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# Comparative Analysis of BRCA1 and BRCA2 Mutation–Associated Breast Cancer in a Japanese Cohort

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## ABSTRACT

Inherited pathogenic alterations in BRCA1 and BRCA2 are established determinants of distinct breast cancer (BC) molecular subtypes. Nevertheless, real-world clinical evidence elucidating how these genomic disparities modulate tumor phenotype and therapeutic choices is scarce, particularly within Japanese cohorts. Given the recent regulatory expansion of PARP inhibitor indications in Japan, BRCA testing has been integrated more routinely into practice, amplifying the necessity for locally derived clinical data. To contrast the clinicopathological profiles, recurrence characteristics, and surgical decision-making between BRCA1-driven and BRCA2-driven BC among Japanese patients, prioritizing the analysis of estrogen receptor (ER)-positive disease. A retrospective cohort analysis was conducted at a single center. We performed a retrospective evaluation of 417 consecutive patients who underwent BRCA1/2 germline testing at one Japanese facility from April 2020 through November 2023. Deleterious variants were confirmed in 38 individuals (12 BRCA1, 26 BRCA2). Clinical and pathological parameters, patterns of relapse, and uptake of prophylactic surgical interventions were systematically compared across the two mutation carrier groups. Malignancies linked to BRCA1 were overwhelmingly triple-negative (75%) and typically detected while still localized (83.3% T1 classification). In contrast, BRCA2-driven tumors were predominantly ER-positive (69.2%) and more apt to present with extensive nodal involvement (⩾2 involved lymph nodes in 42.3%). Ki-67 proliferation indices proved higher among BRCA1 cancers, though this disparity was largely contingent on intrinsic subtype. Of particular note, ER-positive neoplasms harboring BRCA mutations showed a trend toward increased recurrence risk. Decisions regarding risk-reducing surgery also diverged by the specific gene mutated. This single-institution analysis delineates clinically salient distinctions between BRCA1- and BRCA2-associated BC in a Japanese population. BRCA2-linked tumors were predisposed to manifest with more adverse features, whereas BRCA1-associated cancers were more frequently captured at an incipient stage. These insights reinforce the utility of BRCA genotyping beyond PARP inhibitor qualification—extending its value to subtype-informed risk stratification and personalized prevention planning.

**Keywords:** BRCA1/2 mutations, Breast cancer, Japanese patients, Individualized treatment strategies

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## Introduction

Inherited alterations in the BRCA1 and BRCA2 tumor suppressor genes are definitively linked to substantially heightened susceptibility to breast cancer (BC) and ovarian cancer. These genomic changes not only amplify oncogenic risk but also guide management pathways, rendering their detection exceptionally valuable. Reflecting this, the count of Japanese patients found to carry BRCA1/2 mutations has climbed steadily over time.

The landscape of publicly funded BRCA testing and corresponding treatments in Japan has undergone significant change in recent years. In July 2018, poly(ADP-ribose) polymerase (PARP) inhibitors were authorized for reimbursement as pharmacotherapy for metastatic or recurrent BC, a decision grounded in the OlympiAD trial

data [1]. By April 2020, individuals suspected of harboring hereditary breast and ovarian cancer syndrome (HBOC) could access insurance-covered BRCA analysis, and surgical prevention strategies—namely risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO)—became indicated for BRCA-positive BC in Japan. August 2022 brought further expansion: drawing on OlympiA trial outcomes [2], PARP inhibitors gained approval as adjuvant treatment for high-risk BC patients with BRCA1/2 pathogenic variants.

Whether a BRCA defect is present carries implications for prevention, surgical planning, and advanced recurrence management, and the population of patients diagnosed with BRCA1/2-mutated BC continues to expand. Scholarly work has delineated specific clinical and pathological hallmarks separating BRCA1 from BRCA2 mutation carriers. BRCA1-mutated BC (BRCA1 BC) is predominantly aligned with triple-negative BC (TNBC), while BRCA2-mutated BC (BRCA2 BC) tends to concentrate within estrogen receptor (ER)-positive disease [3-5]. Divergent frequencies of other tumor types, most notably ovarian cancer, have likewise been cataloged. Lifetime probabilities of BC and ovarian cancer for BRCA1/2 carriers have been estimated through sizeable multinational cohort studies [6, 7] and buttressed by a contemporary evaluation of BRCA1/2 pathogenic variants in triple-negative versus luminal-like breast malignancies [8]. Beyond BC and ovarian cancer, BRCA1/2 mutations heighten the lifetime likelihood of pancreatic and prostate neoplasms [9]. More recent explorations have even hinted at possible links between BRCA defects and a broader range of tumor sites, including gastric and esophageal cancers [9, 10].

Still, real-world clinical insights drawn from Japanese populations remain comparatively meager, notably relating to distant recurrence risk, chemosensitivity, and responsiveness to endocrine manipulation in BRCA1 BC and BRCA2 BC. The present work endeavors to bridge this knowledge deficit by interrogating the clinical demographics, clinicopathological attributes, and therapeutic preferences of BRCA-positive BC patients managed at a lone Japanese center. The central emphasis is on how distinctions between pathogenic variants in BRCA1 and BRCA2 guide treatment decision-making.

## Materials and Methods

Consecutive subjects who underwent BRCA germline assessment at Nagoya University Hospital between April 2020 and November 2023 were enrolled. Written informed consent was obtained from all participants, and the protocol received ethical clearance. The study population comprised individuals with BC or a prior BC diagnosis who had insurance-reimbursed BRCA testing. Under the Japanese coverage policy, qualifying criteria for BRCA testing include: BC onset at or before age 45; BC onset at or before age 60 with TNBC, bilateral disease, or multiple ipsilateral primaries; male BC; co-diagnosis of ovarian, fallopian tube, or peritoneal cancer alongside BC; or a kindred history of breast, ovarian, or pancreatic cancer within third-degree relatives. Moreover, beginning in 2020, BRCA testing has served as a companion diagnostic for PARP inhibition in advanced or recurrent BC. Since 2022, it has been used to guide perioperative treatment selection in high-risk BC. Diagnostic confirmation of HBOC and all companion testing were performed using the BRCA analysis diagnostic system (Myriad Genetics, Inc., Salt Lake City, Utah). All BRCA1/2 determinations were derived from peripheral blood germline analysis; sequencing of tumor specimens was not performed.

The investigation captured age at BC presentation, clinicopathological parameters, and recurrence events among BRCA1/2 mutation carriers. Histopathological information was sourced exclusively from routine clinical pathology reports. No slide re-examination or de novo histological assessment was undertaken. For surgically treated cases, pathological features were gauged from surgical specimens. In instances involving neoadjuvant chemotherapy (NAC), radiographic assessment established baseline tumor dimensions and nodal status. At our center, suspicious lymph nodes identified on imaging were often verified by cytology or biopsy before NAC, whenever practicable. Among eleven patients who developed more than one primary BC, the clinicopathological evaluation centered on the tumor deemed most advanced or aggressive and therefore the primary focus of treatment. Surveillance was conducted through our outpatient service, in accordance with institutional norms. Outcome events and recurrences were identified via electronic health records, pathology documentation, and imaging reports. Follow-up interval was defined from the date of definitive breast surgery until either the final clinic encounter or death; patients remaining event-free were censored at last known contact. The analytic data freeze occurred in August 2024, with complete ascertainment and no patients lost to observation.

To probe subtype-dependent distinctions, malignancies were reclassified into three categories: Luminal (ER-positive/HER2-negative), Triple Negative, and HER2-positive. This regrouping captured only ER-positive HER2-

positive cases, as no ER-negative HER2-positive tumors were uncovered. The study also captured personal oncological history and familial cancer burden among probands, verified through self-declaration and collateral information from kindred. Uptake of primary preventive measures, exemplified by risk-reducing operations, was likewise scrutinized. For participants with multiple BC episodes, onset age was anchored to the initial diagnosis. Statistical computations were carried out with JMP Pro 17 (SAS Institute Inc., Cary, North Carolina). Categorical comparisons used Fisher's exact test; otherwise, nonparametric methods were used. Owing to the modest cohort size, the analysis was restricted to univariable descriptive methods without multivariable correction; accordingly, all observations should be regarded as hypothesis-generating.
The conduct and documentation of this observational investigation adhere to the STROBE statement [11].

## Results and Discussion

*Comparison of clinicopathological features*
From the 417 individuals screened, 38 (9.1%) were found to carry pathogenic BRCA1/2 alterations, and 11 (2.6%) harbored variants of unclear significance. BRCA1 defects were present in 12 subjects (2.9%), while BRCA2 defects occurred in 26 (6.2%). Subtype profiling revealed pronounced divergence between the cohorts: Luminal-type disease dominated among BRCA2 carriers (69.2%) but was far less common among BRCA1 carriers (16.7%; P = .0010), whereas TNBC was more common among BRCA1-associated cancers (75%) than among BRCA2-associated cancers (11.5%; P < .0001). No meaningful separation emerged for Luminal versus HER2-positive distributions (P = .5363).
Median age at initial diagnosis was 46.5 years for BRCA1 mutation carriers and 45.5 years for BRCA2 carriers, a non-significant disparity (P = .4330). Overall lesion size proved comparable (P = .3241). Yet, T-stage composition set the groups apart: T1 tumors constituted a clear majority in BRCA1 BC (83.3%), while BRCA2 BC included a larger share of T2 disease (30.8%) along with locally advanced (T3/T4) presentations (11.5%). The prevalence of lymph node (LN) spread approached but fell short of statistical significance (P = .0707), with node-negative status observed in 75% of BRCA1 BC versus 53.8% of BRCA2 BC. Involvement of two or more nodes was distinctly more frequent in BRCA2 BC (42.3%) than in BRCA1 BC (8.2%). Histological grading showed no significant discrepancy (P = .6007). Ki-67, a marker of cellular proliferation, reached notably higher levels in BRCA1 BC compared with BRCA2 BC (P = .0271). Chemotherapy utilization was similar between the mutation groups (P = .768); **(Table 1).**

**Table 1.** Clinical and pathological characteristics of 38 patients with BRCA1 (n = 12) and BRCA2 (n = 26) mutations.

| | **BRCA1 vs BRCA2 P-value** | **BRCA2 (n = 26)** | **BRCA1 (n = 12)** | **All (n = 38)** |
|---|---|---|---|---|
| **Age (y), median (IQR)** | P = .4330 | 45.5 (27-71) | 46.5 (37-72) | 46.5 (27-72) |
| **Female sex (%)** | | 26 (100) | 12 (100) | 38 (100) |
| ***BRCA1* mut (%)** | | | | 12 (31.6) |
| ***BRCA2* mut (%)** | | | | 26 (68.4) |
| **Invasive size, median (IQR)** | P = .3241 | 17.5 (0-61) | 15 (2-49) | 16.5 (0-61) |
| **T (%)** | | | | |
| **Tis** | | 1 (3.8) | 0 | 1 (2.6) |
| **T1** | | 14 (53.8) | 10 (83.3) | 24 (60.5) |
| **T2** | | 8 (30.8) | 2 (16.7) | 10 (26.3) |
| **T3, T4** | | 3 (11.5) | 0 | 3 (7.9) |
| **LN metastasis (%)** | P = .0707 | | | |
| **0** | | 14 (53.8) | 9 (75.0) | 23 (60.5) |
| **1** | | 1 (3.8) | 2 (16.7) | 3 (7.9) |
| **⩾2** | | 11 (42.3) | 1 (8.2) | 12 (31.6) |
| **Subtype (%)** | | | | |
| **Luminal** | **P = .0010** | 18 (69.2) | 2 (16.7) | 20 (52.6) |
| **Triple negative** | P < **.0001** | 3 (11.5) | 9 (75.0) | 12 (31.6) |
| **HER2 positive** | P = .5363 | 4 (15.4) | 1 (8.3) | 5 (13.2) |

| | | | | |
|---|---|---|---|---|
| **Grade** | P = .6007 | | | |
| **1** | | 2 (7.7) | 1 (8.3) | 3 (7.9) |
| **2** | | 10 (38.4) | 3 (25.0) | 13 (34.2) |
| **3** | | 8 (30.8) | 6 (50.0) | 14 (36.8) |
| **Unknown** | | 6 (23.1) | 2 (16.7) | 8 (21.1) |
| ***Ki-67, median (IQR)** | **P = .0271** | 20 (2-70) | 40 (10-80) | 20 (2-80) |
| **Operation** | P = .2178 | | | |
| **Mastectomy (%)** | | 22 (84.6) | 8 (66.7) | 30 (79.0) |
| **Partial resection (%)** | | 4 (15.4) | 4 (33.3) | 8 (21.0) |
| **Chemotherapy** | P = .7683 | | | |
| **Yes (%)** | | 16 (61.5) | 8 (66.7) | 24 (63.2) |
| **No (%)** | | 10 (38.5) | 4 (33.3) | 14 (36.8) |

Variables include age, tumor stage, lymph node metastasis, molecular subtypes, grade, Ki-67 index, surgery type, and chemotherapy. Significant differences are observed in molecular subtype distribution (luminal, triple-negative) and Ki-67 index, highlighting distinct profiles between BRCA1 and BRCA2 mutation carriers.

Eight cases with unavailable data were omitted.

Significant P-values ($P \leq 0.05$) appear in bold.

*Histological background, perioperative treatment, and recurrence by subtype*

Data organized according to the three-category schema (Luminal, Triple Negative, HER2-positive) are compiled in **Table 2.** Median ages were 45.5 years for Luminal, 49.5 years for Triple Negative, and 39 years for HER2-positive malignancies (P = .1749). BRCA1 alterations were concentrated within Triple Negative tumors (75%), whereas BRCA2 variants overwhelmingly accounted for Luminal (90%) and HER2-positive (80%) cases. Further clinicopathological details are enumerated in **Table 2.** Median invasive tumor diameters measured 18.5 mm in Luminal, 17.0 mm in Triple Negative, and 13.0 mm in HER2-positive cancers (P = .6739). High-volume nodal involvement ($\geqslant$ 2 nodes) was most often observed in Luminal tumors (50.0%), compared with 8.3% in Triple Negative and 20.0% in HER2-positive disease (P = .0787). Grade distribution also varied: poorly differentiated (grade 3) lesions comprised 25.0% of Luminal cancers, 66.7% of Triple Negative cancers, and 20.0% of HER2-positive cancers (P = .0371). The Ki-67 proliferation index was highest in Triple Negative tumors (median 50%), substantially exceeding values in Luminal (15%) and HER2-positive (15%) cancers (P = .0021).

**Table 2.** Clinical characteristics of BRCA mutation carriers stratified into Luminal (n = 20), Triple Negative (n = 12), and HER2-positive (n = 5) groups.

| | **P-value** | **Luminal HER2 (n = 5)** | **Triple negative (n = 12)** | **Luminal (n = 20)** |
|---|---|---|---|---|
| **Age (y), median (IQR)** | P = .1749 | 39 (30-67) | 49.5 (35-76) | 45.5 (27-67) |
| ***BRCA1* mut (%)** | | 1 (20.0) | 9 (75.0) | 2 (10.0) |
| ***BRCA2* mut (%)** | | 4 (80.0) | 3 (25.0) | 18 (90) |
| **Operation** | P = 1.000 | | | |
| **Mastectomy (%)** | | 4 (80.0) | 10 (83.3) | 16 (80.0) |
| **Partial resection (%)** | | 1 (20.0) | 2 (16.7) | 4 (20.0) |
| **Invasive size, median (IQR)** | P = .6739 | 13 (8-29) | 17 (1.5-53.2) | 18.5 (8-61) |
| **LN metastasis (%)** | P = .0787 | | | |
| **0** | | 4 (80.0) | 9 (75.0) | 9 (45.0) |
| **1** | | 0 (0.0) | 2 (16.7) | 1 (5.0) |
| **$\geqslant$ 2** | | 1 (20.0) | 1 (8.3) | 10 (50.0) |
| **Stage I** | P = .7387 | 3 (60.0) | 8 (66.7) | 9 (45.0) |
| **II** | | 2 (40.0) | 3 (25.0) | 9 (45.0) |
| **III** | | 0 (0.0) | 1 (8.3) | 2 (10.0) |
| **Grade** | P = **.0371** | | | |
| **1** | | 0 (0.0) | 1 (8.3) | 1 (5.0) |
| **2** | | 4 (80.0) | 1 (8.3) | 8 (40.0) |
| **3** | | 1 (20.0) | 8 (66.7) | 5 (25.0) |
| **Unknown** | | 0 (0.0) | 2 (16.7) | 6 (30.0) |
| ***Ki-67, median (IQR)** | P = **.0021** | 15 (2-20) | 50 (10-80) | 15 (10-30) |
| **Chemotherapy** | P = **.0219** | | | |

| | | | | |
|---|---|---|---|---|
| **No (%)** | | 0 (0.0) | 2 (16.7) | 11 (55.0) |
| **Yes (%)** | | 5 (100.0) | 10 (83.3) | 9 (45.0) |
| **- NAC (%)** | | | | 4 (20.0) |
| **- Adjuvant (%)** | | | | 5 (25.0) |
| **Endocrine therapy** | P < .**0001** | | | |
| **No (%)** | | 0 (0.0) | 10 (100.0) | 2 (10.0) |
| **Yes (%)** | | 5 (100.0) | 0 (0.0) | 18 (90.0) |
| **Olaparib (adjuvant)** | P = 1.0000 | | | |
| **No (%)** | | 5 (100.0) | 11 (91.7) | 18 (90.0) |
| **Yes (%)** | | 0 (0.0) | 1 (8.3) | 2 (10.0) |
| **Recurrence** | P = **.0437** | | | |
| **Yes (%)** | | 0 (0.0) | 1 (8.3) | 9 (45.0) |
| **No (%)** | | 5 (100.0) | 11 (91.7) | 11 (55.0) |

One case of Stage 0 has been excluded. Triple-negative tumors were enriched for BRCA1 mutations, showed higher Ki-67 indices, and were more often high-grade.
Eight cases with unavailable data were omitted.
Significant P-values (P ≤ 0.05) appear in bold.

Management approaches reflected the underlying biology. Systemic chemotherapy was given to 45.0% of those with Luminal disease, rising to 83.3% for Triple Negative and encompassing every HER2-positive patient (P = .0219). Endocrine therapy was deployed in 90.0% of Luminal cases. Adjuvant PARP inhibition showed limited uptake during the study timeframe, reaching 10.0% in Luminal, 5.9% in Triple Negative, and none in HER2-positive patients (P = 1.0000). Relapse events were most frequent in the Luminal stratum (45.0%), were considerably rarer in triple-negative tumors (8.3%), and were absent in HER2-positive cases (P = .437).

*Family and personal cancer histories*

Regarding familial BC burden, 91.7% (11 patients) of BRCA1 BC carriers had a positive family history, compared with 8.3% (1 patient) without. Among BRCA2 BC carriers, 69.2% (18 patients) had affected relatives, while 30.8% (8 patients) did not **(Table 3).** BRCA1 BC kindreds more frequently featured ovarian and pancreatic malignancies, whereas BRCA2 BC pedigrees more commonly included gastric, esophageal, and prostate cancers **(Table 4).**

**Table 3.** Patients with a family history of breast cancer.

| | **Without family history** | **With family history** |
|---|---|---|
| **BRCA1 (%)** | 1 (8.3) | 11 (91.7) |
| **BRCA2 (%)** | 8 (30.8) | 18 (69.2) |

Within the third degree of proximity.

**Table 4.** Number of family members with cancers other than breast cancer.

| | **No family history** | **Others** | **Liver** | **Lung** | **Biliary tract** | **Pancreatic** | **Prostate** | **Esophageal** | **Gastric** | **Ovarian** |
|---|---|---|---|---|---|---|---|---|---|---|
| **BRCA1** | 3 | 1 | 1 | 4 | 2 | 4 | 1 | 1 | 4 | 9 |
| **BRCA2** | 8 | 17 | 2 | 2 | 1 | 0 | 6 | 2 | 9 | 6 |

Within the third degree of proximity. Including cases with more than two types of cancer.

The occurrence of multiple primary breast tumors within individual patients was comparable between mutational groups: 33.3% (4 patients) among BRCA1 BC and 26.9% (7 patients) among BRCA2 BC **(Table 5).**

**Table 5.** Patients with more than two breast cancers.

| | **Once** | **More than 2** |
|---|---|---|
| **BRCA1 (%)** | 8 (66.7) | 4 (33.3) |
| **BRCA2 (%)** | 19 (73.1) | 7 (26.9) |

Regarding personal non-BC malignancy history, BRCA1 BC carriers (n = 12) accounted for 3 ovarian cancers, 1 gastric cancer, and 2 other tumor types; 75% (9 patients) had no additional cancer diagnoses. BRCA2 BC carriers

(n = 26) reported no ovarian primaries but included 2 gastric cancers, 1 esophageal cancer, and 3 other malignancies. The majority (84.6%, 22 patients) of BRCA2 BC carriers remained free of cancers apart from BC **(Table 6).**

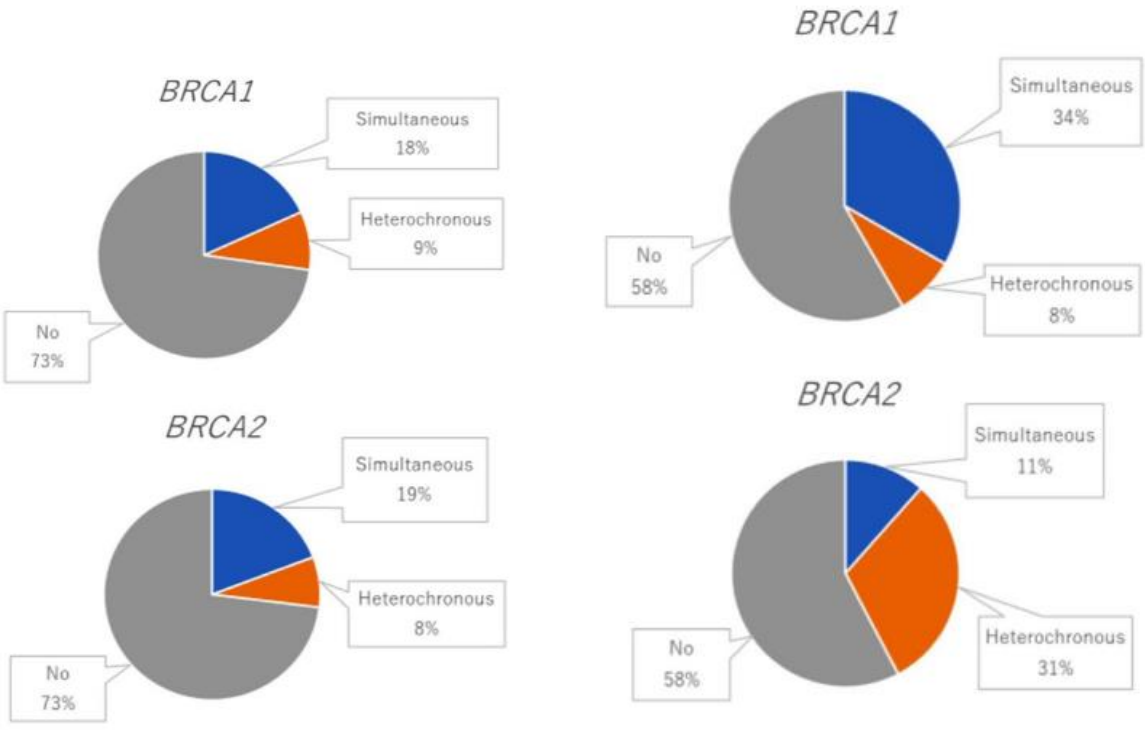
**Table 6.** Patients who experienced other cancers.

| | No experience | Others | Esophageal cancer | Gastric cancer | Ovarian cancer |
|---|---|---|---|---|---|
| **BRCA1** | 9 | 2 | 0 | 1 | 3 |
| **BRCA2** | 22 | 3 | 1 | 2 | 0 |

Including cases with more than two types of cancer.

*Selection of risk-reducing surgery*

Uptake patterns for RRM and RRSO were contrasted between BRCA1 and BRCA2 BC. Among BRCA1 carriers, simultaneous RRM was pursued by 18%, heterochronous RRM by 9%, and the predominant fraction (73%) did not undergo RRM. A nearly identical distribution emerged in BRCA2 BC: 19% simultaneous, 8% heterochronous, and 73% no RRM; thus, RRM choices showed no material difference by gene. For RRSO, however, BRCA1 BC patients elected simultaneous oophorectomy in 34% of cases, heterochronous in 8%, and declined in 58%. In BRCA2 BC, simultaneous RRSO was chosen by 11%, a greater share (31%) opted for heterochronous RRSO, and 58% did not undergo the procedure. Although the cumulative proportion eventually receiving RRSO was equal between groups, simultaneous surgery was favored more by BRCA1 carriers, whereas BRCA2 carriers leaned toward a staged, heterochronous approach **(Figure 1).**




a) b)

**Figure 1.** (a) RRM and (b) RRSO.

This analysis highlighted pronounced differences in both clinical presentation and real-world therapeutic choices between BC patients carrying pathogenic BRCA1 variants and those with BRCA2 mutations. These observations illuminate the extent to which underlying genetic divergence governs tumor behavior and shapes clinical management strategies.

In a departure from the predominant global narrative [7], our dataset failed to identify a meaningful age gap at diagnosis between BRCA1 and BRCA2 carriers. Earlier work by the Japanese HBOC Consortium reported earlier disease onset in BRCA1 carriers compared with BRCA2 carriers [12]. The inconsistency with our own results may be attributable to variations in referral channels, the stringency of testing eligibility criteria, or the inherently

limited sample from a single institution. Chemotherapy administration rates and invasive tumor size were broadly similar across the two mutational groups; however, trends in T-stage composition were divergent. Though BRCA1 BC is conventionally regarded as more biologically aggressive, BRCA1 cases in this series were more often identified while still confined (T1 stage), whereas BRCA2 carriers more frequently debuted with expanded primary tumors and multifocal nodal deposits. One contributing factor may be accelerated detection prompted by the pronounced family cancer histories typical of BRCA1 kindreds, elevating surveillance and awareness [13]. That said, any interpretation must be tempered by the retrospective framework and constrained cohort size. Both tumor dimensions and nodal involvement at diagnosis are heavily contingent on the timing of medical consultation and the circumstances of detection—neither of which was standardized in this study—introducing possible biases. Robust conclusions from these comparisons, therefore, await external replication. Conversely, BRCA2 BC was associated with bulkier primary disease and appeared capable of manifesting as a more advanced malignancy. The disproportionate burden of high-volume nodal spread ($\geqslant 2$ nodes) observed in BRCA2 BC relative to BRCA1 BC bolsters the impression of later-stage capture in these cases. While not reaching statistical significance, this pattern raises the possibility of a more invasive intrinsic phenotype. The higher Ki-67 proliferation index recorded in BRCA1 BC compared with BRCA2 BC almost certainly arises from the heavy concentration of triple-negative tumors within the BRCA1 group rather than representing a mutation-specific biological effect. Given the established association between Ki-67 elevation and TNBC [14, 15], these findings should be appropriately contextualized. Thus, the proliferation differential may not directly reflect the BRCA1 alteration itself, but rather the accompanying subtype distribution. Yet, despite the dominance of Luminal BC among BRCA2 carriers, tumor grade—a metric of histological aggressiveness—did not meaningfully differ between BRCA1 and BRCA2 cohorts **(Table 1),** prompting unease about the malignant potential of Luminal BC in the context of BRCA mutations. This uncertainty motivated our subsequent subtype-focused analysis, which directly contrasted Luminal BC with other subtypes within the BRCA1/2-mutated population.

When Luminal BC was juxtaposed with other subtypes, a notable imbalance in nodal disease burden surfaced: a higher share of Luminal BC patients harbored two or more metastatic nodes relative to the comparison groups. Even though this difference bordered on statistical significance, it brings a consequential trend into focus—one that may carry implications for both prognosis and treatment intensity. Amplified nodal positivity in Luminal BC may signal the need for more aggressive adjuvant strategies. Moreover, grade was not diminished in the Luminal arm, which diverges from the customary portrait of sporadic Luminal BC (characteristically linked to lower Ki-67 and grade) [14]. Despite these warning histological signs, the appreciably lower chemotherapy utilization in Luminal BC patients cannot be disentangled from the influence of their lower Ki-67 readings.

Regarding disease relapse, the Luminal BC group experienced a markedly elevated recurrence rate compared with the remaining subtypes. This aligns with prior evidence indicating that BRCA1/2-mutated Luminal BC carries a 3.4-fold higher BC-attributable mortality risk relative to non-Luminal BC [16]. Taken together, these data underscore the critical role of BRCA genotyping in high-risk Luminal BC to determine mutational status and emphasize the imperative of supplementing endocrine therapy with additional pharmacotherapy for BRCA1/2-mutated Luminal BC.

The integration of adjuvant PARP inhibitors has tangibly improved the outlook for BRCA-mutated BC [2]. In the Japanese healthcare system, PARP inhibition was approved for recurrent, high-risk HER2-negative BC in 2022. In the present study, only 3 patients received adjuvant PARP inhibitor therapy; this sparse use reflects the fact that publicly funded coverage for postoperative PARP inhibitor use was introduced only midway through the observational window. Continued accumulation of cases and extended follow-up documenting PARP inhibitor experience are essential. That said, it is foreseeable that outcomes for BRCA1/2-mutated Luminal BC will be meaningfully enhanced once appropriate companion BRCA testing is systematically performed and linked to the postoperative initiation of PARP inhibitor therapy.

Turning to familial and personal oncological histories, BRCA1 BC was more consistently accompanied by kindred and personal histories of ovarian cancer, a finding that resonates with the 75.6-fold surge in ovarian cancer risk reported in Japanese BRCA1 mutation carriers and the corresponding 11.3-fold increase observed with BRCA2 alterations [9]. Nearly all BRCA1 carriers (91.7%) reported a family history of BC; given the cancer-type specificity of BRCA1, it is plausible that these families maintain a heightened consciousness regarding breast malignancy. BRCA2 BC carriers, on the other hand, more commonly detailed kindred histories of diverse other cancers—most prominently gastric and esophageal primaries. This same pattern extended to personal non-BC cancer occurrences. Beyond prostate and pancreatic disease, epidemiological data specific to the Japanese

population document an elevated gastric cancer risk (5.2-fold for BRCA1 and 4.7-fold for BRCA2) along with a 5.6-fold increased risk of esophageal cancer attributable to BRCA2 positivity [9]. These cumulative observations suggest fundamentally different cancer spectra associated with BRCA1 and BRCA2 mutations, respectively. These insights stand to inform genetic counseling practices, risk-tailored surveillance regimens, and patient-facing education efforts.

Regarding risk-reducing surgery, uptake of RRM was 27% among both BRCA1 carriers (18% simultaneous, 9% heterochronous) and BRCA2 carriers (19% simultaneous, 8% heterochronous) in our series, with no discernible intergroup difference. These figures sit at the lower boundary of published international estimates (30%–40% for BRCA1 and 20%–30% for BRCA2) [6, 7] and align with Japanese registry findings (16.3% versus 8.5%) [17], a pattern plausibly shaped by cultural norms and system-level factors including reimbursement policies, the timing of genetic counseling encounters, individual preferences, and access to reconstructive services. In contrast, RRSO uptake diverged by mutational status: a substantially larger fraction of BRCA1 carriers elected concurrent RRSO (34%) than BRCA2 carriers (11%), likely driven by the more pronounced ovarian cancer susceptibility conferred by BRCA1 [6, 7] and the correspondingly richer family histories of this malignancy. Patients harboring BRCA1 mutations also more frequently develop TNBC and undergo preoperative systemic therapy, circumstances that create supplementary touchpoints for counseling discussions. Of particular note, 31% of BRCA2 carriers ultimately underwent heterochronous RRSO; consequently, the cumulative proportion undergoing RRSO proved comparable across the two groups, illustrating both the inherent shortcomings of ovarian cancer screening and the pivotal role that counseling timing plays in shaping surgical choices.

This investigation revealed meaningful differences between BRCA1- and BRCA2-driven BC. While BRCA1-related tumors were more apt to be identified at an incipient stage, BRCA2-associated malignancies tended to have bulkier primary lesions and heavier nodal metastatic involvement. This pattern became even more apparent when the analysis was focused specifically on the Luminal subtype. Divergences also surfaced in the uptake of prophylactic surgical interventions and in the spectrum of non-breast malignancies. Collectively, these observations highlight the imperative for tailored cancer management paradigms that fully account for BRCA mutational status.

Several constraints of this study warrant acknowledgment. First, the modest cohort size (12 BRCA1 and 26 BRCA2 carriers) curtailed statistical power, particularly for subgroup explorations such as recurrence patterns and nodal involvement. Second, the retrospective, single-institution framework inherently carries risks of selection and information biases, and the applicability of these results to other clinical contexts cannot be assumed. Third, family history information and surgical decision-making data were gleaned from patient self-reports, leaving open the possibility of recall inaccuracies. Moreover, therapeutic choices may have been shaped by institutional protocols and clinician judgment, further circumscribing external generalizability. Fourth, the scheduling of genetic testing hinged on physician discretion and evolving insurance coverage timelines, which may have introduced variation into case inclusion. Finally, the comparatively brief follow-up interval constrained the ability to assess long-term treatment effectiveness and recurrence trajectories. More expansive, multicenter investigations with extended surveillance periods are needed to corroborate and build upon these observations.

## Conclusion

In this single-center retrospective analysis, we delineated subtype-dependent clinical and pathological distinctions between BRCA1- and BRCA2-associated BC in a Japanese population. BRCA2-linked tumors more commonly manifested with larger tumor burdens and multifocal nodal spread, whereas BRCA1-linked cancers were more often captured at an early T-stage. These findings reinforce the importance of integrating BRCA status into personalized therapeutic and preventive strategies, while underscoring the need for larger multicenter cohorts to substantiate these trends.

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**Ethics Statement:** This study was conducted in accordance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Ministry of Health, Labor, and Welfare, Japan) and the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board of Nagoya University Hospital (approval no.: 2022-0244).
Written informed consent was obtained from all participants.

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