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ORIGINAL ARTICLE

Somatic *BRCA* alterations in breast cancer are associated with distinct biological and clinical patterns according to germline *BRCA* status

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Background: Comprehensive genomic profiling increasingly identifies *BRCA* alterations in breast cancer (BC). While germline *BRCA* mutations are well established as biologically and clinically relevant, the significance of somatic *BRCA* alterations remains unclear. We hypothesized that the implications of *BRCA* alterations may differ according to germline *BRCA* alterations.

Patients and methods: Among 5411 BC cases registered in the Center for Cancer Genomics and Advanced Therapeutics database, we analyzed 2978 BC cases with available germline (g) and somatic (s) *BRCA* status. Patients were categorized into four groups (g^+/s^+, g^+/s^-, g^-/s^+, and g^-/s^-). Mutational landscapes, homologous recombination deficiency (HRD)-related alterations, specimen origin, and time to treatment discontinuation (TTD) were evaluated, focusing on estrogen receptor (ER)-positive/HER2-negative and triple-negative breast cancer (TNBC).

Results: g^-/s^+ tumors were more prevalent than g^+/s^+ tumors, and concordance between germline and somatic *BRCA* status was limited. Somatic *BRCA* alterations were more frequently detected in metastatic lesions and were more frequently observed in metastatic specimens. Genomically, g^-/s^+ tumors were enriched for oncogenic signaling mutations, including *PIK3CA* and *TP53*, whereas g^+/s^+ tumors showed HRD-related features dominated by *BRCA* alterations. Non-*BRCA* HRD-related alterations were most frequent in g^-/s^+ tumors (52%; $P = 0.004$). In ER-positive/HER2-negative BC, germline *BRCA* positivity was associated with shorter cyclin-dependent kinase 4 and 6 inhibitor TTD, and g^+/s^+ status remained independently associated with shorter TTD (hazard ratio 1.3, $P < 0.001$), whereas g^-/s^+ tumors were comparable with g^-/s^- tumors. In contrast, g^-/s^+ tumors showed TTD comparable with g^-/s^- tumors. In TNBC, immune checkpoint inhibitor outcomes were not associated with *BRCA* status.

Conclusions: *BRCA* alteration groups defined by combined germline and somatic status showed distinct genomic and clinical patterns in BC. Somatic *BRCA* alterations should not be interpreted in isolation and require integration with germline status and broader genomic context.

Key words: breast cancer, cdk4/6 inhibitors, comprehensive genomic profiling, germline *BRCA*, somatic *BRCA*, tumor evolution

INTRODUCTION

Breast cancer (BC) is the most common malignancy among women worldwide,[1] and defects in homologous recombination repair (HRR) represent one of the most clinically actionable genomic vulnerabilities. Germline pathogenic variants in *BRCA1* and *BRCA2* are well-established drivers of homologous recombination deficiency (HRD) and confer marked sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors through synthetic lethality.[2,3] Pivotal clinical trials, including OlympiAD[4] and EMBRACA,[5] demonstrated significant clinical benefit of PARP inhibition in germline *BRCA*-mutant BCs, establishing *BRCA* status as a central biomarker in precision oncology.

Beyond PARP inhibitors, accumulating evidence suggests that *BRCA* gene alterations may influence response to other systemic therapies. Several studies suggest that patients with germline *BRCA* mutations may derive less benefit from endocrine therapy plus cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors than noncarriers.[6,7] In

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addition, *BRCA* deficiency has been associated with altered tumor immune microenvironments and increased genomic instability, which may influence sensitivity to immune checkpoint blockade.[8] These findings suggest that *BRCA* alterations may influence therapeutic response beyond PARP inhibition, serving as broader determinants of treatment sensitivity and resistance.

Somatic *BRCA* alterations are increasingly identified through comprehensive genomic profiling of tumors in routine clinical practice. While germline *BRCA* pathogenic variants reflect inherited susceptibility and early HRD, somatic *BRCA* alterations arise within an established tumor genome during tumor evolution and may be heterogeneous or subclonal events.[9,10] These differences suggest that the clinical significance of *BRCA* alterations may depend on their origin (germline versus somatic) and allelic status, which is often not captured by tumor-only sequencing. Notably, the TBCRC048 trial demonstrated PARP inhibitor activity in BCs with somatic *BRCA* mutations,[11] and ongoing phase II trials continue to evaluate a molecularly defined subgroup.[12] Nevertheless, clinical trials evaluating *BRCA*-directed therapies have largely focused on germline carriers, and systematic comparisons between germline and somatic *BRCA* alterations within the same clinical framework are lacking.

Addressing this question has been challenging because paired germline and somatic *BRCA* data linked to longitudinal outcomes are limited. Consequently, it remains unclear whether somatic *BRCA* alterations confer the same HRD seen in germline carriers or reflect distinct tumor evolutionary processes with different therapeutic implications. To address this unmet need, we leveraged a large national real-world genomic database integrating germline testing, comprehensive tumor genomic profiling, clinical subtype annotation, and treatment history. By jointly evaluating germline and somatic *BRCA* status, we classified BCs into four genomic-context categories and examined their mutational landscapes, HRD-related genomic features, specimen origin, and treatment outcomes across major systemic therapies. Through this approach, we sought to determine whether the significance of *BRCA* alterations differs according to germline and somatic status, while recognizing that allelic context may also contribute.

PATIENTS AND METHODS

Data source and study population

BC cases registered in the Center for Cancer Genomics and Advanced Therapeutics (C-CAT), a nationwide Japanese real-world genomic database, were analyzed, as we previously reported.[13] Cases were based on tissue comprehensive genomic profiling carried out using FoundationOne CDx (Foundation Medicine, Boston, MA). For each registered patient, one profiled tumor specimen was included in the present analysis, classified according to specimen origin as either primary tumor or metastatic lesion. Among 5411 registered cases from 2019 to 2024, patients with available somatic *BRCA1/2* results from comprehensive genomic profiling, germline *BRCA1/2* testing by BRACAnalysis CDx (Myriad Genetics, Salt Lake City, UT), and BC subtype information as estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative, HER-positive, or triple-negative breast cancer (TNBC) were identified.

Definition of BRCA *status*

Germline *BRCA1/2* alterations (g*BRCA*) were defined as clinically classified pathogenic or likely pathogenic variants identified by BRACAnalysis CDx® (Myriad Genetics). Somatic *BRCA1/2* alterations were defined as tumor comprehensive genomic profiling-reported *BRCA1/2* alterations identified in cases registered in the C-CAT database. Somatic *BRCA* positivity (s^+) was defined as the presence of at least one *BRCA1* or *BRCA2* alteration detected in the tumor. Because somatic *BRCA* status was based on tumor-only sequencing, detected alterations may include variants of germline origin not identified by prior germline testing. Patients were classified into four groups according to their combined germline and somatic *BRCA* status: g^+/s^+, g^+/s^-, g^-/s^+, and g^-/s^-.

Genomic analyses

Somatic mutation data were obtained from comprehensive genomic profiling. Differential mutation frequencies between *BRCA* status groups were evaluated using Fisher's exact test with false discovery rate (FDR) correction. Analysis of non-*BRCA* genomic features excludes *BRCA1/2*. Non-*BRCA* HRD-related alterations were defined as pathogenic variants in established homologous recombination pathway genes (*ATM*, *ATR*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *FANCA*, *FANCD2*, *FNACL*, *PALB2*, *RAD51C*, and *RAD51D*). Variant allele frequency (VAF) was extracted from the reported allele frequency fields for *BRCA1* and *BRCA2* alterations. When multiple *BRCA* alterations were present in a tumor, the maximum VAF across *BRCA1* and *BRCA2* was used as a representative value. To ensure consistency, nonnumeric annotations were removed, and values were analyzed as continuous variables between 0 and 1. To approximate allelic complexity, a multihit status was defined based on the number of *BRCA1/2* alterations reported per tumor, with tumors classified as single-hit tumors (one alteration) or multihit tumors (two or more alterations). This definition does not distinguish *cis* versus *trans* events and was used as a pragmatic surrogate for allelic burden. Global genomic alteration burden was assessed using the following metrics provided by the database: the number of DNA somatic substitutions/insertions/deletions [single-nucleotide variant (SNV)-like], the number of DNA somatic copy number alterations (CAN)-like, and tumor mutational burden (TMB). These variables were analyzed as continuous measures. For comparisons between g^+/s^+ and g^-/s^+ tumors, continuous variables (VAF, SNV-like, CAN-like, and TMB) were compared using the Wilcoxon rank-sum test, and categorical variables (multihit versus single-hit) were compared using Fisher's exact test. Multiple testing correction was carried out using the Benjamini–Hochberg

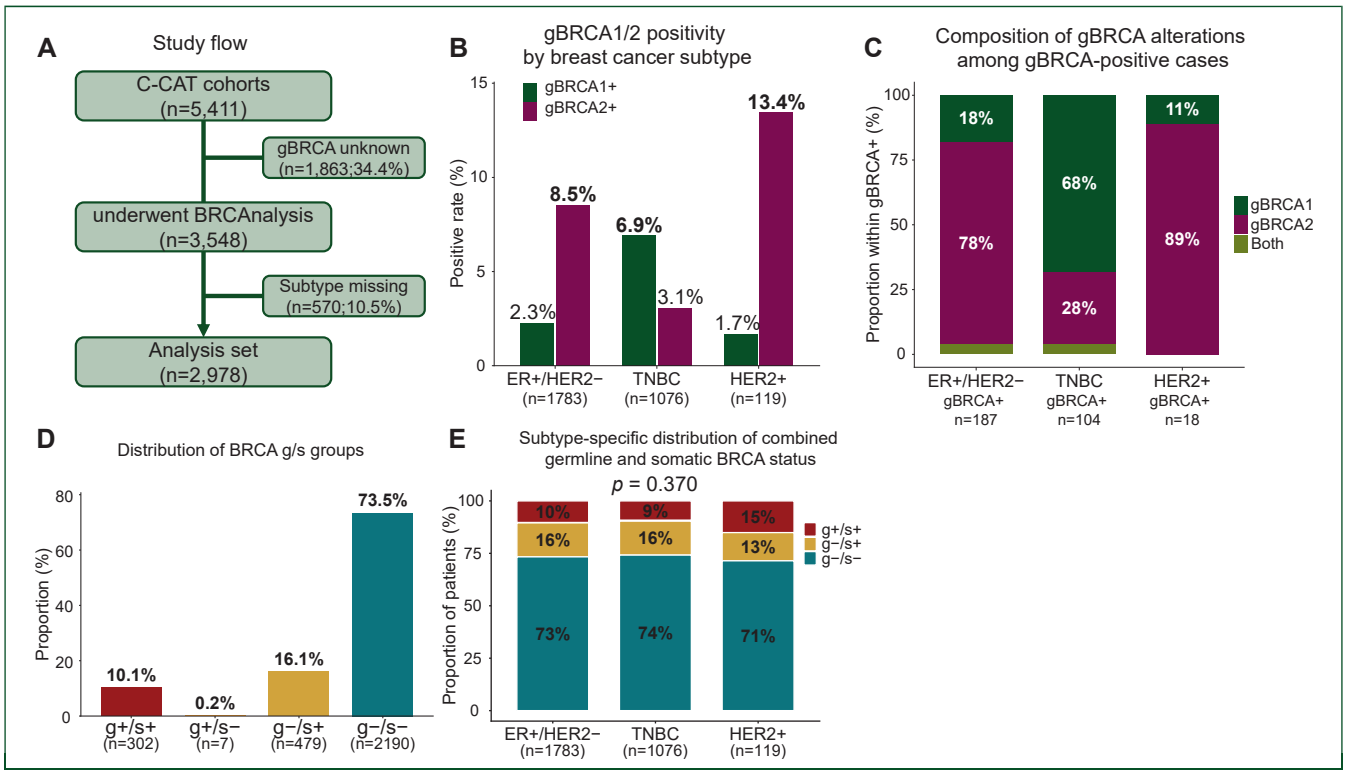

Figure 1. Study cohort and distribution of germline and somatic *BRCA* alterations. (A) Study flow diagram showing patient selection from the C-CAT database. (B) Prevalence of germline *BRCA1* and *BRCA2* alterations according to BC subtype. (C) Composition of germline *BRCA1* and *BRCA2* alterations among germline *BRCA*-positive cases by subtypes. (D) Overall distribution of combined germline and somatic *BRCA* status (g^+/s^+, g^+/s^-, g^-/s^+, and g^-/s^-). (E) Subtype-specific distribution of combined germline and somatic *BRCA* status in ER-positive/HER2-negative, TNBC, and HER2-positive BC. *P* values were calculated using Fisher's exact test with a Monte Carlo simulation.

BC, breast cancer; C-CAT, Center for Cancer Genomics and Advanced Therapeutics; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

FDR method. VAF was defined as the maximum reported allele frequency among *BRCA1/2* alterations.

Treatment outcome analyses

Because standardized radiographic progression data were not available across the cohort, we used time to treatment discontinuation (TTD) as a pragmatic real-world endpoint. TTD was operationally defined as the interval from initiation of a given therapy to the recorded start date of the subsequent treatment line. Patients without subsequent recorded treatment were censored at the last available follow-up. As treatment changes or discontinuation in routine practice may occur for multiple reasons, including disease progression, treatment-related toxicity, physician decision, or patient preference, TTD reflects real-world treatment duration but does not directly measure treatment efficacy or resistance. Analyses focused on CDK4/6 inhibitors (abemaciclib and palbociclib) in ER-positive/HER2-negative BC and immune checkpoint inhibitors in TNBC. Because ribociclib has not been approved for BC in Japan, no real-world treatment data were available for inclusion.

Statistical analysis

TTD was estimated using the Kaplan—Meier method and compared using log-rank tests. Multivariable Cox proportional hazards models were constructed, adjusting for treatment line and specimen origin, with selected models including *TP53* and *PIK3CA* status. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. All analyses were carried out using R software (R Foundation for Statistical Computing, Vienna, Austria). Two-sided *P* values <0.05 were considered statistically significant. FDR indicates FDR-adjusted *P* values calculated using the Benjamini—Hochberg method.

RESULTS

Subtype-specific frequencies with a conserved asymmetry between germline and somatic BRCA *alterations*

A total of 5411 BC cases registered in the C-CAT database were screened (Figure 1A). Among these, 2978 cases with complete germline *BRCA*, somatic *BRCA*, and BC subtype information were included in the final analysis. The prevalence and composition of g*BRCA* varied by subtype (Figure 1B and C). In ER-positive/HER2-negative BC ($n = 187$), germline *BRCA* alterations were detected in 10.8%, predominantly *BRCA2*. In TNBC ($n = 104$), germline alterations were more frequently *BRCA1*-associated (68%), whereas *BRCA2* predominated in HER2-positive BC ($n = 18$). Overall germline *BRCA* prevalence was ~10%, consistent with previous reports in Japanese and other East Asian populations.[14]

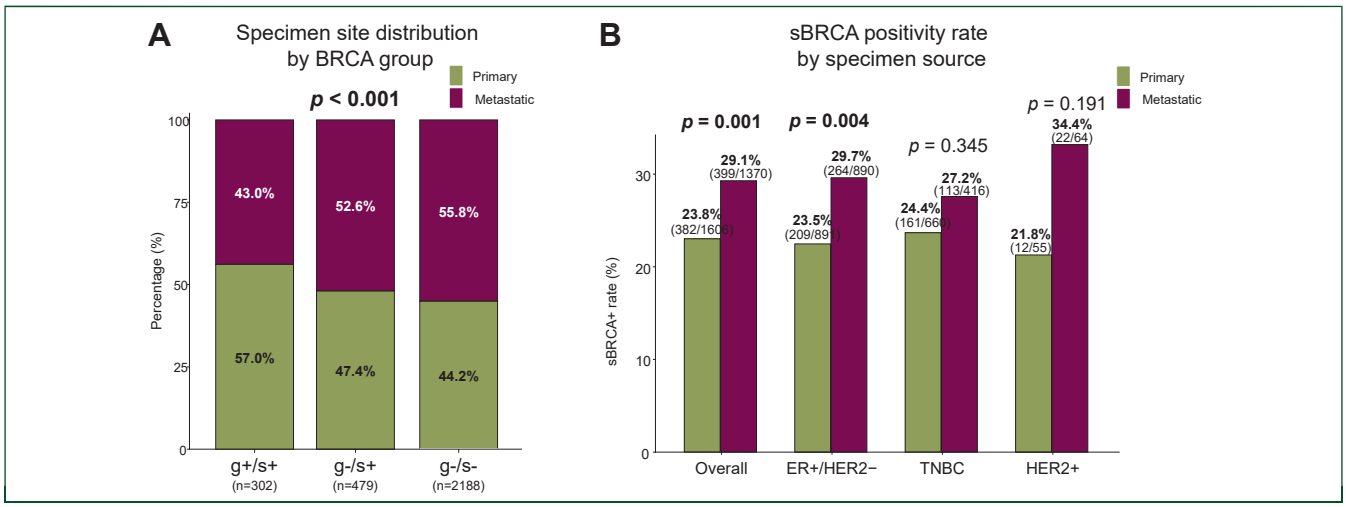

Figure 2. Specimen origin and detection patterns of somatic *BRCA* alterations. (A) Distribution of specimen collection sites according to combined germline and somatic *BRCA* status. The proportions of primary and metastatic lesions are shown for g^+/s^+, g^-/s^+, and g^-/s^- tumors. (B) Somatic *BRCA* positivity rates according to specimen source (primary compared with metastatic), shown for the overall cohort and stratified by BC subtype: ER-positive/HER2-negative, TNBC, and HER2-positive. Percentages indicate the proportion of somatic *BRCA*-positive tumors within each specimen category.
BC, breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

When classified by combined germline and somatic *BRCA* status, 10.2% of tumors were g^+/s^+, 0.2% were g^+/s^-, 16.2% were g^-/s^+, and 73.4% were g^-/s^- (Figure 1D). Baseline clinicopathological characteristics of the study population stratified by combined germline and somatic *BRCA* status are shown in Supplementary Table S1. Because of the small number of g^+/s^- tumors, subsequent comparative analyses focused on the remaining three groups. Similar distributions were observed across major BC subtypes, with no statistically significant difference in *BRCA* status distribution (Figure 1E) ($P = 0.370$). Notably, g^-/s^+ tumors were consistently more frequent than g^+/s^+ tumors across subtypes.

Somatic BRCA *alterations were modestly enriched in metastatic specimens*

To explore whether somatic *BRCA* detection differed according to specimen origin, we compared primary tumor and metastatic lesion specimens recorded in the C-CAT database. The distribution of specimen sources differed significantly across combined germline/somatic *BRCA* groups (Figure 2A). Primary tumors ($n = 1602$) accounted for 57% of g^+/s^+ cases, whereas metastatic lesions ($n = 1367$) were more common in g^-/s^+ and g^-/s^- groups (Figure 2A) (52.6% and 55.8%, respectively; $P < 0.001$). Overall, somatic *BRCA* alterations were more frequently detected in metastatic than in primary specimens (Figure 2B) (29.1% versus 23.8%). Similar trends were observed across major BC subtypes. In subtype-stratified genome-wide analyses, *ESR1* was the only significantly differentially expressed gene after FDR correction between metastatic and primary samples in ER-positive/HER2-negative BC, whereas no significant differences were observed in TNBC (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.108311). Notably, *BRCA1/2* were not among the most strongly differential genes in these exploratory comparisons. These findings indicate modest enrichment of somatic *BRCA* alterations in metastatic specimens, although longitudinal acquisition cannot be inferred.

Asymmetric concordance and distinct genomic patterns between germline and somatic BRCA *groups*

We next examined the relationship between germline and somatic *BRCA* status. Among germline *BRCA*-positive cases, the corresponding *BRCA* alteration was detectable in tumor samples in >85% of cases across subtypes (Figure 3A). In contrast, only a minority of tumors with somatic *BRCA* alterations had an underlying germline variant (37.4% for *BRCA1* and 35.3% for *BRCA2* overall), with subtype-specific variation (Figure 3B). We then compared genomic profiles between g^+/s^+ and g^-/s^+ tumors. In ER-positive/HER2-negative BC, g^-/s^+ tumors showed higher mutation frequencies in several oncogenic pathway genes, including *PIK3CA* and *TP53*, whereas *BRCA2* alterations were more frequent in the g^+/s^+ tumors (Figure 3C). In TNBC, *BRCA1* alterations were more frequent in g^+/s^+ tumors, whereas *BRCA2* alterations were more common in g^-/s^+ tumors (Figure 3D). To further characterize the allelic features of *BRCA* alterations, VAF and the number of *BRCA* alterations per tumor were examined. Among somatic *BRCA*-positive tumors, *BRCA* VAF was significantly higher in g^+/s^+ than in g^-/s^+ tumors in the overall cohort [median 0.74 (interquartile range 0.62-0.83) versus 0.49 (0.33-0.59), $P < 0.001$; $n = 152$ versus 340], and this pattern was directionally consistent across subtypes (Figure 3E). Tumors harboring multiple *BRCA* alterations (multihit) were also more frequent in the g^+/s^+ than in g^-/s^+ tumors (Figure 3F) (36.4% versus 10.2%, $P < 0.001$; $n = 302$ versus 479), with similar trends observed across subtypes. In contrast, global genomic burden metrics, including TMB,

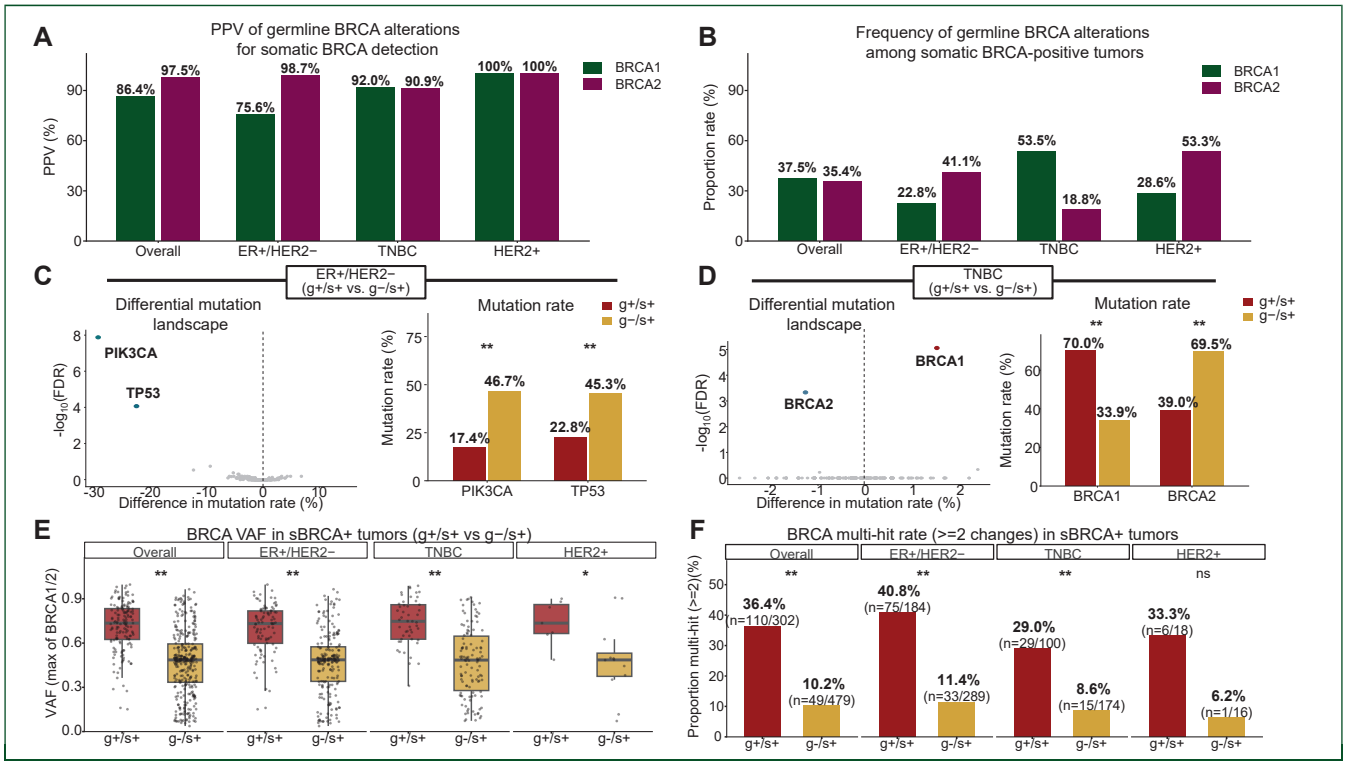

Figure 3. Germline-somatic *BRCA* relationships and subtype-specific mutational profiles. (A) PPV of germline *BRCA* alterations for detecting corresponding somatic *BRCA* alterations, shown for the overall cohort and stratified by BC subtype (ER-positive/HER2-negative, TNBC, and HER2-positive). (B) Proportion of germline *BRCA* alterations among tumors with somatic *BRCA* alterations, displayed by subtype. (C) In ER-positive/HER2-negative BC, the differential mutational landscape between g^+/s^+ and g^-/s^+ tumors. The left panel shows a volcano plot of gene-wise mutation frequency differences. The right panel depicts mutation rates of representative genes with significant differences between the two groups. (D) In TNBC, differential mutation patterns between g^+/s^+ and g^-/s^+ tumors highlight subtype-specific discriminating genes. Mutation frequency comparisons were carried out using Fisher's exact test with FDR correction. (E) Comparison of *BRCA* VAF (maximum of *BRCA1/2*) between g^+/s^+ and g^-/s^+ tumors in the overall cohort and stratified by subtype. (F) Proportion of tumors harboring multiple *BRCA* alterations (multihit, $\geq$2 alterations) in g^+/s^+ and g^-/s^+ groups, shown for the overall cohort and by subtype. *P* values were calculated using the Wilcoxon rank-sum test. ns, $P \geq 0.05$; *, $P < 0.01$; **, $P < 0.001$.

BC, breast cancer; ER, estrogen receptor; FDR, false discovery rate; HER2, human epidermal growth factor receptor 2; PPV, positive predictive value; TNBC, triple-negative breast cancer; VAF, variant allele frequency.

SNV counts, and copy number alterations (CNAs), showed only modest or inconsistent differences (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2026.108311).

*Differential distribution of non-*BRCA *HRD-related gene alterations according to combined germline and somatic* BRCA *status*

Given the marked differences in mutational landscapes between g^+/s^+ and g^-/s^+ tumors, we next examined whether these distinct genomic contexts were also reflected in the distribution of HRD-related gene alterations beyond *BRCA*. In the overall cohort, the prevalence of non-*BRCA* HRD-related gene alterations differed modestly but significantly among groups, occurring in 42.7% of g^+/s^+ tumors, 47% of g^-/s^+ tumors, and 40.2% of g^-/s^- tumors (Figure 4A) ($P = 0.023$). Subtype-specific analyses revealed heterogeneity. In ER-positive/HER2-negative BC, these alterations were more frequent in the g^-/s^+ group (51.6%) than in g^+/s^+ (42.9%) and g^-/s^- tumors (40.9%) (Figure 4B, left) ($P = 0.004$). In contrast, no significant differences were observed in TNBC (Figure 4B, right) (45%, 40.2%, and 39.5%, respectively).

Germline, but not somatic-only, BRCA *status was associated with shorter CDK4/6 inhibitor treatment duration*

To determine whether the biological differences associated with germline-somatic *BRCA* status translated into differences in treatment duration, we next evaluated TTD across major systemic therapies. In TNBC, pembrolizumab TTD did not differ by germline *BRCA* status (Figure 5A, left) (log-rank $P = 0.818$) or across the three *BRCA* groups (Figure 5A, right) ($P = 0.902$). In contrast, in ER-positive/HER2-negative BC, CDK4/6 inhibitor TTD differed by *BRCA* status. In the combined CDK4/6 inhibitor cohort, germline *BRCA*-positive patients had shorter TTD than germline *BRCA*-negative patients (Figure 5B, left) ($P < 0.001$), and a significant difference was also observed across the three *BRCA* groups (Figure 5B, right) ($P < 0.001$). For abemaciclib, TTD differed by germline *BRCA* status (Figure 5C, left) ($P = 0.026$), whereas the three-group comparison was not statistically significant (Figure 5C, right) ($P = 0.075$). For palbociclib, significant differences were observed in both the germline-based comparison (Figure 5D, left) ($P = 0.011$) and the three-group comparison (Figure 5D) ($P = 0.003$). In multivariable Cox proportional hazards analysis, as expected, later treatment line was independently associated

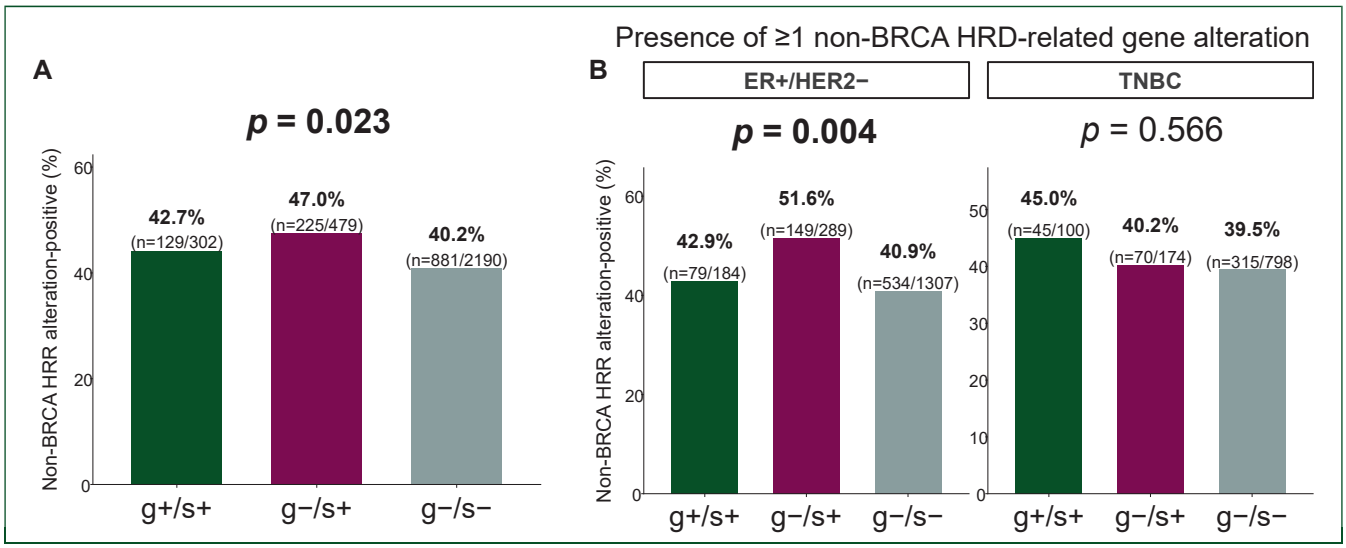

Figure 4. Non-*BRCA* HRD-related alterations according to combined germline and somatic *BRCA* status. (A) Prevalence of non-*BRCA* HRD-related gene alterations among g^+/s^+, g^-/s^+, and g^-/s^- tumors in the overall cohort. (B) Subtype-specific distribution of non-*BRCA* HRD-related alterations in ER-positive/HER2-negative BC (left) and TNBC (right). Percentages indicate the proportion of tumors harboring at least one alteration in predefined HRD-related genes.
BC, breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; TNBC, triple-negative breast cancer.

with shorter CDK4/6 inhibitor TTD (Figure 5E) (HR 1.03 per additional line, 95% CI 1.02-1.05, $P < 0.001$). After adjustment for treatment line, specimen origin, *TP53*, and *PIK3CA* status, g^+/s^+ status remained independently associated with shorter TTD compared with g^-/s^- tumors (Figure 5E) (HR 1.46, 95% CI 1.21-1.74, $P < 0.001$), whereas g^-/s^+ status was not

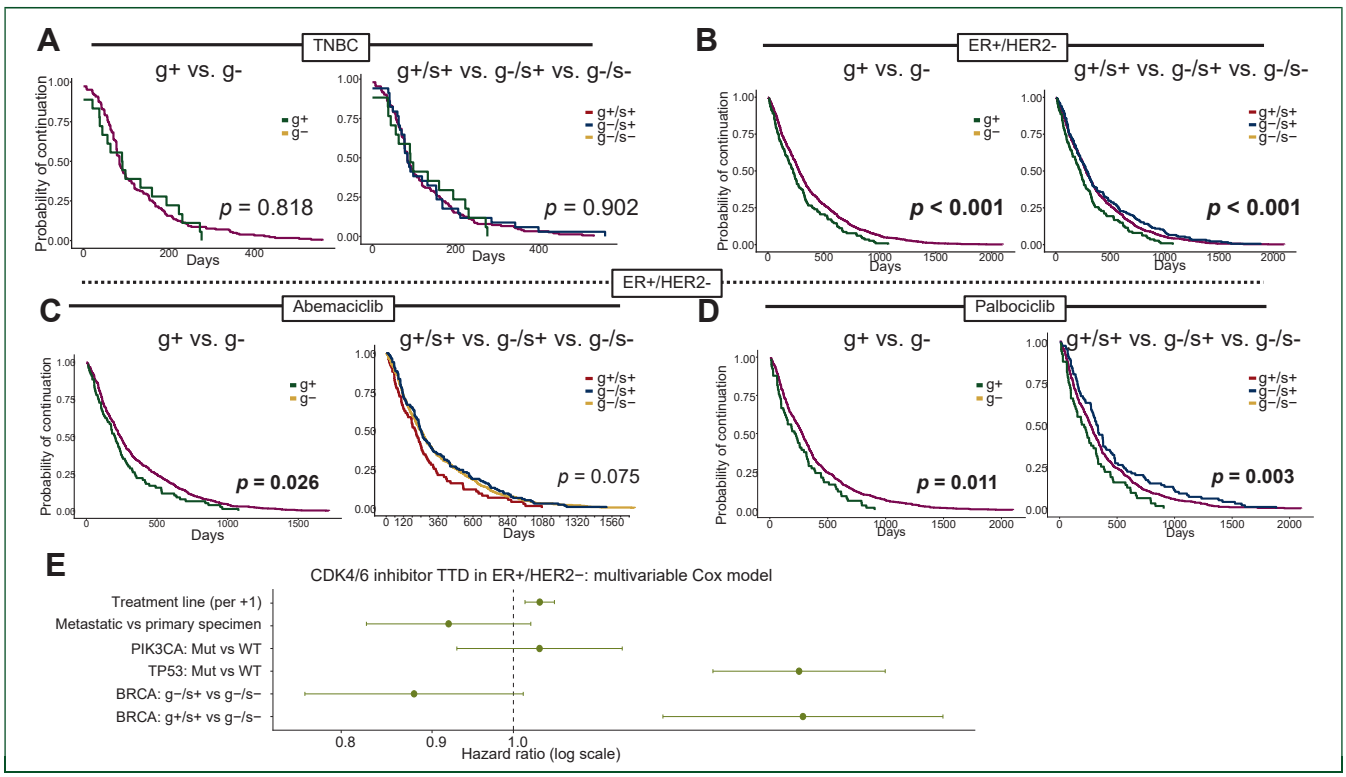

Figure 5. Impact of germline and somatic *BRCA* status on treatment duration across systemic therapies. (A) Kaplan—Meier curves of TTD for pembrolizumab in TNBC, comparing germline *BRCA*-positive versus *BRCA*-negative patients (left) and the 3 *BRCA* status groups (g^+/s^+, g^-/s^+, and g^-/s^-; right). (B) Kaplan—Meier curves of TTD for CDK4/6 inhibitors in ER-positive/HER2-negative BC using the combined CDK4/6 inhibitor cohort, shown for germline *BRCA* status (left) and for the three groups (right). (C) Kaplan—Meier curves of TTD for abemaciclib according to germline *BRCA* status (left) and the three BRCA status groups (right). (D) Kaplan—Meier curves of TTD for palbociclib according to germline BRCA status (left) and the three *BRCA* status groups (right). (E) Multivariable Cox proportional hazards model for CDK4/6 inhibitor TTD in ER-positive/HER2-negative BC. The model was adjusted for treatment line, specimen origin, *TP53* and *PIK3CA* status, and BRCA status groups (g^+/s^+ and g^-/s^+, with g^-/s^- as reference). HRs and 95% CIs are shown.
BC, breast cancer; CDK4/6, cyclin-dependent kinase 4 and 6; CIs, confidence intervals; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HRs, hazard ratios; TNBC, triple-negative breast cancer; TTD, time to treatment discontinuation.

significantly different from g^-/s^- status (Figure 5E) (HR 0.88, $P = 0.075$). *TP53* mutation was also independently associated with shorter TTD, whereas no independent association was observed for *PIK3CA* mutation. Detailed results of the multivariable Cox regression analysis are provided in Supplementary Table S2.

DISCUSSION

Previous studies have established subtype-specific differences in germline *BRCA1/2* prevalence,[15,16] forming the basis of current genetic testing strategies in BC. However, these findings largely derive from hereditary cancer or clinically enriched cohorts. Using a large real-world genomic database, we confirmed germline *BRCA* frequencies across BC subtypes consistent with prior reports, supporting the validity of our cohort. Importantly, we extend existing knowledge by demonstrating that somatic *BRCA* alterations account for a substantial proportion of *BRCA*-altered tumors across all subtypes, with limited concordance between germline and somatic status. This finding highlights that *BRCA* alterations detected by comprehensive genomic profiling cannot be interpreted in isolation. Rather, both somatic and germline *BRCA* alterations must be contextualized with respect to the presence or absence of a germline pathogenic variant, allelic status, and their functional consequences, as approximated by available HRD-related genomic surrogates. Somatic and germline *BRCA* alterations are not uniform biological entities, and their clinical significance depends on genomic context and the extent of functional inactivation. These findings highlight the limitations of mutation-centered or germline-centric classification frameworks and support an integrated approach incorporating germline status, zygosity, and functional readouts. Defining this landscape is essential for interpreting differences in tumor biology and treatment response.

The increasing use of comprehensive genomic profiling has led to the frequent identification of somatic *BRCA* alterations in BC; however, whether these alterations represent biological equivalents of germline *BRCA* deficiency has remained unclear. Prior studies have reported limited concordance between germline and tumor-only *BRCA* alterations, particularly in advanced disease settings, raising concerns regarding interpretation of somatic *BRCA* findings in clinical practice.[17,18] In the present real-world cohort, we observed a pronounced asymmetry between germline and somatic *BRCA* alterations. While germline *BRCA*-positive tumors almost uniformly harbored corresponding somatic *BRCA* events, the majority of somatic *BRCA*-positive tumors lacked germline alterations. This directional discordance is consistent with the previous pan-cancer and BC-specific analyses based on tumor-only sequencing[18,19] and underscores that somatic *BRCA* positivity does not necessarily indicate inherited HRD. Notably, the rarity of the g^+/s^- group may be biologically informative and is consistent with the established two-hit model of *BRCA*-associated tumorigenesis. However, technical factors such as tumor purity, assay sensitivity, copy number resolution, and specimen quality may also influence the detection of secondary somatic events, and therefore, this finding should be interpreted with caution. Importantly, somatic *BRCA* alterations were more frequently detected in metastatic lesions than in primary tumors. Similar enrichment of *BRCA* and other DNA repair-related alterations in metastatic samples has been reported in large-scale sequencing efforts.[20,21] Because our analysis used cross-sectional, nonpaired samples, we could not determine whether somatic *BRCA* alterations were acquired during tumor evolution or reflected treatment-related selection or sampling bias. Genome-wide comparisons between primary and metastatic tumors identified only limited mutation differences confined to ER-positive/HER2-negative disease and absent in TNBC, suggesting that the enrichment of somatic *BRCA* alterations in metastatic lesions is unlikely to be driven solely by generalized genomic instability. Beyond detection patterns, our data demonstrate that the genomic patterns associated with somatic *BRCA* alterations differ according to germline *BRCA* classification. Despite sharing somatic *BRCA* positivity, g^+/s^+ and g^-/s^+ tumors exhibited clearly distinct mutational landscapes. In ER-positive/HER2-negative BC, g^-/s^+ tumors were enriched for oncogenic signaling-related alterations such as *PIK3CA* and *TP53*, whereas g^+/s^+ tumors showed preferential accumulation of *BRCA1/2*-centered alterations, consistent with a *BRCA*-centered genomic pattern potentially related to HRD. Similar germline-dependent divergence was observed in TNBC, where *BRCA1/2* alterations dominated the discriminating features between the two groups. These findings extend prior observations that *BRCA*-altered tumors are genomically heterogeneous[22,23] by demonstrating that such heterogeneity is not random but, instead, associated with germline classification, although unresolved allelic status may contribute. In this framework, somatic *BRCA* alterations in g^-/s^+ tumors appear to arise within a genomic context enriched for oncogenic signaling-related alterations, whereas in g^+/s^+ tumors, they represent part of a genomic context for HRD-related alterations.

In ER-positive/HER2-negative BC, the present study revealed a marked difference in CDK4/6 inhibitor treatment duration according to the germline-somatic mutation status of *BRCA* alterations. While germline *BRCA*-positive tumors, particularly those with concurrent somatic *BRCA* alterations (g^+/s^+), showed significantly shorter treatment duration, tumors with somatic *BRCA* alterations alone (g^-/s^+) exhibited treatment outcomes comparable with *BRCA*-negative tumors. This finding appears paradoxical, as g^-/s^+ tumors were enriched for oncogenic signaling-related mutations, including *TP53* and *PIK3CA*, which have been associated with aggressive tumor biology and reduced endocrine sensitivity. However, prior studies have suggested that such oncogenic alterations modulate, but do not abolish, dependence on the RB-Cyclin D-CDK4/6 axis.[24-26] Consistent with this concept, the presence of these mutations alone did not translate into shorter CDK4/6 inhibitor treatment duration in the absence of germline *BRCA* deficiency. In contrast, germline *BRCA* alterations represent an early and systemic defect in HRR, shaping tumor evolution from its earliest stages. Prior studies have suggested that chronic genomic instability associated with germline *BRCA*

deficiency may influence the cell-cycle regulatory pathway and CDK4/6 dependence.[27,28] In our cohort, multivariable analyses showed that g^+/s^+ status remained independently associated with treatment line and specimen origin, together with *TP53* mutation. These findings suggest that the clinical associations of *BRCA* alterations may differ according to combined germline and somatic status. Collectively, the results support biological heterogeneity among somatic *BRCA*-positive tumors, although the mechanisms underlying these differences remain uncertain. This mutation status-dependent framework may offer one possible interpretation for the preserved CDK4/6 inhibitor treatment duration observed in g^-/s^+ tumors despite frequent oncogenic signaling alterations.

TTD is a composite real-world endpoint reflecting treatment duration, tolerability, and clinical decision making. Therefore, the shorter TTD observed in germline *BRCA*-positive tumors should be interpreted as an association in this dataset rather than direct evidence of reduced treatment efficacy, biological resistance, or any specific underlying mechanism. TTD differences may reflect multiple measured and unmeasured factors and cannot be attributed to any single cause.[29-31] These findings require validation using datasets with direct endpoints such as progression-free survival or overall survival.

A key question raised by our results is whether the differences between g^+/s^+ and g^-/s^+ tumors reflect the germline background itself or unresolved differences in allelic status, such as biallelic versus monoallelic *BRCA* inactivation. We acknowledge that allelic status cannot be comprehensively determined in the current dataset and that g^+/s^+ tumors may be enriched for biallelic events, whereas g^-/s^+ tumors likely represent a heterogeneous mixture of allelic states. Nevertheless, we observed distinct genomic patterns between these groups. For example, in ER-positive/HER2-negative disease, g^-/s^+ tumors were enriched for oncogenic signaling-related alterations, whereas g^+/s^+ tumors showed a more *BRCA*-centered genomic profile. In addition, VAF and multihit analyses suggest differences in the allelic architecture of *BRCA* alterations between groups. However, the relative contribution of germline status versus functional *BRCA* inactivation cannot be definitively separated in the current dataset. Accordingly, these findings should be interpreted as group-level differences associated with the combined germline/somatic classification used in this study, rather than direct evidence of germline-specific biological effects. Future studies incorporating paired tumor-normal sequencing, copy number resolution, and allele-specific analyses will be required to disentangle these effects.

The clinical use of PARP inhibitors in BC has recently expanded beyond germline *BRCA* alterations through MyChoice-guided olaparib selection. However, real-world evidence for PARP inhibitor efficacy in tumors with somatic *BRCA* alterations remains limited. Our findings show that germline and somatic *BRCA* alterations arise in distinct genomic contexts, indicating that *BRCA* alterations cannot be interpreted uniformly across biological settings. These findings raise a critical unanswered question: whether somatic *BRCA* alterations, particularly those arising in a genomic background not clearly enriched for HRD-related features, are associated with sensitivity to PARP inhibition? Given the biological heterogeneity observed among somatic *BRCA*-positive tumors, future studies will be needed to evaluate PARP inhibitor outcomes according to combined germline and somatic *BRCA* status rather than *BRCA* status alone. Integration of HRD assessment with germline status may help refine patient stratification in future studies. Longitudinal real-world datasets and molecularly stratified clinical studies will be required to clarify whether somatic *BRCA* alterations represent clinically meaningful therapeutic vulnerabilities or broader genomic markers of tumor evolution.

This study has several limitations. Although based on a large real-world genomic database, its retrospective design precludes causal inference. Most analyses were cross-sectional and lacked a detailed treatment history, limiting assessment of temporal acquisition and treatment-driven selection. Somatic *BRCA* alterations were identified from single timepoint tumor samples, preventing direct evaluation of genomic evolution; thus, their enrichment in metastatic lesions is compatible with but does not prove acquisition during tumor progression. Moreover, specimen origin was closely linked to disease stage and prior treatment exposure and could not be fully disentangled. Functional data were also limited, including information on biallelic inactivation, loss of heterozygosity, and HRD status. Because the study largely relied on tumor-only sequencing, allelic status could not be determined, and somatic *BRCA*-positive tumors likely represent a heterogeneous mixture, precluding assumptions of biological equivalence with germline *BRCA* alterations. In addition, HRD was inferred using mutation-based proxies rather than validated genomic scar metrics, mutational signatures, or functional assays, and CNAs and transcriptomic consequences such as aberrant splicing or nonsense-mediated decay could not be systematically assessed. Treatment outcomes were evaluated using TTD, a pragmatic real-world endpoint that may be influenced by toxicity, patient preference, and treatment sequencing. Finally, although the cohort reflects nationwide practice in Japan, ethnic and health care system differences may limit generalizability. Accordingly, these findings should be considered hypothesis generating and warrant prospective validation with paired tumor-normal sequencing, longitudinal sampling, and functional HRD assessment.

Conclusion

Our study demonstrates that *BRCA* alteration groups defined by combined germline and somatic status show distinct genomic and clinical patterns in BC. These findings highlight an important limitation of tumor-only, mutation-centered interpretation, particularly in the absence of information on allelic status and functional inactivation. Because the current dataset cannot fully disentangle these

factors, future integrative genomic approaches incorporating germline status, allele-specific analyses, and functional readouts to more accurately define clinically meaningful *BRCA* deficiency.

INFORMED CONSENT

Not applicable, as this study used deidentified secondary data.

ETHICAL APPROVAL

The use of C-CAT data in this study was reviewed and approved by the Ethical Advisory Committee of YCU (IRB approval number: F250900014). All data analyzed were fully deidentified in accordance with applicable ethical guidelines.

DATA AVAILABILITY

The C-CAT dataset is available upon application to the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) and approval by relevant ethical committees in Japan (F2509 00014). Additional data generated in this study are available from the corresponding author upon reasonable request.

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DISCLOSURE

The authors have declared no conflicts of interest.

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