT remains uncharacterized and was documented only twice in ClinVar. To confirm whether this PALB2 pathogenic variant has a founder effect, further studies are needed to evaluate the carriers’ haplotypes. In addition, we observed variants that are recurrent in African populations: ATM:c.7913G>A [35, 36], BRCA1:c.815_824dupAGCCATGTGG [37, 38] and FAM175A:c.1011delA [39]. In addition, in the present study, cancer risk assessment tools like Myriad Risk, PENN II Risk, and BRCAPRO demonstrated an overall moderate efficiency at detecting high-risk individuals (Supplementary Table 2 and Supplementary Fig. 3). Larger population studies are needed to validate our findings to further improve the utility of risk prediction models in diverse populations.

This study has several limitations. First, the sample size is relatively small, which limits the study’s power to detect variants with lower frequencies. Second, the recruitment of the participants was clinic based and therefore may not represent true population frequencies. Lastly, the BROCA gene panel was not designed to include ancestry informative markers in the assay; therefore, we were unable to perform genetic ancestry analysis. An advanced targeted gene panel with ancestry informative markers included, or accompanied with a genotyping assay capturing that information, may improve the risk assessment based on a person’s ethnic background.

In summary, this study sought to investigate whether the high mutation rates observed in Nigeria, Cameroon, and Uganda are also present in Brazilian women of African ancestry using a validated multi-gene panel. As costs of genomic testing continues to drop, this study provides additional evidence in support of broader access to genetic

| Table 3 | Comparison of the high-risk mutational profile among Black women across the African Diaspora and White women |
|---------|---------------------------------------------------|
| **Study population** | **Brazilian (this study)** | **Nigerian (Ref. [7])** | **Cameroonian and Ugandan (Ref. [8])** | **African American (Ref. [22])** | **CARRIERS (Ref. [26])** |
| **Case/control** | **Number of individuals** | **173 (67% Black)** | **1,136** | **997** | **196** | **5,054** | **4,993** | **32,247 (78.9% White)** | **32,544 (76.2% White)** |
| | **Ave. age (years)** | 44.1 | 52.2 | 47.5 | 47.0 | 46.6 | 46.2 | 46.9 | 62.1 | 61.2 |
| | **BRCA1** | 12 (6.9%) | 0 | 80 (7.0%) | 3 (0.3%) | 11 (5.6%) | 2 (1.1%) | 81 (1.6%) | 1 (0.02%) | 275 (0.9%) |
| | **BRCA2** | 10 (5.8%) | 0 | 47 (4.1%) | 4 (0.3%) | 11 (5.6%) | 0 | 98 (1.9%) | 12 (0.2%) | 417 (1.3%) |
| | **PALB2** | 3 (1.7%) | 0 | 47 (4.1%) | 4 (0.3%) | 11 (5.6%) | 0 | 2 (0.1%) | 148 (0.5%) | 38 (0.1%) |
| | **TP53** | 1 (0.6%) | 0 | 47 (4.1%) | 4 (0.3%) | 11 (5.6%) | 0 | 50 (1.0%) | 38 (0.1%) | 2 (0.01%) |
| | **Other genes** | 11 (6.4%) | 0 | 24 (2.1%) | 1 (0.1%) | 11 (1.1%) | 0 | 6.1% | 179 (5.5%) | 95 (0.3%) |
testing for previously underserved and understudied Black women at high risk of young onset and aggressive forms of breast cancer. The fact that one in five patients carried a loss-of-function variant in BRCA1, BRCA2, or another breast cancer gene with a highly heterogeneous mutational spectrum underscores the importance of utilizing next-generation sequencing-based testing to develop screening and risk-reducing strategies in Northeast Brazil.

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Data availability All data described and analyzed here are available upon request.

Code availability Not applicable.

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