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Cancer patterns and recurrent variants in BRCA1 and BRCA2 carriers from a Brazilian oncogenetics cohort

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Abstract

Background

Data on pathogenic/likely pathogenic *BRCA1* and *BRCA2* variant carriers from Latin America remain limited, yet local phenotype and variant patterns may inform surveillance and testing strategies. We characterized gene- and sex-specific clinical and molecular patterns in a Brazilian oncogenetics cohort.

Methods

We conducted a retrospective observational cohort study of adults carrying isolated pathogenic/likely pathogenic germline *BRCA1* or *BRCA2* variants tested at two tertiary private oncogenetics services in São Paulo, Brazil, between October 2008 and January 2024. Clinical, pathologic, and molecular data were abstracted from institutional records. Outcomes included cancer status, tumor-site distribution by gene and sex, age at diagnosis by cancer-event order, tumor multiplicity, and variant repertoire. Categorical variables were compared using Pearson's χ^2 or Fisher's exact test; ages were compared using one-way analysis of variance with Welch correction when appropriate.

Results

We included 412 carriers: 338 women (82.0%) and 74 men (18.0%); 212 (51.5%) carried *BRCA1* and 200 (48.5%) carried *BRCA2* variants. At the last available record, 257 carriers (62.4%) had at least one cancer diagnosis, with 336 primary tumors recorded. Two or more primary cancers occurred in 64/257 carriers with cancer (24.9%), and three or more occurred in 13/257 (5.1%). Tumor-site composition differed by gene ($p < 0.001$). In *BRCA1* carriers, breast and ovary/fallopian tube tumors comprised 70.1% and 16.0% of tumors, respectively. In *BRCA2* carriers, breast tumors predominated (62.4%), while prostate and pancreatic tumors each accounted for 4.7%. Among male *BRCA2* carriers, male breast and prostate cancers each represented 30.4% of tumors. Median ages at first, second, and third primary cancers were 39.0, 43.0, and 57.0 years for *BRCA1* carriers versus 47.0, 62.0, and 65.5 years for *BRCA2* carriers ($p < 0.001$, $p < 0.001$, and $p = 0.092$, respectively). *BRCA1* c.5266dupC and c.3331_3334del accounted for 45/140 variant records among *BRCA1* carriers with cancer (32.1%) and recurred among carriers without cancer. *BRCA2* showed greater allelic heterogeneity.

Conclusions

Carriers from this Brazilian oncogenetics cohort showed gene- and sex-specific clinical and molecular patterns. Findings support gene- and sex-tailored surveillance, longitudinal management after a first cancer, and selected founder-informed testing strategies embedded within comprehensive oncogenetic counseling and reflex testing.

Background

The identification of *BRCA1* and *BRCA2* as central genes in homologous recombination DNA repair transformed hereditary cancer medicine. What initially reshaped the understanding of inherited breast and ovarian cancer risk has since expanded into a broader clinical framework that includes pancreatic, prostate, melanoma, and other cancers [1–4]. Large international cohorts and meta-analyses have refined cumulative-risk estimates, confirmed the predominance of triple-negative breast cancer among *BRCA1* carriers, and demonstrated clinically meaningful differences between *BRCA1* and *BRCA2* in age at onset, tumor spectrum, and outcomes [4–8]. These data have moved germline testing from a purely diagnostic tool to a core component of oncology care, with direct implications for genetic counseling, risk-reducing surgery, surveillance, cascade testing, and targeted therapies, particularly poly(ADP-ribose) polymerase inhibitors in *BRCA*-related tumors [9–11].

However, the evidence base that informs hereditary cancer practice remains disproportionately shaped by populations from North America, Europe, and selected Asian cohorts. Data from Latin America are still comparatively limited, fragmented, and unevenly incorporated into clinical decision-making [12, 13]. This gap is especially relevant in Brazil, where extensive genetic admixture, regional ancestry differences, and unequal access to genetic testing may influence both the molecular repertoire of *BRCA1/BRCA2* variants and the way hereditary cancer risk is recognized in practice [14–20]. In this context, the key clinical question is not only which variants are present, but whether locally recurrent variants and gene- and sex-specific cancer patterns can help refine surveillance, counseling, cascade testing, and resource-conscious testing strategies.

Previous Brazilian studies have identified recurrent and founder-signal variants in *BRCA1* and *BRCA2*, including *BRCA1*c. 5266dupC and other recurrent alleles, while also highlighting the coexistence of additional hereditary cancer syndromes, such as the *TP53* p.R337H-associated condition [14, 16–18, 21–27]. These observations suggest that Brazilian hereditary cancer cohorts may contain clinically actionable recurrence patterns. Their interpretation, however, requires integration with phenotype, including cancer status, tumor spectrum, sex, age at diagnosis, and multiplicity of primary tumors. In the gynecologic component of the *BRCA*-associated spectrum, pathologic insights into ovarian carcinoma subtypes and high-grade serous carcinoma pathogenesis are also important for interpreting ovary/fallopian tube events and risk-reducing strategies in carriers [28].

In this study, we describe the clinical and molecular landscape of carriers of pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* followed at two tertiary private oncogenetics services in São Paulo, Brazil. We provide gene- and sex-resolved analyses of primary tumor sites, ages at diagnosis according to cancer-event order, tumor multiplicity, and variant distribution among carriers with and without cancer at the last available record. By integrating clinical phenotype with recurrent-variant patterns, we aimed to identify findings that are directly relevant to hereditary cancer practice, particularly in settings where access to comprehensive germline testing and longitudinal oncogenetic care remains heterogeneous.

The primary objective was to describe the gene- and sex-resolved clinical phenotype of *BRCA1/BRCA2* carriers, including tumor-site distribution, age at diagnosis by cancer-event order, and tumor multiplicity. Secondary objectives were to delineate the *BRCA1/BRCA2* variant spectrum, identify recurrent founder-signal variants, compare variant distributions among carriers with and without cancer at the last available record, and translate these findings into pragmatic considerations for hereditary cancer surveillance and testing strategies in Brazil and other middle-income settings.

Methods

Study design and setting

We conducted a retrospective observational cohort study of adults carrying pathogenic or likely pathogenic (P/LP) germline variants in *BRCA1* or *BRCA2* who underwent germline testing at two tertiary private oncogenetics services in São Paulo, Brazil: Hospital Sírio-Libanês and BP – A Beneficência Portuguesa de São Paulo. The study period extended from October 2008 to January 2024. Clinical, pathologic, and molecular data were abstracted from institutional records, consolidated into a study database, and reviewed for consistency. The study was reported in accordance with STROBE recommendations [29].

Participants

Individuals of either sex were eligible if they were aged ≥ 18 years at germline testing and had a confirmatory molecular report showing an isolated P/LP variant in *BRCA1* or *BRCA2*, regardless of cancer status at registry entry or at the last available institutional record. Cancers diagnosed before adulthood were retained when the individual subsequently met eligibility criteria for germline testing and registry inclusion.

We excluded individuals with benign or likely benign variants, variants of uncertain significance, unspecified *BRCA1/BRCA2* variant information, missing cancer-diagnosis data required for the main analyses, critical clinical incompleteness, or concomitant P/LP variants in other cancer-predisposition genes. Each carrier was included once in the analytic cohort.

For descriptive analyses, carriers were classified according to cancer status at the last available institutional record. Carriers with at least one documented primary malignant tumor were classified as with cancer; carriers without a recorded malignancy were classified as without cancer. The latter category indicates absence of cancer recorded at the last available record and does not imply lifetime absence of cancer.

Variables and outcomes

Clinical variables included center, sex, age at germline testing, age at last available record, cancer status, age at diagnosis of first, second, and third primary tumors, tumor multiplicity, anatomic tumor site, histology, and self-reported race/skin color when available. For carriers without cancer, age in the baseline table refers to age at germline testing; for carriers with cancer, age refers to age at first primary cancer diagnosis.

Synchronous primary tumors at initial presentation were counted separately in tumor-site analyses but as a single first cancer event in event-level age analyses. Tumor-site analyses included all recorded first through fourth primary tumors. Ovary and fallopian tube cancers were grouped as ovary/fallopian tube tumors.

Genetic variables included affected gene, HGVS coding DNA and protein nomenclature when available, molecular consequence, exon-level location when available, and variant recurrence. Molecular consequences were grouped as frameshift, missense, nonsense, splice-site, in-frame, or other structural/noncanonical events, including exon deletions or duplications, mobile-element insertions, and start-loss variants. Germline testing was performed in certified laboratories using clinically validated assays, including next-generation sequencing multigene panels, with confirmatory testing as clinically indicated. Variant classification followed ACMG/AMP criteria current at the time of reporting [30].

The primary outcomes were tumor-site distribution by gene and sex, age at diagnosis by cancer-event order, and tumor multiplicity. Secondary outcomes included the *BRCA1/BRCA2* variant repertoire, recurrent/founder-signal variants, and descriptive comparison of variant patterns among carriers with and without cancer. Founder-signal interpretation was descriptive, because no haplotype or ancestry-informative marker analysis was performed. Heatmaps were used as descriptive visual summaries of recurrent variants by gene and cancer status; cell shading represented the within-gene, within-status percentage. Complete variant lists are provided in Additional file 1 and Additional file 2.

Statistical analysis

Analyses were performed using IBM SPSS Statistics, version 29.0.2.0. Categorical variables were summarized as counts and percentages; continuous variables were summarized as mean ± standard deviation or median with range/interquartile range, as appropriate. Baseline characteristics were described for the overall cohort and by cancer status, without formal inferential comparison between cancer-status groups because status reflected ascertainment at the last available record.

Comparisons between *BRCA1* and *BRCA2* carriers were performed using Pearson's χ^2 test or Fisher's exact test, as appropriate. Age at diagnosis by cancer-event order was compared using one-way analysis of variance, with Welch correction when indicated after assessment of residual normality and variance homogeneity. All tests were two-sided, with $\alpha = 0.05$, and analyses used available cases without imputation.

Use of AI-assisted language tools

During manuscript preparation, an AI-assisted language tool was used for editorial, language, and formatting support. All scientific content, analyses, interpretation, and final wording were critically reviewed and approved by the authors, who take full responsibility for the integrity and accuracy of the manuscript.

Results

Cohort derivation and baseline characteristics

From hereditary cancer registries at two tertiary private oncogenetics services in São Paulo, Brazil, 470 individuals harboring pathogenic or likely pathogenic (P/LP) *BRCA1*/*BRCA2* variants were identified. Of these, 38 were excluded because of unspecified variant information or missing cancer-diagnosis data, and 20 were excluded because of concomitant P/LP variants in other cancer-predisposition genes: *ATM* (n = 4), *TP53* (n = 3), *PMS2* (n = 3), *MUTYH* (n = 2), *POLE* (n = 2), *MLH1* (n = 1), *MSH6* (n = 1), *APC* (n = 1), *CHEK2* (n = 1), *RAD50* (n = 1), and *CDKN2A* (n = 1). The final analytic cohort included 412 unique carriers with isolated P/LP variants in *BRCA1* or *BRCA2* **(**Fig. 1**)**. At the last available record, 257 carriers (62.4%) had at least one cancer diagnosis and 155 (37.6%) had no recorded malignancy.

[Figure 1]

The analytic cohort included 338 women (82.0%) and 74 men (18.0%). P/LP variants were distributed almost equally between genes: 212 carriers (51.5%) had *BRCA1* variants and 200 (48.5%) had *BRCA2* variants. The cohort was recruited predominantly from Hospital Sírio-Libanês (HSL; n = 272; 66.0%), followed by BP – A Beneficência Portuguesa de São Paulo (n = 140; 34.0%).

Cancer status at the last available record differed across baseline strata. Among women, 235/338 (69.5%) had a recorded cancer diagnosis, compared with 22/74 men (29.7%). Among *BRCA1* carriers, 140/212 (66.1%) had cancer recorded, whereas among *BRCA2* carriers, 117/200 (58.5%) had cancer recorded. Among carriers without cancer, the median age at germline testing was 38 years (range, 18–76). Among carriers with cancer, the median age at first cancer diagnosis was 42 years (range, 17–81). Baseline characteristics by cancer status are shown in Table 1.

Table 1
Baseline characteristics of carriers of pathogenic/likely pathogenic BRCA1/BRCA2 variants by cancer status at last record.

Characteristic	Category	Analytic cohort (n = 412), n (%)	Carriers without cancer at last record (n = 155), n (%)	Carriers with cancer at last record (n = 257), n (%)
Center	Hospital Sírio-Libanês (HSL)	272 (66.0)	102 (65.8)	170 (66.1)
	Beneficência Portuguesa (BP)	140 (34.0)	53 (34.2)	87 (33.9)
Sex	Female	338 (82.0)	103 (66.5)	235 (91.4)
	Male	74 (18.0)	52 (33.5)	22 (8.6)
Gene with P/LP variant	BRCA1	212 (51.5)	72 (46.5)	140 (54.5)
	BRCA2	200 (48.5)	83 (53.5)	117 (45.5)
Age at germline testing, years	Median (range)	—	38 (18–76)	—
Age at 1st cancer diagnosis, years	Median (range)	—	—	42 (17–81)

Note: Cancer status was defined at the last available institutional record. Percentages in each column refer to the corresponding column denominator. For carriers without cancer, age refers to age at germline testing. For carriers with cancer, age refers to age at first primary cancer diagnosis. Dashes indicate not applicable. Percentages may not sum exactly to 100.0 because of rounding.
Abbreviations: BP, Beneficência Portuguesa de São Paulo; HSL, Hospital Sírio-Libanês; P/LP, pathogenic or likely pathogenic.

[Table 1]

Self-reported race/skin color, as recorded in the medical records, was available for 277 carriers. Among these, 260 (93.9%) were White, 11 (4.0%) were Asian/Yellow according to the Brazilian race/skin-color classification, 3 (1.1%) were Black, and 3 (1.1%) were classified as Other. Self-reported race/skin color distribution did not differ by gene (p = 0.872).

Age at diagnosis by cancer-event order

Among carriers with cancer, age at diagnosis differed between *BRCA1* and *BRCA2* carriers. At first primary cancer, the median age was 39.0 years among *BRCA1* carriers (n = 134; range, 17–69; mean, 40.7) and 47.0 years among *BRCA2* carriers (n = 113; range, 18–81; mean, 47.4; p < 0.001).

The same pattern was observed for second primary cancers. Among carriers with multiple primary tumors, the second primary cancer occurred earlier in *BRCA1* carriers, with a median age of 43.0 years (n = 31; range, 32–68; mean, 46.0), compared with 62.0 years in *BRCA2* carriers (n = 24; range, 30–76;

mean, 59.3; $p < 0.001$). At third primary cancer, median ages were 57.0 years for *BRCA1* carriers (n = 8; range, 52–72; mean, 58.7) and 65.5 years for *BRCA2* carriers (n = 4; range, 60–76; mean, 66.7); this difference did not reach statistical significance ($p = 0.092$), likely reflecting the smaller number of third cancer events.

Overall, age distributions showed earlier first and second cancer events among BRCA1 carriers and later cancer events among BRCA2 carriers, with chronological progression across successive primary cancers (Fig. 2).

[Figure 2]

Tumor multiplicity and total tumor burden

Across the 257 carriers with cancer, 336 primary tumors were recorded. These included 266 first primary tumors, 55 second primary tumors, 13 third primary tumors, and 2 fourth primary tumors. The number of first primary tumors exceeded the number of carriers with cancer because nine carriers had two synchronous primary tumors at initial presentation.

When synchronous tumors were considered multiple primaries, 64/257 carriers with cancer (24.9%) had two or more primary tumors, 13/257 (5.1%) had three or more primary tumors, and 2/257 (0.8%) had four primary tumors.

Overall tumor-site distribution

Considering all recorded first through fourth primary tumors (n = 336), breast cancer was the most frequent tumor site, accounting for 224 tumors (66.7%), followed by ovary/fallopian tube tumors (n = 50; 14.9%). Prostate and lung cancers each accounted for 9 tumors (2.7%), pancreatic cancer for 8 tumors (2.4%), thyroid cancer for 5 tumors (1.5%), and all remaining individual sites each represented 1.2% or less of the total tumor count (Table 2).

Table 2
Distribution of primary cancer sites by cancer-event order among carriers of pathogenic/likely pathogenic *BRCA1/BRCA2* variants.

Cancer site	First primary (n = 266), n (%)	Second primary (n = 55), n (%)	Third primary (n = 13), n (%)	Fourth primary (n = 2), n (%)	Total tumors (n = 336), n (%)
Breast	187 (70.3)	31 (56.4)	4 (30.8)	2 (100.0)	224 (66.7)
Ovary/FT	43 (16.2)	5 (9.1)	2 (15.4)	0 (0.0)	50 (14.9)
Prostate	7 (2.6)	2 (3.6)	0 (0.0)	0 (0.0)	9 (2.7)
Lung	4 (1.5)	4 (7.3)	1 (7.7)	0 (0.0)	9 (2.7)
Pancreas	6 (2.3)	1 (1.8)	1 (7.7)	0 (0.0)	8 (2.4)
Thyroid	3 (1.1)	2 (3.6)	0 (0.0)	0 (0.0)	5 (1.5)
Lymphoma	3 (1.1)	1 (1.8)	0 (0.0)	0 (0.0)	4 (1.2)
Colon	3 (1.1)	0 (0.0)	1 (7.7)	0 (0.0)	4 (1.2)
Melanoma	2 (0.8)	2 (3.6)	0 (0.0)	0 (0.0)	4 (1.2)
Other	2 (0.8)	1 (1.8)	0 (0.0)	0 (0.0)	3 (0.9)
CNS	1 (0.4)	0 (0.0)	1 (7.7)	0 (0.0)	2 (0.6)
Leukemia	1 (0.4)	1 (1.8)	0 (0.0)	0 (0.0)	2 (0.6)
Uterine corpus	1 (0.4)	1 (1.8)	0 (0.0)	0 (0.0)	2 (0.6)
SCC	0 (0.0)	0 (0.0)	2 (15.4)	0 (0.0)	2 (0.6)
Gallbladder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Cervix	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Bladder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Ureter	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.3)
Kidney	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.3)
H&N carcinoma	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.3)
BCC	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.3)

Note: Among the 257 carriers with cancer, nine had two synchronous primary cancers at initial presentation, yielding 266 first-primary tumors. Percentages refer to the denominator of each event-order column. Total percentages refer to all recorded first through fourth primary tumors (n = 336). Ovary and fallopian tube tumors were grouped for anatomic-site analyses. Because percentages are rounded to one decimal place, column percentages may not sum exactly to 100.0. **Abbreviations**: BCC, cutaneous basal cell carcinoma; CNS, central nervous system; FT, fallopian tube; H&N, head and neck; SCC, cutaneous squamous cell carcinoma.

Cancer site	First primary (n = 266), n (%)	Second primary (n = 55), n (%)	Third primary (n = 13), n (%)	Fourth primary (n = 2), n (%)	Total tumors (n = 336), n (%)
Ampulla of Vater	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	1 (0.3)

Note: Among the 257 carriers with cancer, nine had two synchronous primary cancers at initial presentation, yielding 266 first-primary tumors. Percentages refer to the denominator of each event-order column. Total percentages refer to all recorded first through fourth primary tumors (n = 336). Ovary and fallopian tube tumors were grouped for anatomic-site analyses. Because percentages are rounded to one decimal place, column percentages may not sum exactly to 100.0. **Abbreviations**: BCC, cutaneous basal cell carcinoma; CNS, central nervous system; FT, fallopian tube; H&N, head and neck; SCC, cutaneous squamous cell carcinoma.

Among 162 breast tumors with available histology, ductal carcinoma, invasive or in situ, predominated (85.2%), followed by lobular carcinoma (6.8%), breast carcinoma not otherwise specified (5.6%), and other histologic subtypes (2.4%).

[Table 2]

Tumor-site distribution by gene and sex

Considering all recorded first through fourth primary tumors, tumor-site composition differed significantly by gene ($p < 0.001$). Among *BRCA1* carriers, 187 tumors were recorded. Breast cancer and ovary/fallopian tube tumors comprised 70.1% and 16.0% of *BRCA1*-associated tumors, respectively, with smaller contributions from lung, lymphoma, colon, melanoma, central nervous system, thyroid, pancreas, leukemia, uterine corpus, prostate, and other low-frequency sites.

Among *BRCA2* carriers, 149 tumors were recorded. Breast cancer remained the largest category, accounting for 62.4% of tumors, followed by ovary/fallopian tube tumors (13.4%). Pancreatic and prostate cancers each accounted for 4.7% of *BRCA2*-associated tumors, with additional contributions from lung, thyroid, melanoma, and other low-frequency sites.

Sex-stratified analyses further refined these patterns. Among women, breast cancer predominated in both genes, accounting for 73.0% of tumors in female *BRCA1* carriers (n = 178 tumors) and 68.3% of tumors in female *BRCA2* carriers (n = 126 tumors). Ovary/fallopian tube tumors were the second most common category in both groups, representing 16.9% of tumors in female *BRCA1* carriers and 15.9% in female *BRCA2* carriers. Pancreatic cancer accounted for 3.2% of tumors among female *BRCA2* carriers.

Among men, the number of tumors was smaller, particularly in *BRCA1* carriers. In male *BRCA2* carriers (n = 23 tumors), male breast cancer and prostate cancer each represented 30.4% of tumors. Lung cancer accounted for 17.4% and pancreatic cancer for 13.0% of tumors in this group. Male *BRCA1*-associated tumors (n = 9) were distributed across prostate, colon, and other single-site events. The gene- and sex-stratified distribution of primary tumor sites is shown in Fig. 3.

[Figure 3]

Variant repertoire and recurrent variants by cancer status

Among carriers with cancer, truncating variants predominated, with frameshift and nonsense variants representing the largest molecular-consequence categories, followed by missense, splice-site, in-frame, and structural or noncanonical events.

Among *BRCA1* carriers with cancer (n = 140), two recurrent variants were prominent: c.5266dupC (35/140; 25.0%) and c.3331_3334del (10/140; 7.1%). Together, these two variants accounted for 45/140 *BRCA1* variant records among carriers with cancer (32.1%). Other recurrent *BRCA1* variants among carriers with cancer included c.181T > G (6/140; 4.3%), c.1687C > T (5/140; 3.6%), c.441 + 2T > A (4/140; 2.9%), and c.5096G > A (4/140; 2.9%).

Among *BRCA2* carriers with cancer (n = 117), the variant repertoire was more heterogeneous, with no single variant showing comparable predominance. The most frequent variants were c.2T > G, a start-loss variant (6/117; 5.1%); c.156_157insAlu, a mobile-element insertion (5/117; 4.3%); c.5576_5579del (5/117; 4.3%); and c.8488-1G > A (4/117; 3.4%). These were followed by multiple low-frequency frameshift, nonsense, splice-site, missense, in-frame, and structural or noncanonical variants, each individually accounting for 2.6% or less of the *BRCA2* cancer subgroup. The complete variant distribution among carriers with cancer is provided in **Additional file 1: Supplementary Table S1**.

Among carriers without cancer at the last available record, recurrent variant patterns again differed by gene. In *BRCA1*carriers without cancer (n = 72), c.5266dupC and c.3331_3334del were again the most frequent variants, each appearing in 10/72 records (13.9%). These were followed by c.798_799del (4/72; 5.6%), c.1687C > T (3/72; 4.2%), and c.211A > G (3/72; 4.2%), with the remaining variants occurring at lower frequencies.

In *BRCA2* carriers without cancer (n = 83), the variant distribution remained more dispersed. The most frequent variants were c.156_157insAlu (6/83; 7.2%), c.2T > G (5/83; 6.0%), c.6405_6409del (5/83; 6.0%), c.6656C > G (4/83; 4.8%), and c.1138delA (3/83; 3.6%). The remaining *BRCA2* variants occurred at lower individual frequencies. The complete variant distribution among carriers without cancer at the last available record is provided in **Additional file 2: Supplementary Table S2**.

Heatmap visualization of the most frequent variants highlighted a clinically relevant contrast between the two genes. In *BRCA1*, variant recurrence was concentrated around c.5266dupC and c.3331_3334del in both cancer-status strata, with c.5266dupC showing the highest frequency among carriers with cancer **(**Fig. 4A**)**. In *BRCA2*, the heatmap showed a more heterogeneous allelic pattern, with several moderately recurrent variants and no single dominant allele across cancer-status strata **(**Fig. 4B**)**. This visual pattern reinforced the recurrent *BRCA1* signal and the broader allelic heterogeneity observed in *BRCA2*.

Discussion

In this Brazilian cohort from two tertiary private oncogenetics services, carriers of pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* showed clinically relevant gene- and sex-resolved patterns with direct implications for hereditary cancer practice. Three findings are particularly informative. First, age at diagnosis followed a gene-specific gradient, with earlier first and second primary cancers among *BRCA1* carriers than among *BRCA2* carriers. Second, tumor-site distribution differed by gene and sex, with breast and ovary/fallopian tube tumors predominating in women and a broader male cancer spectrum among *BRCA2* carriers. Third, the molecular landscape showed a concentrated recurrent-variant pattern in *BRCA1*, especially involving c.5266dupC and c.3331_3334del, whereas *BRCA2* displayed greater allelic heterogeneity. Together, these findings support a practical interpretation of local *BRCA1/BRCA2* data: hereditary cancer management should be tailored not only by gene, but also by sex, age, tumor multiplicity, and recurrent variant patterns that may inform testing strategies.

The earlier age at cancer diagnosis among *BRCA1* carriers is consistent with international evidence showing gene-specific differences in cancer penetrance, age at onset, and tumor phenotype [1–8]. In our cohort, the median age at first primary cancer was 39 years for *BRCA1* carriers and 47 years for *BRCA2* carriers, while the median age at second primary cancer was 43 and 62 years, respectively. Although the difference at third primary cancer was not statistically significant, probably because of the smaller number of events, the overall pattern reinforces the importance of early risk identification and longitudinal follow-up. Tumor multiplicity was also clinically meaningful: nearly one quarter of carriers with cancer had two or more primary tumors. This supports care models that do not end after the first cancer diagnosis, but instead incorporate repeated risk communication, reassessment of surveillance needs, and prevention strategies across the life course.

The tumor-site distribution observed in this cohort recapitulates the established *BRCA1/BRCA2*-associated cancer spectrum while adding a clinically useful sex-stratified perspective. Among *BRCA1* carriers, breast and ovary/fallopian tube tumors accounted for most recorded tumors. Among *BRCA2* carriers, breast cancer also predominated, but pancreatic and prostate cancers contributed more visibly to the tumor spectrum. The sex-stratified analysis was particularly informative: among men with *BRCA2* variants, male breast cancer and prostate cancer each represented 30.4% of tumors, followed by lung and pancreatic cancers (Fig. 3). These findings reinforce the cross-tumor relevance of germline *BRCA1/BRCA2* testing and support clinical workflows that connect genetic diagnosis to breast, gynecologic, prostate, and pancreatic surveillance when indicated [9–11].

The gynecologic burden observed among *BRCA1* carriers has important implications for counseling. The grouping of ovarian and fallopian tube cancers is biologically appropriate, given the contemporary understanding of high-grade serous carcinoma pathogenesis and the role of the fallopian tube in many tumors historically classified as ovarian cancer [28]. In practice, the observed frequency of ovary/fallopian tube tumors among *BRCA1* carriers reinforces the importance of timely, individualized counseling regarding risk-reducing salpingo-oophorectomy, consistent with international and Brazilian recommendations [9, 11, 32, 33]. At the same time, decision-making around risk-reducing gynecologic surgery is complex and may be affected by age, reproductive plans, information needs, perceived cancer

risk, and decisional conflict [34, 35]. Although our study did not evaluate uptake or timing of risk-reducing surgery, the observed age and tumor-site patterns support the need for structured counseling pathways for female *BRCA1* carriers.

The molecular findings add a second layer of practical relevance. The heatmap visualization emphasized a clear contrast between genes: *BRCA1* showed a concentrated recurrent-variant pattern, whereas *BRCA2* showed a more dispersed allelic distribution (Fig. 4). Among *BRCA1* carriers with cancer, c.5266dupC and c.3331_3334del together accounted for 32.1% of variant records. Both variants were also recurrent among carriers without cancer at the last available record, reinforcing that their presence in the cohort was not restricted to the affected subgroup. In contrast, the most frequent *BRCA2* variants each accounted for a smaller proportion of records, with several variants recurring at moderate or low frequencies. By transforming long variant tables into a visual summary, the heatmaps make this contrast immediately interpretable: *BRCA1* appears more suitable for founder-informed discussions, whereas *BRCA2* requires a broader sequencing strategy because of its allelic dispersion. This pattern is consistent with previous Brazilian and Latin American studies reporting recurrent or founder-signal *BRCA1/BRCA2* variants, while also reflecting the broader global mutational heterogeneity of *BRCA2* [12, 13, 16–27, 31].

These molecular patterns should be interpreted with appropriate caution. The recurrence of specific variants in this cohort is compatible with founder-signal enrichment, particularly for *BRCA1* c.5266dupC, but our study did not include haplotype analysis or ancestry-informative markers. Therefore, the term “founder-signal” is more appropriate than definitive founder attribution. In addition, the comparison between carriers with and without cancer was descriptive and should not be interpreted as variant-specific penetrance or risk estimation. The subgroup without cancer represents carriers without a recorded malignancy at the last available institutional record, not individuals proven to be cancer-free over a lifetime. Even with these limitations, the parallel visualization of variants in carriers with and without cancer is useful because it shows which alleles are repeatedly encountered in clinical oncogenetics practice.

From an implementation perspective, the distinction between recurrent *BRCA1* variants and heterogeneous *BRCA2* findings is important. In Brazil and other middle-income settings, access to comprehensive germline testing remains uneven, and delays in testing may limit opportunities for prevention, cascade testing, and treatment selection [14–20]. Recurrent founder-signal variants may support tiered or founder-informed testing strategies in selected contexts, particularly when comprehensive sequencing is not immediately available. However, such strategies should not replace multigene panel testing when clinically indicated. The heterogeneity observed in *BRCA2*, and the coexistence of other hereditary cancer syndromes in Brazil, argue for reflex testing pathways and careful genetic counseling whenever a limited founder-informed approach is used.

The clinical findings also point to practical surveillance priorities. For women with *BRCA1* or *BRCA2* variants, the early age at first cancer diagnosis supports guideline-based breast surveillance beginning

at young ages, including magnetic resonance imaging and mammography according to age and risk recommendations [9, 11]. For *BRCA1* carriers, the gynecologic tumor burden supports early counseling about risk-reducing salpingo-oophorectomy [9, 11, 32, 33]. For men with *BRCA2* variants, the observed contribution of prostate and male breast cancer supports prostate-specific antigen-based early detection at guideline-recommended ages, as well as education regarding male breast cancer awareness [9, 36]. For selected carriers meeting established criteria, pancreatic surveillance may also be considered in experienced programs [9, 37]. These points should be understood as practice implications derived from the observed phenotype, rather than as direct evidence of surveillance effectiveness, because our study did not evaluate adherence, uptake of risk-reducing interventions, cancer-specific mortality, or treatment outcomes.

This study has several strengths. It includes a clearly defined cohort of carriers with isolated P/LP variants in *BRCA1* or *BRCA2*, harmonized data abstraction from two oncogenetics services, gene- and sex-resolved tumor-site analyses, event-level age analyses, longitudinal capture of multiple primary tumors, and a detailed variant catalog. The inclusion of carriers with and without cancer at the last available record allowed recurrent variant patterns to be described beyond the affected subgroup. The use of heatmaps also improved the interpretability of long variant tables by making the contrast between *BRCA1* recurrence and *BRCA2* heterogeneity immediately visible.

The study also has limitations. Its retrospective design makes it dependent on the completeness and accuracy of institutional records. The cohort was drawn from two tertiary private centers in São Paulo, which may have increased access to genetic testing and specialized follow-up but limits generalizability to the broader Brazilian population and to the public health system. The number of events was small for several tumor sites, particularly among men and for third and fourth primary cancers. Race/skin color data were missing for a substantial proportion of individuals and were self-reported rather than genetically inferred. The absence of genomic ancestry markers limits the ability to distinguish founder effects from recurrent observations based only on variant frequencies. Finally, the study did not capture payer type, authorization pathway, out-of-pocket costs, time from diagnosis to testing, time from testing to counseling, cascade testing uptake, surveillance adherence, or risk-reducing surgery uptake.

Despite these limitations, this cohort provides clinically actionable information for hereditary cancer practice in Brazil. The findings reinforce the need for gene- and sex-tailored surveillance, long-term management of multiple primary cancer risk, and counseling strategies that address the distinct clinical trajectories of *BRCA1* and *BRCA2* carriers. They also suggest that founder-informed testing may have a role in selected implementation contexts, provided that it is embedded within comprehensive oncogenetic counseling and reflex testing pathways. Future studies integrating clinical, genetic, genomic ancestry, surveillance, and administrative data will be essential to refine local risk estimates and address persistent implementation gaps in hereditary cancer care.

Conclusions

In this Brazilian oncogenetics cohort, carriers of pathogenic/likely pathogenic variants in *BRCA1* or *BRCA2* showed gene- and sex-specific clinical and molecular patterns with practical implications for hereditary cancer care. *BRCA1* carriers had earlier cancer onset, greater ovary/fallopian tube tumor burden, and a concentrated recurrent-variant profile driven mainly by c.5266dupC and c.3331_3334del. *BRCA2* carriers showed a broader tumor spectrum, particularly among men, with relevant contributions from prostate and male breast cancer, and a more heterogeneous variant distribution. The frequency of multiple primary tumors reinforces the need for longitudinal, gene- and sex-tailored surveillance and repeated risk communication across the life course. These findings support the use of local phenotype and variant data to guide counseling, surveillance, cascade testing, and selected founder-informed testing strategies, provided that limited approaches are embedded within comprehensive oncogenetic counseling and reflex testing. Future studies linking clinical, genomic ancestry, surveillance, and administrative data are needed to refine local risk estimates and address implementation gaps in Brazil and other middle-income settings.

Abbreviations

ACMG
American College of Medical Genetics and Genomics
AMP
Association for Molecular Pathology
ANOVA
analysis of variance
BCC
basal cell carcinoma
BP
Beneficência Portuguesa de São Paulo
CNS
central nervous system
FT
fallopian tube
H&N
head and neck
HGVS
Human Genome Variation Society
HSL
Hospital Sírio-Libanês
IQR
interquartile range
P/LP
pathogenic or likely pathogenic

PARP
poly(ADP-ribose) polymerase
PSA
prostate-specific antigen
SCC
squamous cell carcinoma
SD
standard deviation
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional research ethics committees of both participating centers: the Comitê de Ética em Pesquisa da Sociedade Beneficente de Senhoras Hospital Sírio-Libanês (CEPesq/HSL), São Paulo, Brazil, approval/reference number; and the Comitê de Ética em Pesquisa – BP, Hospital BP – A Beneficência Portuguesa de São Paulo / Real e Benemérita Associação Portuguesa de Beneficência, São Paulo, Brazil, approval/reference number 6631725. The study was conducted in accordance with the Declaration of Helsinki and Brazilian National Health Council Resolution No. 466/2012. Because of the retrospective design and the use of de-identified data abstracted from institutional records, the requirement for individual informed consent was waived by the institutional research ethics committees.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain sensitive clinical and genetic information. De-identified aggregate data may be available from the corresponding author on reasonable request, subject to institutional policies and ethics committee approval.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LLMZ and FOF contributed equally to this work and share first authorship. BMR conceptualized and supervised the study. FOF and BMR developed the methodology. LLMZ curated the data. JPP and EMMS performed pedigree construction and contributed to the database groundwork. FOF performed the formal analysis and drafted the original manuscript. FOF, LLMZ, RLS, MDV, PDRN, MIWA, GCG, and BMR critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Authors' information

Not applicable.

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Figures

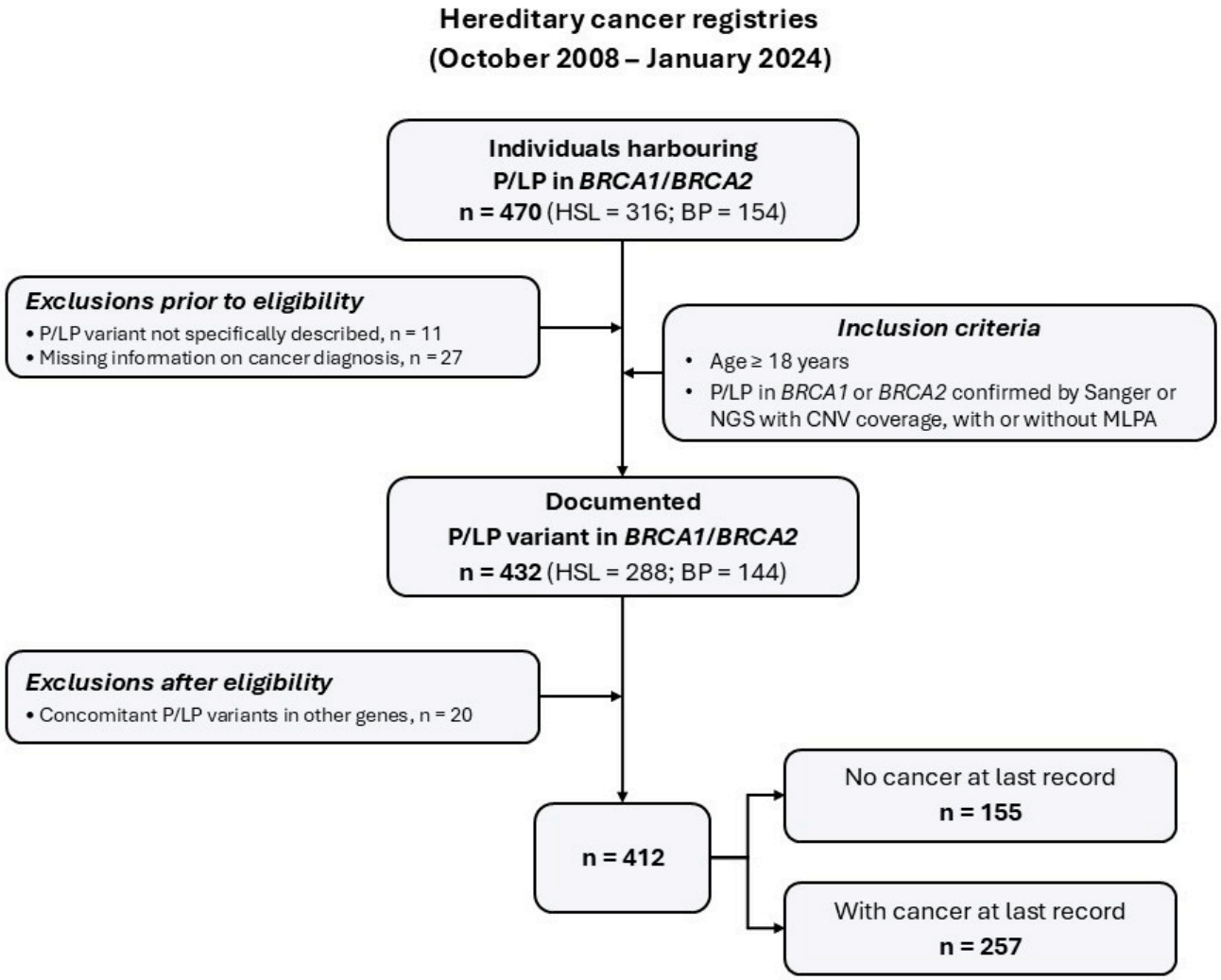
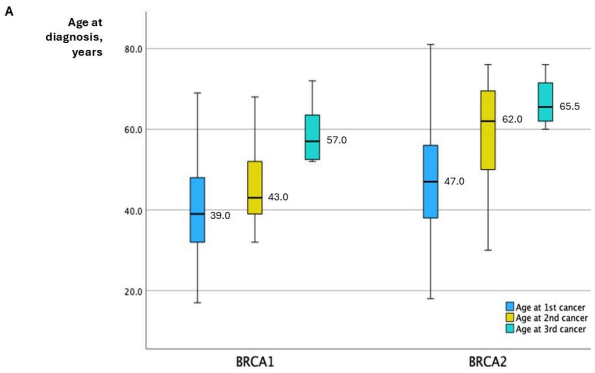


Figure 1

Study flow and analytic cohort

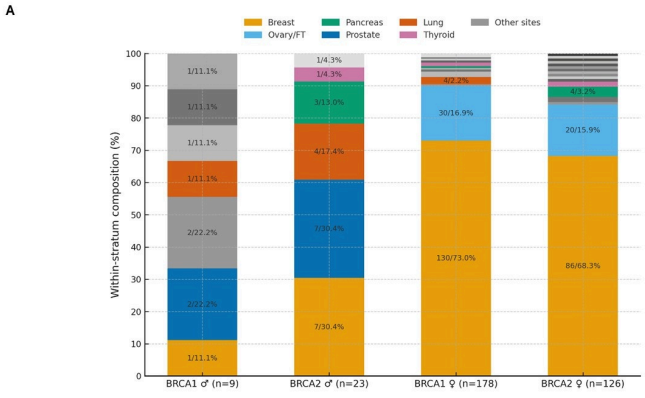


B

Outcome	Gene	n	%	Median, years	Range, years	Mean, years	P value
Age at 1st cancer	*BRCA1*	134	95.7	39.0	17–69	40.7	<0.001
	BRCA2	113	96.6	47.0	18–81	47.4	—
Age at 2nd cancer	*BRCA1*	31	22.1	43.0	32–68	46.0	<0.001
	BRCA2	24	20.5	62.0	30–76	59.3	—
Age at 3rd cancer	*BRCA1*	8	5.7	57.0	52–72	58.7	0.092
	BRCA2	4	3.4	65.5	60–76	66.7	—

Figure 2

Age at first, second, and third primary cancers by gene



B

Cancer site	Male *BRCA1* (n=9 tumors), n (%)	Male *BRCA2* (n=23 tumors), n (%)	Female *BRCA1* (n=178 tumors), n (%)	Female *BRCA2* (n=126 tumors), n (%)
Breast	1 (11.1)	7 (30.4)	130 (73.0)	86 (68.3)
Ovary/FT	0 (0.0)	0 (0.0)	30 (16.9)	20 (15.9)
Prostate	2 (22.2)	7 (30.4)	0 (0.0)	0 (0.0)
Colon	2 (22.2)	0 (0.0)	1 (0.6)	1 (0.8)
Lung	1 (11.1)	4 (17.4)	4 (2.2)	0 (0.0)
Lymphoma	1 (11.1)	0 (0.0)	3 (1.7)	0 (0.0)
Melanoma	1 (11.1)	0 (0.0)	1 (0.6)	2 (1.6)
CNS	1 (11.1)	0 (0.0)	1 (0.6)	0 (0.0)
Pancreas	0 (0.0)	3 (13.0)	1 (0.6)	4 (3.2)
Thyroid	0 (0.0)	1 (4.3)	2 (1.1)	2 (1.6)
Leukemia	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.8)
Uterine corpus	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.8)
SCC	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.8)
Cervix	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Bladder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Ureter	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Kidney	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
H&N carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
BCC	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Ampulla of Vater	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Gallbladder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Other	0 (0.0)	1 (4.3)	2 (1.1)	0 (0.0)
Total	**9 (100.0)**	**23 (100.0)**	**178 (100.0)**	**126 (100.0)**

Figure 3

Distribution of primary cancer sites by gene and sex

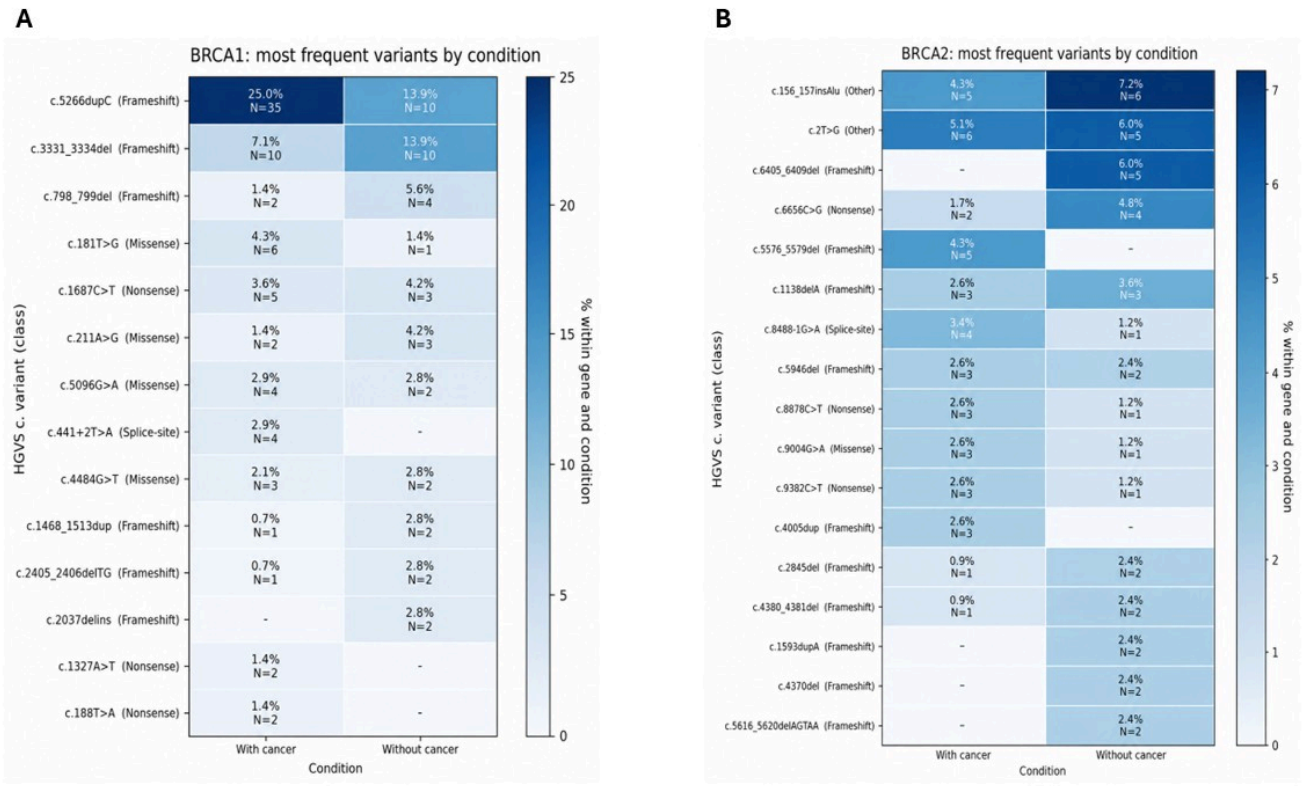


Figure 4

Recurrent *BRCA1* and *BRCA2* variants by cancer status

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1VariantsidentifiedinBRCA1andBRCA2.docx
- SupplementaryTableS2VariantsidentifiedinBRCA1andBRCA2amongcarrierswithoutcancer.docx
- Additionalfilesinfo.docx