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Japanese nationwide observational multicenter study of tumor *BRCA1/2* variant testing in advanced ovarian cancer

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Abstract

The association between germline *BRCA1* and *BRCA2* pathogenic variants (mutations: g*BRCA*m) and ovarian cancer risk is well established. Germline testing alone cannot detect somatic *BRCA1/2* pathogenic variants (s*BRCA*m), which is calculated based on the proportion of tumor *BRCA*m (t*BRCA*m) from tumor samples and g*BRCA*m. Homologous recombination deficiency (HRD) results mainly from genetic/epigenetic alterations in homologous recombination repair-related genes and can be evaluated by genomic instability status. In Japan, the prevalence of t*BRCA*m, s*BRCA*m, and HRD remains unclear. This multicenter, cross-sectional, observational study, CHaRacterIzing the croSs-secTional approach to invEstigate the prevaLence of tissue *BRCA1/2* mutations in newLy diagnosEd advanced ovarian cancer patients (CHRISTELLE), evaluated the prevalence of t*BRCA*m, s*BRCA*m, and HRD in tumor specimens from newly diagnosed patients with ovarian cancer who underwent g*BRCA* testing. Of the 205 patients analyzed, 26.8% had a t*BRCA*m, including t*BRCA*1m (17.6%) and t*BRCA*2m (9.3%). The overall prevalence of t*BRCA*m, g*BRCA*m, s*BRCA*m, and HRD-positive status was 26.8%, 21.5%, 6.3%, and 60.0%, respectively. The calculated s*BRCA*m/t*BRCA*m ratio was 23.6% (13/55), and the prevalence of g*BRCA* variant of uncertain significance was 3.9%. These results suggest g*BRCA* testing alone cannot clearly identify the best course of treatment, highlighting the importance of s*BRCA* testing in Japan. The present results also suggest that testing for t*BRCA* and HRD should be encouraged in advanced ovarian cancer patients to drive precision medicine.

KEYWORDS
BRCA, epithelial ovarian cancer, genetic testing, germline pathogenic variant, homologous recombination

Abbreviations: CI, confidence interval; FAS, full analysis set; FFPE, formalin-fixed paraffin-embedded; FIGO, International Federation of Gynecology and Obstetrics; g*BRCA*m, germline *BRCA* mutation (pathogenic variant); HRD, homologous recombination deficiency; LGR, large genomic rearrangement; PARP, poly(ADP-ribose) polymerase; PPS, per-protocol set; Q1, first quartile; Q3, third quartile; s*BRCA*m, somatic *BRCA* mutation; SD, standard deviation; t*BRCA*m, tumor *BRCA* mutation; VUS, variant of uncertain significance.

1 | INTRODUCTION

Globally, ovarian cancer is the third most frequent gynecologic malignancy and the second most frequent cause of gynecologic cancer death.[1] Despite the considerable advances in cancer screening and therapeutic and surgical treatment methods in the past few decades, the improvements in survival among patients with ovarian cancer have not been remarkable.[2–4] Important reasons for the lack of improvement in survival and prognosis among women with ovarian cancer are ineffective screening methods and late-stage diagnosis due to the absence of specific symptomatology. Furthermore, recent trends observed in Japan indicate that the age-adjusted incidence rate of ovarian cancer has increased (from 4.0 to 15.0 per 100,000 women between 1975 and 2013).[5]

The association between germline *BRCA1* and *BRCA2* (*BRCA1/2*) pathogenic variants (g*BRCA* mutation [g*BRCA*m]) and ovarian cancer risk is well established.[6] These germline pathogenic variants result in a risk of developing ovarian cancer of 40%–60% with *BRCA1*m and 11%–27% with *BRCA2*m.[7] Although g*BRCA*m have been associated with hereditary breast and ovarian cancer syndrome,[8] roughly 35%–40% of women with g*BRCA*m lack any relevant family history.[9–13] The CHARLOTTE study found that among Japanese women with newly diagnosed ovarian cancer, the prevalence of g*BRCA1/2*m was 14.7%, with a higher proportion of g*BRCA1*m (9.9%) than g*BRCA2*m (4.7%). This study also reported a prevalence of g*BRCA*m of 4.9% in stage I–II patients and 24.1% in stage III–IV patients. The prevalence of g*BRCA*m was 28.5% in high-grade serous ovarian cancer.[14] The presence of g*BRCA*m is associated with enhanced sensitivity to platinum-based chemotherapy[15,16] and poly(ADP-ribose) polymerase (PARP) inhibitors, as well as improved survival.[15]

BRCA mutations are either germline or somatic pathogenic variants (s*BRCA*m). Germline pathogenic variants in *BRCA1* or *BRCA2* are associated with an inherited susceptibility to epithelial ovarian cancer, present in approximately 15% of patients.[17] Somatic pathogenic variants of the *BRCA1* and *BRCA2* genes are responsible for non-hereditary epithelial ovarian cancer.[17] Given the differences in the origin of these pathogenic variants, s*BRCA*m cannot be detected by germline testing methods alone.[18,19] The proportion of s*BRCA*m can be calculated by subtracting the proportion of g*BRCA*m obtained by germline testing from the proportion of tumor *BRCA*m (t*BRCA*m) obtained by tumor tissue sample testing.[15,18,19]

Several studies have shown that ovarian cancers with s*BRCA*m respond similarly to platinum-based chemotherapy and PARP inhibitors[15,20–23] as ovarian cancers with g*BRCA*m. For these reasons, identifying patients with ovarian cancer and s*BRCA*m is critical. Homologous recombination deficiency (HRD) is caused by various types of genetic/epigenetic alterations, including g*BRCA*m and s*BRCA*m, as well as promoter hypermethylation of *BRCA1* and *RAD51C*, and other HRD-related genetic disorders.[24] It has been reported that roughly 50% of epithelial ovarian cancers present defective DNA repair by HRD. This distinctive characteristic of epithelial ovarian cancers, particularly the high-grade serous subtype, has important implications for disease management, as targeting HRD-positive cells allows for cancer-specific lethality without affecting normal cells.[24] Furthermore, HRD induces genomic instability status with extensive chromosomal copy number variations, and the HRD score can be a predictive biomarker for PARP inhibitors in ovarian cancer.

The phase III PAOLA-1 trial in patients who were being treated with platinum chemotherapy and bevacizumab followed by bevacizumab for newly diagnosed advanced ovarian cancer recently reported that a new maintenance regimen consisting of olaparib and bevacizumab showed survival benefits in patients with HRD-positive tumors.[25] Of note, the prevalence of different *BRCA*m statuses, specifically t*BRCA*m and s*BRCA*m status, and HRD scores of patients with ovarian cancer in Japan have not been clarified.

This study, CHaRacterIzing the croSs-secTional approach to invEstigate the prevaLence of tissue *BRCA1/2* mutations in newLy diagnosEd advanced ovarian cancer patients (CHRISTELLE), aimed to determine the prevalence of t*BRCA*m, s*BRCA*m, and HRD scores in tumor specimens from newly diagnosed patients with ovarian cancer. The t*BRCA*m-positive status was identified using the Myriad myChoice test (Myriad Genetics, Inc.), and g*BRCA*m-positive status was identified by BRACAnalysis (Myriad Genetics, Inc.). The s*BRCA*m-positive status was defined as t*BRCA*m-positive status without the presence of g*BRCA*m, that is, when *BRCA*m is present only in tumor cells, and not in normal cells: this was calculated by subtracting the number of patients with g*BRCA*m from the number of patients with t*BRCA*m.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multicenter, cross-sectional, observational study (UMIN000039226) undertaken at 20 sites throughout Japan between March 2020 and December 2020. The study sites were selected from every region of Japan to minimize locational bias. This study consecutively enrolled patients with newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) stage III–IV ovarian cancer who had undergone or were planning to undergo Myriad BRACAnalysis to detect g*BRCA* status. This study was carried out in accordance with the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects, and Ethical Guidelines for Human Genome and Genetic Analysis Research. The protocol was approved by the institutional review board or ethics committee at each individual study site as well as a central ethics committee (Non-Profit Organization MINS Institutional Review Board, approval ID: MINS-REC-190248).

2.2 | Patients

Patients enrolled in this study were women who: (i) were aged 20 years or older at the time of providing written informed consent

(the age at the time of death, if the patient was deceased); (ii) had been newly diagnosed with FIGO stage III–IV epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (or a combination of these) after January 2019; (iii) had archived formalin-fixed paraffin-embedded (FFPE) samples of primary or peritoneal metastatic tumors collected after 1 January 2019; (iv) had undergone or planned to undergo BRACAnalysis for g*BRCA* testing; and (v) provided written informed consent to participate in this study (opt-out was applicable if the patient had died).

2.3 | Data collection and measurements

Archived FFPE samples from enrolled patients were forwarded to the central laboratory for tumor *BRCA*m testing using the Myriad myChoice test, recently approved in Japan (November 2020).[26] Possible test results were deleterious/suspected deleterious variants, uncertain/variant of uncertain significance (VUS), or mutation absent. Histopathology was assessed by the central pathologists using serial sections of the submitted FFPE samples.

BRAC Analysis was undertaken using a blood sample to determine the number and percentage of patients with g*BRCA*m, and the result was obtained from patient charts. Patients' clinical background information, sample collection information, and other relevant data were also collected from their medical records. The calculation to determine the number of s*BRCA*m consisted of subtracting the number of deleterious variants or suspected deleterious variants obtained from BRACAnalysis (g*BRCA*m) from the number of deleterious variants or suspected deleterious variants according to Myriad myChoice (t*BRCA*m). That is, s*BRCA*m = t*BRCA*m measured by Myriad myChoice − g*BRCA*m measured by BRACAnalysis.

BRCA variants and HRD status were also assessed by Myriad myChoice. The HRD score (genomic instability score) was defined as the unweighted numeric sum of the loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. The HRD score cutoff value was 42 based on a previous study.[27] The HRD status was considered positive if the score was ≥42 or t*BRCA1*m or t*BRCA2*m was detected by mutation analysis, and negative if the score was <42 and no t*BRCA1*m or t*BRCA2*m or unknown (failed) was detected. The HRD status was reported as unknown (failed) when the HRD score was not determined and no t*BRCA1*m or t*BRCA2*m was detected by mutation analysis.

2.4 | Study end-points

2.4.1 | Primary end-point

The primary end-point was the prevalence of t*BRCA*m, including t*BRCA1* and t*BRCA2*. A patient was considered as having a t*BRCA1*m and/or t*BRCA2*m if the gene test results showed a deleterious mutation or suspected deleterious mutation (i.e., mutation present). A patient was considered to have no t*BRCA*m if the gene test results showed a VUS or mutation absent.

2.4.2 | Secondary end-points

The secondary end-points were the prevalence of g*BRCA*m, the prevalence of s*BRCA*m, and the ratio of s*BRCA*m to t*BRCA*m. A patient was considered as having a *BRCA1*m and/or *BRCA2*m if the gene test results showed a deleterious mutation or suspected deleterious mutation (i.e., mutation present). A patient was not considered to have *BRCA*m if the gene test results showed a VUS or uncertain clinical significance/favor polymorphism or mutation absent or not specified (i.e., no mutation present).

2.4.3 | Exploratory end-points

As exploratory end-points, t*BRCA*m variants, HRD score (positive/negative), and prevalence of t*BRCA*m, g*BRCA*m, and HRD by subgroup (age, menopausal status, cancer type, histological classification, FIGO stage, medical history, family history of cancer, and smoking history) were assessed. Furthermore, concordance between t*BRCA*m, g*BRCA*m, and HRD status was assessed.

2.5 | Rationale for sample size and statistical analysis

Considering that roughly 50% of the 10,000 newly diagnosed ovarian cancer patients per year[28,29] would be diagnosed at an advanced stage (FIGO III–IV) and an estimated prevalence of t*BRCA*m of 30% among patients newly diagnosed with ovarian cancer in Japan,[14,30] the enrollment of at least 166 patients was estimated to yield a ≥90% probability of obtaining a point estimate with an exact 95% confidence interval (CI) of ±7.5%. After considering patient withdrawal and loss to follow-up, the planned sample size was 200 patients.

The analytical populations of the study were the full anaysis set (FAS) and the per-protocol set (PPS). The FAS was defined as enrolled patients who underwent g*BRCA*m and t*BRCA*m tests and had histological specimens available for central pathologist confirmation. The PPS consisted of enrolled patients with valid g*BRCA*m and t*BRCA*m results and underwent histopathological assessment by the central pathologist.

Continuous variables were summarized using mean (SD), median, first quartile (Q1), and third quartile (Q3), and categorical variables were summarized using *n* (%). No missing data or unknown responses were counted for percentage calculations, and missing data were not imputed. The statistical software package used was SAS version 9.4 or greater (SAS Institute Inc.).

3 | RESULTS

3.1 | Patients

Figure 1 shows the patient disposition. Of the 217 patients enrolled, 11 were excluded, and 206 were included in the FAS. Of the patients included in the FAS, one patient with a cancer type that was not confirmed as eligible by central pathology was excluded. Thus, 205 patients comprised the PPS. The regional distributions of the patients and the numbers enrolled at each site are shown in Figure S1 and Table S1.

Table S2 summarizes the main characteristics of patients. Patients in the PPS had a mean (SD) age of 59.4 (10.9) years, with 80.0% (164/205) of patients aged 50 years or older, 73.7% (151/205) having postmenopausal status, and 19.0% (39/205) having received neoadjuvant chemotherapy. Of note, 83.4% (171/205) had epithelial ovarian cancer, followed by primary peritoneal cancer (9.8%, 20/205) and fallopian tube cancer (6.8%, 14/205). Histologically, 79.5% (163/205) had high-grade serous ovarian carcinoma, followed by endometrioid carcinoma (12.7%, 26/205), clear cell carcinoma (6.3%, 13/205), and others (1.5%, 3/205). All patients had advanced ovarian cancer; specifically, 66.8% (137/205) had FIGO stage III, and 33.2% (68/205) had FIGO stage IV.

3.2 | Study end-points

3.2.1 | Primary end-point

In the PPS, 26.8% (55/205) of patients had a t*BRCA*m. Of these, 17.6% (36/205) of patients had a t*BRCA1*m, and 9.3% (19/205) had t*BRCA2*m. However, 73.2% (150/205) had no t*BRCA*m present (VUS or mutation absent). Gene test results of 11/205 patients showed VUS, with a prevalence of 5.4%, and 139/205 were mutation absent, with a prevalence of 67.8%. The prevalence of t*BRCA1* VUS was 1.5% (3/205), that of t*BRCA2* VUS was 3.4% (7/205), and that of t*BRCA1/2* VUS was 0.5% (1/205) (Figure 2A).

3.2.2 | Secondary end-points

The prevalence of g*BRCA*m was 21.5% (44/205), of which g*BRCA1*m was 14.1% (29/205) and g*BRCA2*m was 7.3% (15/205); g*BRCA*m was absent in 74.6% (153/205). The prevalence of g*BRCA* VUS was 3.9% (8/205), that of g*BRCA1* VUS was 1.0% (2/205), that of g*BRCA2* VUS was 2.4% (5/205), and that of g*BRCA1/2* VUS was 0.5% (1/205) (Figure 2B).

The concordance between g*BRCA*m and t*BRCA*m is shown in Table 1. Of the patients with t*BRCA1*m ($n = 36$), 29 had g*BRCA1*m. None had g*BRCA2*m or g*BRCA1/2*m, but 2 had g*BRCA* VUS, and 5 had g*BRCA*m absent status. Therefore, 7 had s*BRCA1*m. Of those with t*BRCA2*m ($n = 19$), 13 were positive for g*BRCA2*m, and 6 had g*BRCA*m absent status. Therefore, 6 had s*BRCA2*m. t*BRCA* VUS and g*BRCA*m absent was documented in 2.4% (5/205) of patients, and t*BRCA* absent and g*BRCA*m absent was documented in 66.8% (137/205) of patients.

Overall, the prevalence of s*BRCA*m was 6.3% (13/205), of which s*BRCA1*m accounted for 3.4% (7/205), and s*BRCA2*m, 2.9% (6/205). The percentage of s*BRCA*m/t*BRCA*m was 23.6% (13/55), that of s*BRCA1*m/t*BRCA1*m was 19.4% (7/36), and that of s*BRCA2*m/t*BRCA2*m was 31.6% (6/19). Of note, two patients were positive for g*BRCA2*m without t*BRCA*m detection (one t*BRCA* VUS and one t*BRCA*m absent).

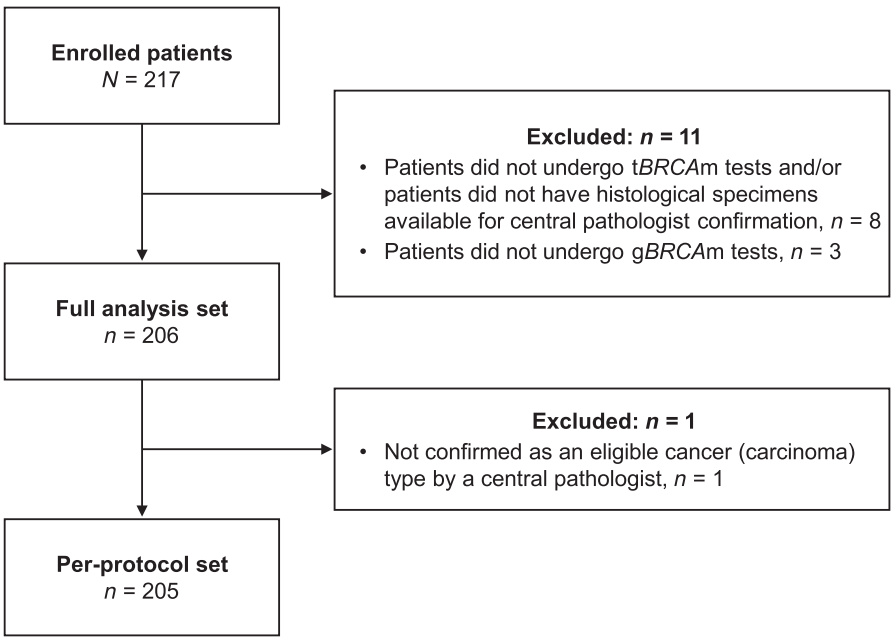
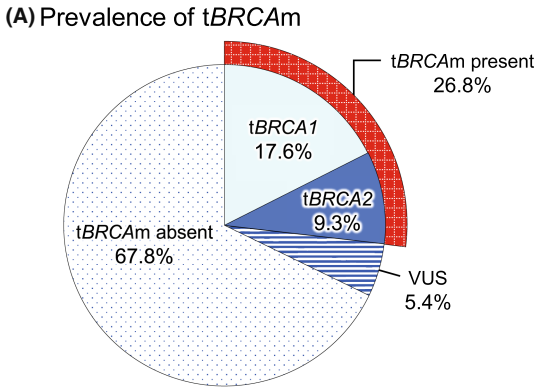
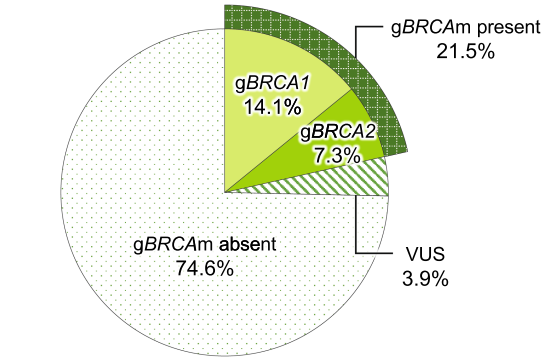


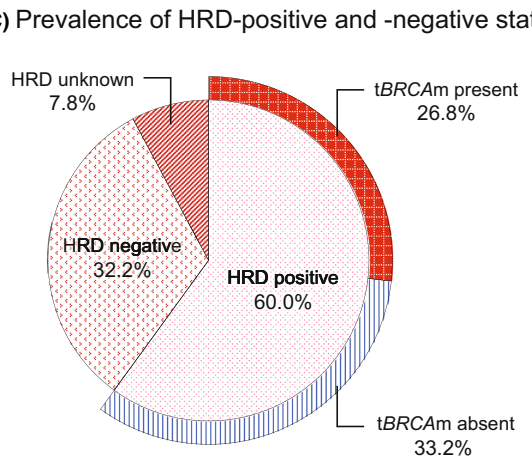
FIGURE 1 Patient disposition among study participants with advanced ovarian cancer. g*BRCA*m, germline *BRCA* mutation; t*BRCA*m, tumor *BRCA* mutation.



	n = 205[a] n (%)
tBRCAm present	55 (26.8)
tBRCA1	36 (17.6)
tBRCA2	19 (9.3)
tBRCA1/2	0
VUS	11 (5.4)
tBRCA1 VUS	3 (1.5)
tBRCA2 VUS	7 (3.4)
tBRCA1/2 VUS	1 (0.5)
Mutation absent	139 (67.8)



	n = 205[a] n (%)
gBRCAm present	44 (21.5)
gBRCA1	29 (14.1)
gBRCA2	15 (7.3)
gBRCA1/2	0
VUS	8 (3.9)
gBRCA1 VUS	2 (1.0)
gBRCA2 VUS	5 (2.4)
gBRCA1/2 VUS	1 (0.5)
Mutation absent	153 (74.6)



	n = 205[a] n (%)
HRD positive[b]	123 (60.0)
tBRCAm present	55 (26.8)
tBRCA1	36 (17.6)
tBRCA2	19 (9.3)
tBRCA1/2	0
tBRCAm absent	68 (33.2)
HRD negative[c]	66 (32.2)
HRD unknown[d]	16 (7.8)

FIGURE 2 Prevalence of (A) tumor *BRCA* mutation (t*BRCA*m), (B) germline *BRCA* mutation (g*BRCA*m), and (C) homologous recombination deficiency (HRD)-positive and -negative status among Japanese patients with advanced ovarian cancer. [a]Per-protocol set. [b]HRD status was defined as positive if the HRD score was ≥42 or mutated t*BRCA1* or t*BRCA2* was present. [c]HRD status was defined as negative if the HRD score was <42, and there was no mutated t*BRCA1* or t*BRCA2*. [d]HRD status was defined as unknown (failed) if the HRD score could not be determined, and t*BRCA1* or t*BRCA2* was not mutated or was canceled. VUS, variant of uncertain significance

3.2.3 | Exploratory end-points

Table S3 summarizes the variant description of t*BRCA*m. Among the 36 (17.6%) patients with variant type t*BRCA1*m, 34 (16.6%) had sequencing variants, of which the most common variants were nonsense variants (7.3%, 15/205) and frameshift variants (6.8%, 14/205). Among the 19 (9.3%) patients with t*BRCA2*m, 19 (9.3%) had sequencing variants, of which the most common variants were nonsense variants (3.9%, 8/205) and frameshift variants (3.9%, 8/205).

Regarding the HRD prevalence, 60.0% (123/205) of patients were HRD positive, 32.2% (66/205) were HRD negative, and 7.8% (16/205) were HRD unknown (failed) in the PPS (Figure 2C).

A swarm plot with box chart shows the distribution of the genomic instability score for patients with t*BRCA*m present, absent, or VUS (Figure 3). The median genomic instability score was 66.0 in patients with t*BRCA*m present, 42.0 in those with t*BRCA*m absent, and 61.0 in those with t*BRCA* VUS. Figure S2 shows the distribution of the genomic instability score for patients with g*BRCA*m present, absent, or VUS. The median genomic instability score was 65.5 in patients with g*BRCA*m present, 45.0 in those with g*BRCA*m absent, and 54.0 in those with g*BRCA* VUS.

Table 2 shows the prevalence of t*BRCA*m, g*BRCA*m, and HRD by patient and ovarian cancer characteristics. Regarding patient characteristics, numerically higher proportions of patients aged less

TABLE 1 Concordance between germline *BRCA1/2* (g*BRCA1/2*) and tumor *BRCA1/2* (t*BRCA1/2*) mutation status in Japanese patients with advanced ovarian cancer

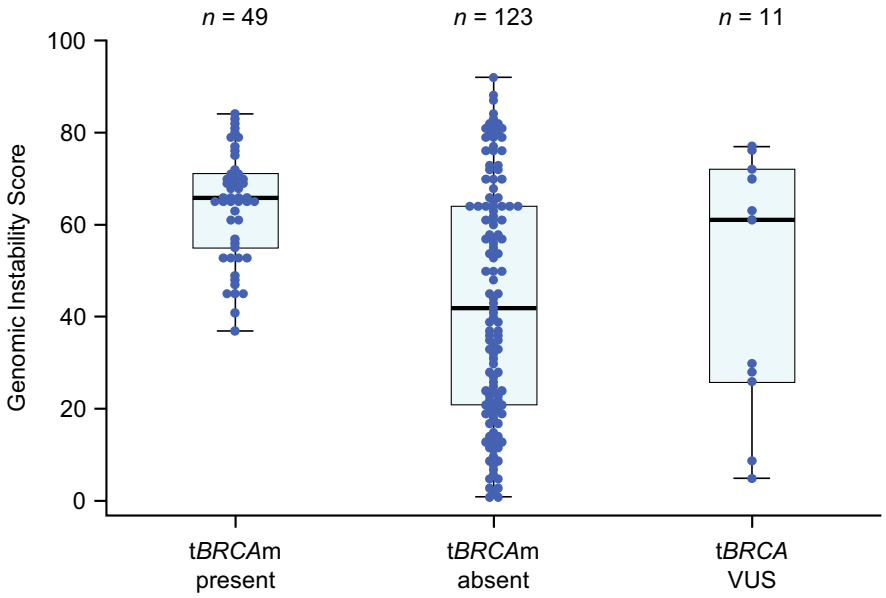
	g*BRCA*m present			No g*BRCA*m present		
	g*BRCA1*	g*BRCA2*	g*BRCA1/2*	g*BRCA* VUS	g*BRCA*m absent	Total
t*BRCA*m present						
t*BRCA1*	29 (14.1)	0 (0.0)	0 (0.0)	2 (1.0)[a]	5 (2.4)[a]	36 (17.6)
t*BRCA2*	0 (0.0)	13 (6.3)	0 (0.0)	0 (0.0)	6 (2.9)[a]	19 (9.3)
t*BRCA1/2*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
t*BRCA*m negative (VUS or absent)						
t*BRCA* VUS	0 (0.0)	1 (0.5)[b]	0 (0.0)	5 (2.4)	5 (2.4)	11 (5.4)
t*BRCA*m absent	0 (0.0)	1 (0.5)[b]	0 (0.0)	1 (0.5)	137 (66.8)	139 (67.8)
Total	29 (14.1)	15 (7.3)	0 (0.0)	8 (3.9)	153 (74.6)	205 (100.0)

Note: Values are *n* (%).

Abbreviations: VUS, variant of uncertain significance.

[a]Somatic *BRCA*m ($n = 13$).

[b]g*BRCA*m without the detection of t*BRCA*m ($n = 2$).



	tBRCAm present	tBRCAm absent	tBRCA VUS
Q3	71.0	64.0	72.0
Median	66.0	42.0	61.0
Q1	55.0	21.0	26.0

FIGURE 3 Genomic instability score distribution by tumor *BRCA* mutation (t*BRCA*m) present, absent, or variant of uncertain significance (VUS) status in the per-protocol set of Japanese patients with advanced ovarian cancer. Circles indicate each patient by mutation. In the box plot, the box height indicates the interquartile range, with the first quartile (Q1) at the bottom and third quartile (Q3) at the top. The midline indicates the median.

than 50 years had t*BRCA*m and g*BRCA*m and were HRD positive. In this age group, the prevalence of t*BRCA*m was 36.6% (15/41), and that of g*BRCA*m was 29.3% (12/41), while 68.3% (28/41) were HRD positive. Among premenopausal women, the prevalence of t*BRCA*m, g*BRCA*m, and HRD positivity was 37.3% (19/51), 31.4% (16/51), and 66.7% (34/51), respectively, which were numerically higher than in postmenopausal women. By type of cancer, the prevalence of t*BRCA*m was highest among patients with epithelial ovarian cancer (28.1%, 48/171), followed by fallopian tube cancer (21.4%, 3/14) and primary peritoneal cancer (20.0%, 4/20) with similar prevalence. g*BRCA*m was more prevalent among patients with epithelial ovarian cancer (22.8%, 39/171) and fallopian tube cancer (21.4%, 3/14) than those with primary peritoneal cancer (10.0%, 2/20). No numerical differences were observed in the prevalence of HRD-positive status across all three cancer types. By cancer histology, the prevalence of t*BRCA*m, g*BRCA*m, and HRD-positive status were highest in high-grade serous carcinoma (30.1% [49/163], 24.5% [40/163], and 66.9% [109/163], respectively), followed by endometrioid carcinoma (15.4% [4/26], 11.5% [3/26], and 34.6% [9/26]), and clear cell carcinoma (7.7% [1/13], 7.7% [1/13], and 23.1% [3/13]). No numerical differences were observed in the prevalence of t*BRCA*m, g*BRCA*m, or HRD-positive status between FIGO stages III and IV.

TABLE 2 Prevalence of tumor *BRCA* mutation (t*BRCA*m), germline *BRCA* mutation (g*BRCA*m), and homologous recombination deficiency (HRD) by patient and ovarian cancer characteristics in the per-protocol set

		t*BRCA*m		g*BRCA*m		HRD		
	n = 205[a]	Present	Not present[b]	Present	Not present[b]	Positive	Negative	Failed
Patient factors								
Age, years								
<50	41	15 (36.6)	26 (63.4)	12 (29.3)	29 (70.7)	28 (68.3)	10 (24.4)	3 (7.3)
≥50 to <65	84	24 (28.6)	60 (71.4)	21 (25.0)	63 (75.0)	54 (64.3)	23 (27.4)	7 (8.3)
≥65	80	16 (20.0)	64 (80.0)	11 (13.8)	69 (86.3)	41 (51.3)	33 (41.3)	6 (7.5)
Menopausal status								
Postmenopausal	151	36 (23.8)	115 (76.2)	28 (18.5)	123 (81.5)	89 (58.9)	52 (34.4)	10 (6.6)
Premenopausal	51	19 (37.3)	32 (62.7)	16 (31.4)	35 (68.6)	34 (66.7)	11 (21.6)	6 (11.8)
Unknown	3	0 (0.0)	3 (100.0)	0 (0.0)	3 (100.0)	0 (0.0)	3 (100.0)	0 (0.0)
Ovarian cancer factors								
Cancer type								
Epithelial ovarian	171	48 (28.1)	123 (71.9)	39 (22.8)	132 (77.2)	106 (62.0)	52 (30.4)	13 (7.6)
Primary peritoneal	20	4 (20.0)	16 (80.0)	2 (10.0)	18 (90.0)	10 (50.0)	8 (40.0)	2 (10.0)
Fallopian tube	14	3 (21.4)	11 (78.6)	3 (21.4)	11 (78.6)	7 (50.0)	6 (42.9)	1 (7.1)
Histology								
High-grade serous carcinoma	163	49 (30.1)	114 (69.9)	40 (24.5)	123 (75.5)	109 (66.9)	41 (25.2)	13 (8.0)
Endometrioid carcinoma	26	4 (15.4)	22 (84.6)	3 (11.5)	23 (88.5)	9 (34.6)	15 (57.7)	2 (7.7)
Clear cell carcinoma	13	1 (7.7)	12 (92.3)	1 (7.7)	12 (92.3)	3 (23.1)	9 (69.2)	1 (7.7)
Others	3	1 (33.3)	2 (66.7)	0 (0.0)	3 (100)	2 (66.7)	1 (33.3)	0 (0.0)
FIGO stage								
III	137	36 (26.3)	101 (73.7)	28 (20.4)	109 (79.6)	85 (62.0)	42 (30.7)	10 (7.3)
IV	68	19 (27.9)	49 (72.1)	16 (23.5)	52 (76.5)	38 (55.9)	24 (35.3)	6 (8.8)

Note: Values are *n* (%) unless otherwise stated.

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

[a]Per-protocol set.

[b]No mutation present was defined as having a gene test result of variant of uncertain significance or mutation absent.

Table S4 shows the prevalence of t*BRCA*m by patients with a medical history. Among 18 patients with a medical history of breast cancer, 50.0% (9/18) had t*BRCA1*m and 5.6% (1/18) had t*BRCA2*m.

Table S5 shows the prevalence of t*BRCA*m by family history of cancer. Of 30 patients with a family history of breast cancer, 40.0% (12/30) had t*BRCA1*m and 16.7% (5/30) had t*BRCA2*m. Of 17 patients with a family history of ovarian cancer, 58.8% (10/17) had t*BRCA1*m and 17.6% (3/17) had t*BRCA2*m.

4 | DISCUSSION

To the best of our knowledge, this is the first observational study to determine the prevalence of t*BRCA*m, s*BRCA*m, and HRD-positive status among Japanese patients with advanced ovarian cancer. In this study, the prevalence of t*BRCA*m was 26.8%, that of g*BRCA*m was 21.5%, and that of s*BRCA*m was 6.3%; the calculated s*BRCA*m / t*BRCA*m ratio was 23.6%. The HRD prevalence among Japanese patients with advanced ovarian cancer was 60.0%; HRD was negative in 32.2% and unknown in 7.8% of patients. The median HRD score in HRD-positive and t*BRCA*m-negative patients was 42.0, indicating that half of this cohort was HRD positive, which would be missed by t*BRCA*m testing alone. Therefore, it is important to assess HRD status regardless of the presence or absence of t*BRCA*m. The prevalence of t*BRCA*m (26.8%) found in this study is consistent with previously reported prevalence data ranging from 19% to 24%.[15,31,32] Of note, these studies had heterogeneous patient populations in terms of stage and primary or recurrent disease. Additionally, the cohort in this study had already undergone g*BRCA* testing in the real-world setting, and selection bias for g*BRCA* testing is possible. A similar prevalence was reported in other phase III multinational trials, such as the PAOLA-1 trial (prevalence of t*BRCA*m of 29.9%),[25] the PRIMA trial (prevalence of t*BRCA*m of 30.4%),[33] and the VELIA trial (prevalence of t*BRCA*m of 26.1%),[34] which included a large number of patients with stage III and IV ovarian cancer. However, the inclusion criteria

in some of these studies were defined by platinum sensitivity and other factors that might have affected the rate of HRD and t*BRCA*m. The prevalence of g*BRCA*m (21.5%) was also consistent with previous reports, including our Japanese study, the advanced ovarian cancer cohort in the CHARLOTTE study (24.1%),[14] and the PAOLA-1 trial (19.3%) in a French cohort,[18] among others.[15,32]

The prevalence of s*BRCA*m (6.3%) observed in the present Japanese cohort is also supported by the prevalence reported in previous overseas studies, ranging from 3% to 7.5%.[15,18,19,30,32] Overall, 13 of 55 patients (23.6%) with a t*BRCA*m had the mutation in somatic tumor tissues.

Results from the tumor tissue testing show that HRD-positive status was 60.0%; this is consistent with the results of the PRIMA and PAOLA-1 trials,[25,33] which reported HRD-positive status in approximately 50% of patients. Of note, the percentage of patients with both HRD-positive and t*BRCA*m-negative status overall was 33.2%, which is higher than previously reported (PRIMA: niraparib, 19.5% [95/487] and placebo, 22.4% [55/246]; PAOLA-1: olaparib + bevacizumab, 19.4% [104/537] and placebo + bevacizumab, 23.4% [63/269]).[25,33] Although our study includes patients regardless of platinum sensitivity, this suggests that the ratio of t*BRCA*m-negative/HRD-positive patients might be higher in Japan. As two-thirds of the patients with HRD-positive status were not identified by g*BRCA* testing, these patients would likely not receive PARP inhibitors, even though they are recommended in the first-line setting for ovarian cancer with g*BRCA*m and HRD-positive status and t*BRCA*m.

For two patients, g*BRCA* testing was positive, whereas t*BRCA* testing was negative. As per the concordance of data between t*BRCA* and g*BRCA* status in the PAOLA-1 trial,[18] one patient had a positive g*BRCA* test, but a negative t*BRCA* test. The reason for this discrepancy could be that different methods were used to assess the status of each; g*BRCA*m status was analyzed by BRACAnalysis using Sanger sequencing and multiplex PCR, whereas t*BRCA*m and HRD score were analyzed using Myriad myChoice, which is based on next-generation sequencing.

The data from this patient revealed the presence of a large genomic rearrangement (LGR) consisting of the deletion of exons 1 and 2 of the *BRCA1* gene. In the CHRISTELLE study, an uncharacterized LGR of *BRCA2* was observed in one of the patients who was g*BRCA2*m positive. Additionally, one other patient had an LGR of *BRCA1*. A previous study suggested that chemotherapy can affect intratumoral heterogeneity and HRD prevalence.[35] However, these patients did not receive neoadjuvant chemotherapy, and it is unlikely that chemotherapy affected their t*BRCA* status. Therefore, the presence of LGR might affect the detection of t*BRCA*m, and the presence of g*BRCA*m could be overlooked without g*BRCA* testing. Again, this might be because of the different methods used in each test. Additionally, the timings of sample collections were not always simultaneous for g*BRCA*m and t*BRCA*m, and the blood sample collection for g*BRCA*m was flexible in this study.

In 7.8% of patients in this study, HRD presence was unknown or failed. The failure rate was relatively lower than reported previously, with 18% in the PAOLA-1 trial[25] and 15% in the PRIMA trial.[33] This finding suggests that stocked samples are appropriate for HRD testing in a real-world setting.

The distribution of the genomic instability score sorted by patients with mutations, without mutations, or VUS in t*BRCA* and g*BRCA* showed some tendencies in each group. Among patients with t*BRCA*m present (median HRD score, 66.0), those with a genomic instability score ≥42 represented the majority of the population, which is consistent with previously reported data.[27] Among patients with t*BRCA*m absent, the distribution of genomic instability scores was bimodal and varied widely. It could be that several patients were categorized as HRD negative due to having a genomic instability score just below the cut-off value. Furthermore, some patients with t*BRCA*m absent had high genomic instability scores, indicating that a high HRD prevalence did not necessarily predict *BRCA*m. For patients with g*BRCA*m absent, the genomic instability scores also varied widely and had a bimodal distribution. Furthermore, some samples presented a high genomic instability score despite g*BRCA* being negative. These high HRD scores in patients with no *BRCA*m could indicate genomic instabilities in genes other than *BRCA*, or instabilities that might not yet be detected as mutations in *BRCA*. Based on these findings, determining HRD prevalence might lead to the treatment of advanced ovarian cancer patients despite the absence of g*BRCA*m.

One of the main strengths of this study is that it achieved consecutive enrollment at 20 sites with well-balanced locations across Japan, which helps minimize bias due to location. Furthermore, 94.9% of patients who were enrolled in this study were included in analysis. As 99.0% of cases were surviving patients, there was no bias toward death cases. In the central pathology assessment, approximately 70% of the cases were consistent among the three pathologists, and the remaining cases were consistent as a result of their consultation. In terms of the external validity, the demographics and background characteristics of patients enrolled in the CHRISTELLE study were consistent with those reported by the National Cancer Registration.[36] Furthermore, the target sample size was met, ensuring an accurate estimation of the results.

However, this study has some limitations. Selection bias could have occurred as physicians may have suspected hereditary breast and ovarian cancer syndrome for many of the patients enrolled, because eligible patients were to have undergone or were scheduled to undergo BRACAnalysis. The timing of g*BRCA*m testing and t*BRCA*m/HRD testing was not controlled by the study protocol. The status of g*BRCA*m was obtained from the result of the Myriad BRACAnalysis test, undertaken for patients at each site in usual practice. This means that the timings of Myriad BRACAnalysis tests varied among patients, which could have caused a variation in the results of the g*BRCA*m analysis (e.g., variant first judged as "VUS" might have been changed to "deleterious" or "suspected deleterious" after the Myriad BRACAnalysis test). Additionally, a change of mutation status between two gene tests within a patient could not be analyzed in this study. However, samples for g*BRCA*m testing and for t*BRCA*m/HRD testing were collected from January 2019 to November 2020; therefore, testing was not separated by more than 2 years. We did not evaluate genetic sequences from

g*BRCA*. Thus, the concordance of the mutated sequence between g*BRCA* and t*BRCA* was not evaluated. In addition, this study did not measure the presence of homologous recombination repair mutations or promoter hypermethylation of *BRCA1* or *RAD51C*, which can cause HRD. Further studies will be necessary to investigate these aspects of ovarian cancer in Japan.

In this study, t*BRCA*m was observed in 55 (26.8%) out of 205 Japanese patients with FIGO stage III and IV ovarian cancer, g*BRCA*m was observed in 44 (21.5%), and HRD-positive status was observed in 123 (60.0%). The prevalence of s*BRCA*m was 6.3%. Notably, one in four to five patients with ovarian cancer and t*BRCA*m could be positive for s*BRCA*m. Furthermore, most HRD-positive patients were not identified by g*BRCA* testing. These results suggest g*BRCA* testing alone cannot clearly identify the best course of treatment, highlighting the importance of s*BRCA* testing in Japan. The present results also suggest that testing for t*BRCA* and HRD should be encouraged in advanced ovarian cancer patients to drive precision medicine.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization, methodology, and writing, reviewing and editing the manuscript. Katsutoshi Oda, Daisuke Aoki, Hitoshi Tsuda, Hiroshi Nishihara, Muneaki Shimada, and Takayuki Enomoto contributed to data presentation and visualization. Hisanori Aoyama contributed to project administration and writing the original draft. Hyoe Inomata contributed to funding acquisition. Takayuki Enomoto supervised the research planning and execution.

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DISCLOSURE

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DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

ETHICS STATEMENT

Approval of the research by an institutional review board: This study was approved by the ethics committee of each participating institution as well as a central independent ethics committee (Non-Profit Organization MINS Institutional Review Board, approval ID: MINS-REC-190248) and performed in accordance with the Declaration of Helsinki, the ethical guidelines specified in the International Conference on Harmonization Guideline for Good Clinical Practice, the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and the Ethical Guidelines for Human Genome and Genetic Analysis Research.

Informed consent: All participants gave informed consent prior to enrollment.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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