


# Association of gBRCA1/2 mutation locations with ovarian cancer risk in Japanese patients from the CHARLOTTE study

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## Abstract

Whether germline (g) breast cancer susceptibility gene (BRCA) mutations are located within or outside the ovarian cancer cluster region (OCCR) (1380-4062 bp for gBRCA1, and between 3249-5681 bp and 6645-7471 bp for gBRCA2) may influence risk variations for ovarian cancers. This ad hoc analysis of the CHARLOTTE epidemiological study in Japan assessed the distribution of gBRCA1/2 mutations in patients with newly diagnosed ovarian cancer, and investigated an association between gBRCA1/2 mutation locations and ovarian cancer risk. Differences in patient background and clinical characteristics in subgroups stratified by gBRCA1/2 mutation locations were also evaluated. We analyzed the data of 93 patients (14.7%) from the CHARLOTTE study who were positive for gBRCA1/2 mutations. After excluding 16 cases with L63X founder mutation, 28 (65.1%) of gBRCA1 mutations were within the OCCR. Of 30 gBRCA2 mutations, 15 (50.0%) were within the OCCR. Of 27 patients (one patient excluded for unknown family history) with gBRCA1 mutations located in the OCCR, 11 (40.7%) had a family history of ovarian cancer; the proportion of patients with a family history of ovarian cancer and gBRCA1 mutations outside the OCCR was lower (13.3%). Sixty percent of patients with gBRCA1 mutations outside the OCCR had a family history of breast cancer; the proportion of patients with a family history of breast cancer and gBRCA1 mutations within the OCCR was relatively lower (33.3%). Understanding the mutation locations may contribute to more accurate risk assessments of susceptible individuals and early detection of ovarian cancer among gBRCA mutation carriers.

## KEYWORDS

BRCA1 gene, BRCA2 gene, mutation, ovarian cancer, ovarian cancer cluster region

**Abbreviations:** BCCR, breast cancer cluster region; BRCA1, breast cancer susceptibility gene 1; BRCA2, breast cancer susceptibility gene 2; FIGO, International Federation of Gynecology and Obstetrics; g, germline; m, mutation; OB, oligonucleotide binding; OCCR, ovarian cancer cluster region; SAS, Statistical Analysis Software.

**Clinical trial registration:** ClinicalTrials.gov, NCT03229122; University hospital Medical Information Network Clinical Trials Registry, UMIN000025597

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## 1 | INTRODUCTION

Ovarian cancer is the 7th most common cancer in women, with an estimated 239 000 new cases and 152 000 deaths worldwide per annum.<sup>1</sup> It has been estimated that approximately 1.3% of women in the general population will develop ovarian cancer at some point in their lives.<sup>2</sup>

Breast cancer susceptibility gene 1 (*BRCA1*) and *BRCA2*<sup>3</sup> encode proteins *BRCA1* and *BRCA2*, which play important roles in DNA repair, transcriptional regulation in response to DNA damage, maintenance of chromosomal stability, and regulation of the cell cycle and apoptosis.<sup>3</sup> Germline (g) mutations of these genes are associated with a well established high risk of developing breast and ovarian cancer.<sup>4–9</sup> It has been recently estimated that approximately 44% of women who inherit *gBRCA1* mutations and approximately 17% of those who inherit *gBRCA2* mutations will develop ovarian cancer by 80 y of age.<sup>6</sup> It has also been reported that the spectrum of *gBRCA1/2* mutations in breast and ovarian cancer patients also varies across different races and ethnicities.<sup>10–12</sup>

The importance of *gBRCA* mutation testing is growing as the *gBRCA1/2* status is not only important for breast/ovarian cancer risk assessment, but also for the selection of therapy.<sup>13</sup> Recent studies<sup>6,8,14</sup> have shown the importance of estimating cancer risk among individuals with a family history of ovarian or breast cancer by *gBRCA* testing before the onset of cancer. Data from the SOLO1 study, in which women with *BRCA1/2*-mutated advanced ovarian cancer were randomly assigned to receive olaparib or placebo after first-line chemotherapy, reported a 70% reduction in the hazard risk for disease progression or death with olaparib after a median follow-up of 41 mo.<sup>15</sup> A clinical benefit of this magnitude is likely to change the clinical treatment algorithm for this patient population,<sup>16</sup> and these data are of critical interest to physicians.

In addition to knowing the *gBRCA* mutation status, it is important to assess the location of the mutation to estimate the risk for certain cancers. A recent observational study on a large sample of women with ovarian and breast cancer and *gBRCA1/2* mutations showed that the risk of developing breast and ovarian cancer varied by the type and location of the mutation.<sup>8</sup> In a previous study, Rebbeck et al identified an ovarian cancer cluster region (OCCR) that was associated with a relative decrease and an increase in the risks of breast and ovarian cancers, respectively.<sup>8</sup>

The CHARLOTTE (Characterizing the cross-sectional approach to ovarian cancer: Genetic testing of *BRCA*) study evaluated the prevalence of *gBRCA1/2* mutations in Japanese patients with ovarian cancer, and reported the prevalence of 9.9% and 4.7% for *gBRCA1* and *gBRCA2* mutations, respectively, in 634 patients.<sup>14</sup> Additionally, this study has shown that there was a slightly higher prevalence of *gBRCA* mutations in patients with high-grade serous carcinoma and a family history of ovarian cancer. However, the prevalence of *gBRCA1/2* mutations within the OCCR has never been evaluated in Japanese ovarian cancer patients, highlighting the importance of this analysis. Furthermore, the most common sites of *gBRCA1/2* mutations in ovarian cancer patients, and the

relationship between family history and *gBRCA* mutation site, remain to be clarified.

Based on the previously reported OCCR,<sup>8</sup> this ad hoc analysis aimed to assess the prevalence of the *gBRCA* mutation according to its location inside or outside the OCCR, using data from patients in the Japanese CHARLOTTE study. Additionally, we aimed to evaluate patient background characteristics and their family history stratified by *gBRCA* mutation locations.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and data sources

The CHARLOTTE study was a collaborative cross-sectional study (NCT03229122; UMIN000025597) involving 63 study sites throughout Japan, and the methodology and primary analysis have been described previously.<sup>14</sup> The study was conducted in accordance with the principles of the Declaration of Helsinki, and ethical approval was obtained from the institutional review board of each participating institution. Written informed consent was obtained from all patients for study participation and histopathological analysis.

The present ad hoc analysis was based on anonymized patient data collected during the CHARLOTTE study,<sup>14</sup> including patient demographics and clinical characteristics (medical history, medications, menopausal status, obstetric history, and blood biochemical testing) and ovarian cancer data (date of diagnosis, pathological and histological classification, type and grade on diagnosis, and International Federation of Gynecology and Obstetrics [FIGO] classification).

The procedures conducted during the CHARLOTTE study have been described previously.<sup>14</sup> Briefly, testing of patient blood samples for the presence or absence of *gBRCA* mutations and mutation locations was performed centrally using BRACAnalysis® by Myriad Genetics, Inc. The histological diagnosis was confirmed centrally by a pathologist assigned by the Japanese Gynecologic Oncology Group using hematoxylin and eosin slide specimens from tumor tissues. Only deleterious or suspected deleterious mutations were defined as *gBRCA* mutations. All patients had undergone pre-genetic testing counseling by a trained obstetrician-gynecologist or oncologist, clinical geneticist, or certified genetic counselor.

### 2.2 | Patients

In the CHARLOTTE study,<sup>14</sup> patients were selected in serial order to avoid selection bias. Japanese women aged ≥20 y with newly diagnosed, histologically confirmed FIGO stage I-IV ovarian cancer, based on surgically resected specimens, and with histological specimens evaluated by central pathological review were included in the CHARLOTTE study.<sup>14</sup>

Grounds for exclusion were acute or chronic medical disease, mental illness, histological classification of the surgically resected

specimen, and if participation in the study was judged to be inappropriate by the investigator. The present ad hoc analysis focused on the subgroup of patients with confirmed *gBRCA1* and *gBRCA2* mutations; patients with exon deletion were not included in this analysis.

## 2.3 | Study outcomes

The study outcomes were the prevalence of *gBRCA1/2* mutations in patients with newly diagnosed ovarian cancer by the location of *gBRCA* mutations within and outside the OCCR, which were between 1380 and 4062 bp for *gBRCA1*, and between 3249–5681 bp and 6645–7471 bp for *gBRCA2*.<sup>8</sup> The patient background and clinical characteristics in subgroups stratified by the location of *gBRCA* mutations were also evaluated. Ovarian cancer patients with *gBRCA1* founder mutation (L63X) were analyzed as a subgroup.<sup>17</sup>

## 2.4 | Additional analysis

A further analysis was conducted to determine the location of *gBRCA* mutations within and outside the OCCR using previously reported breast cancer prevalence data from 7051 breast cancer patients and 11 241 female controls of Japanese ancestry.<sup>18</sup> In that study, 102 patients were positive for *gBRCA1* mutations and 191 patients were positive for *gBRCA2* mutations.

## 2.5 | Statistical methods

Details of the statistical analysis have been previously described in the main report of the CHARLOTTE study.<sup>14</sup> Demographic and clinical characteristic data are shown using descriptive statistics, with *n* (%) for categorical variables and mean  $\pm$  SD for continuous variables. The statistical software used for the ad hoc analysis was Statistical Analysis Software (SAS) 9.4 (SAS Institute).

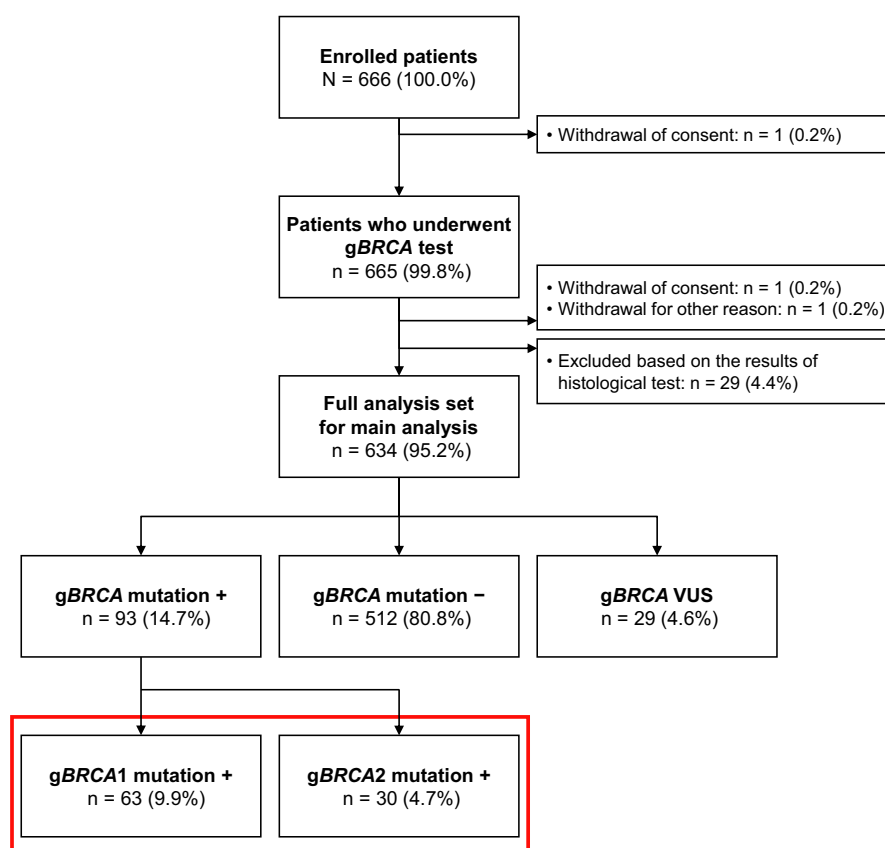
## 3 | RESULTS

### 3.1 | Study flow

Of the 666 patients enrolled in the CHARLOTTE study, 665 patients underwent *gBRCA* testing and 634 patients were evaluated (Figure 1). This ad hoc analysis focused on the data of 93 patients (14.7%); 63 patients were positive for *gBRCA1* mutations and 30 patients were positive for *gBRCA2* mutations.

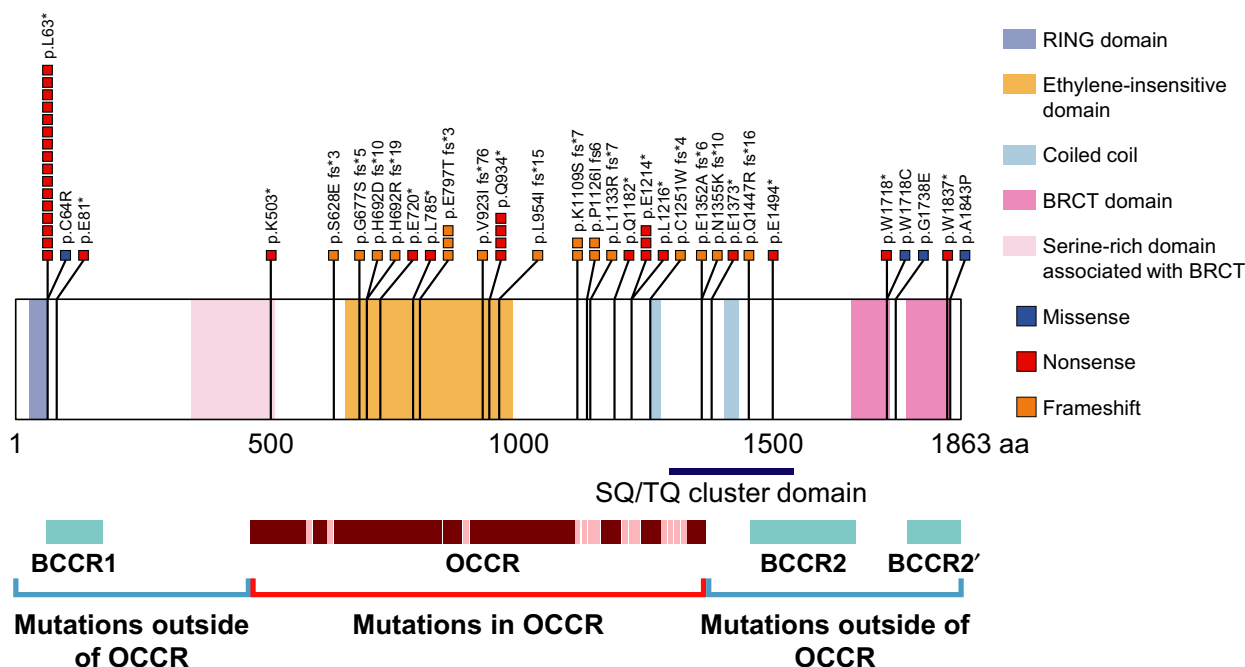
### 3.2 | Prevalence of *gBRCA1/2* mutation by location

Among the 93 patients positive for *gBRCA1* or *gBRCA2* mutations, the overall prevalence of *gBRCA1* mutation was 9.9% and that of *gBRCA2* mutation was 4.7% (Figure 1).

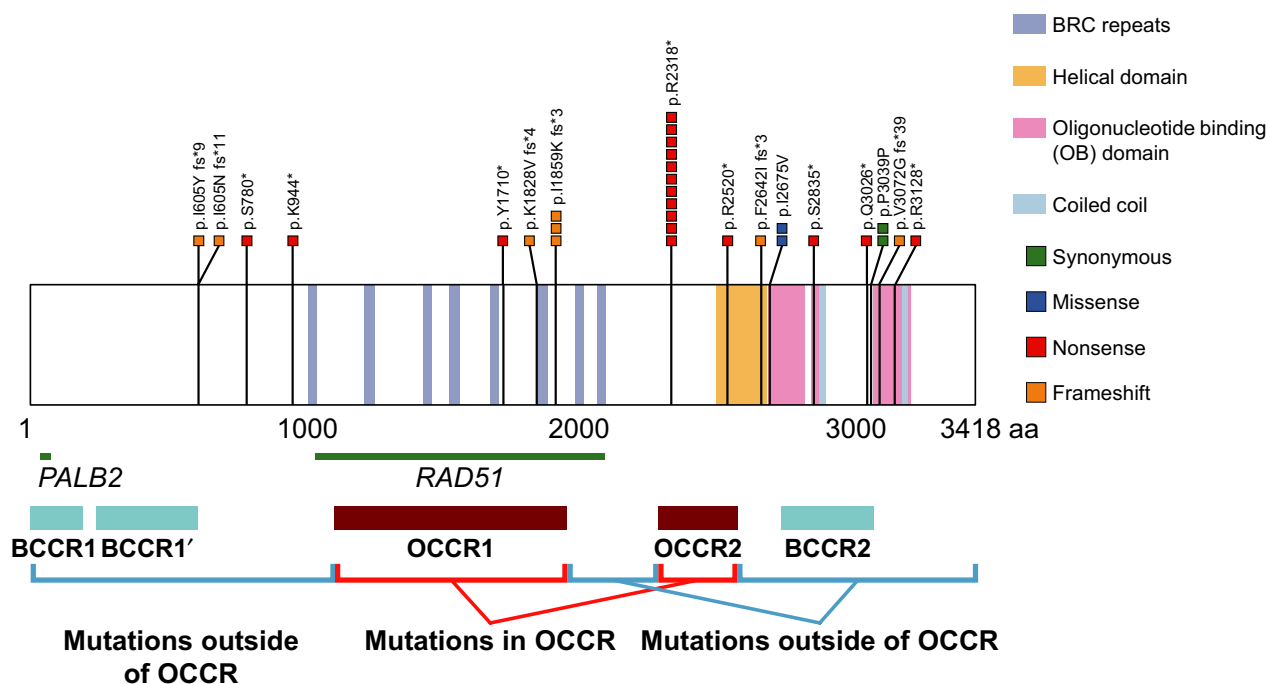


**FIGURE 1** Study flow. BRCA, breast cancer susceptibility gene; g, germline; VUS, variants of uncertain significance. The red box encloses the 2 groups of patients included in the present analysis, corresponding to the patients enrolled in the CHARLOTTE study who were positive for *gBRCA1/2* mutations

(A)

**gBRCA1<sup>†</sup>**

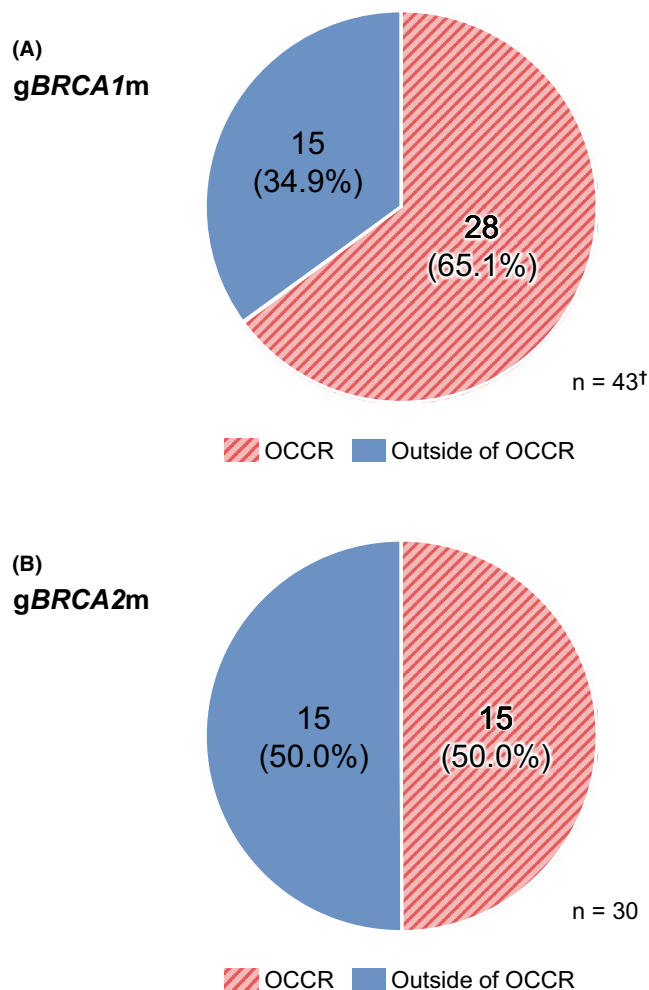
(B)

**gBRCA2**

**FIGURE 2** Prevalence of (A) gBRCA1<sup>†</sup> and (B) gBRCA2 mutations by location. Adapted from Rebbeck et al. JAMA. 2015;313:1347-1361. <sup>†</sup>Four patients with silent gBRCA1 mutations (exon deletion) are not indicated in the figure. aa, amino acid; BCCR, breast cancer cluster region; BRCA, breast cancer susceptibility gene; BRCT, BRCA1 C-terminal; g, germline; OB, oligonucleotide binding; OCCR, ovarian cancer cluster region; PALB2, partner and localizer of BRCA2; RAD51, RAD51 recombinase; RING, really interesting new gene

Figure 2A,B show the prevalence of *gBRCA1* and *gBRCA2* mutations according to their locations, ie, inside or outside the OCCR. For *gBRCA1*, the mutations were largely concentrated in the middle of the OCCR. For *gBRCA2*, the most frequent mutation was the R2318\* nonsense mutation within the OCCR.

Among ovarian cancer patients with *gBRCA1* mutation, when excluding 16 patients with L63X founder mutation and 4 with silent mutations, 65.1% (28/43) were distributed within the OCCR and 34.9% (15/43) were distributed outside of the OCCR (Figure 3A). When including patients with the founder mutation (27.1%, 16/59), the prevalence of *gBRCA1* mutations within the OCCR was 47.5% (28/59) and outside the OCCR was 25.4% (15/59) (Figure S1a). Among ovarian cancer patients with *gBRCA2* mutation, 50.0% were distributed within the OCCR and 50.0% were distributed outside of the OCCR (Figure 3B).



**FIGURE 3** Prevalence of (A) *gBRCA1* and (B) *gBRCA2* mutations by location in the 93 newly diagnosed Japanese ovarian cancer patients from the CHARLOTTE study who were positive for mutations. †Four patients with silent *gBRCA1* mutations (exon deletion) are not indicated in the figure; 16 patients with L63X founder mutation are also excluded. BRCA, breast cancer susceptibility gene; OCCR, ovarian cancer cluster region

### 3.3 | Patient background and clinical characteristics in subgroups stratified by *gBRCA* mutation locations

Table 1 shows patient background and clinical characteristics in subgroups stratified by *gBRCA* mutation locations. No marked difference was found in patient age, birth history, disease stage, histopathological classification, history of breast cancer, and family history of prostate and pancreatic cancers, by mutation site. Approximately half of the patients at stage IV had *gBRCA* mutations located within the OCCR and half had *gBRCA* mutations outside the OCCR.

Among patients with *gBRCA1* mutations, 40.7% and 33.3% of patients with mutations within the OCCR had a family history of ovarian cancer and breast cancer, respectively. Meanwhile, 13.3% and 60.0% of patients with mutations outside of the OCCR had a family history of ovarian cancer and breast cancer, respectively (Table 2). Among patients with *gBRCA1* mutations and a family history of ovarian cancer, the percentage of patients with mutations within the OCCR was larger (40.7%) compared with that outside the OCCR (13.3%). Among patients with *gBRCA1* mutations and a family history of breast cancer, the percentage of mutations within the OCCR was relatively smaller (33.3%) than that outside the OCCR (60.0%).

Figure S2 shows the geographic distribution of patients by the location of their mutations within the OCCR. Almost all cases with *gBRCA1* L63X founder mutation (15/16) were treated at centers in eastern Japan. For *gBRCA2* mutation, the proportions of patients with mutations outside and inside the OCCR were the same in both the East and West of Japan.

### 3.4 | Prevalence of *gBRCA1/2* mutations by location in 7051 Japanese breast cancer patients from the study by Momozawa et al<sup>18</sup>

Figure 4A shows the prevalence of *gBRCA1* mutations within the OCCR and outside the OCCR in a large sample of Japanese breast cancer patients. Most *gBRCA1* mutations (62.3%) were outside the OCCR. When accounting for 25 cases (24.5%) with L63X founder mutation, 28.4% and 47.1% of mutations were located inside and outside of the OCCR, respectively (Figure S1b). Figure 4B shows the prevalence of *gBRCA2* mutations within the OCCR and outside the OCCR. The distribution of *gBRCA2* mutations within the OCCR and outside the OCCR was similar, with a slightly higher prevalence of *gBRCA2* mutations outside the OCCR (52.4%).

## 4 | DISCUSSION

The main purpose of this ad hoc analysis was to report the prevalence of *gBRCA1* and *gBRCA2* mutations within and outside the OCCR using data from newly diagnosed Japanese ovarian cancer patients from the CHARLOTTE study.<sup>14</sup> To the best of our knowledge, this is the first study to report the prevalence of *gBRCA1* and

**TABLE 1** Prevalence of gBRCA1/2 mutations in subgroups stratified by gBRCA mutation location and patient background and clinical characteristics

	gBRCA mutations				gBRCA1 mutations <sup>a</sup>			gBRCA2 mutations	
	Present	gBRCA1 only	gBRCA2 only	Absent	Inside the OCCR	Outside the OCCR	Founder mutation (L63X)	Inside the OCCR	Outside the OCCR
All, n	93	63	30	512	28	15	16	15	15
Age, y									
20-29	0	0	0	4 (0.8)	0	0	0	0	0
30-39	3 (3.2)	3 (4.8)	0	29 (5.7)	1 (3.6)	1 (6.7)	1 (6.3)	0	0
40-49	24 (25.8)	19 (30.2)	5 (16.7)	113 (22.1)	8 (28.6)	5 (33.3)	6 (37.5)	3 (20.0)	2 (13.3)
50-59	22 (23.7)	16 (25.4)	6 (20.0)	153 (29.9)	8 (28.6)	3 (20.0)	3 (18.8)	3 (20.0)	3 (20.0)
60-69	37 (39.8)	20 (31.7)	17 (56.7)	136 (26.6)	7 (25.0)	6 (40.0)	5 (31.3)	8 (53.3)	9 (60.0)
70-79	5 (5.4)	3 (4.8)	2 (6.7)	66 (12.9)	3 (10.7)	0	0	1 (6.7)	1 (6.7)
≥80	2 (2.2)	2 (3.2)	0	11 (2.1)	1 (3.6)	0	1 (6.3)	0	0
≤40	4 (4.3)	4 (6.3)	0	36 (7.0)	2 (7.1)	1 (6.7)	1 (6.3)	0	0
≥41	89 (95.7)	59 (93.7)	30 (100.0)	476 (93.0)	26 (92.9)	14 (93.3)	15 (93.8)	15 (100.0)	15 (100.0)
≤49	27 (29.0)	22 (34.9)	5 (16.7)	146 (28.5)	9 (32.1)	6 (40.0)	7 (43.8)	3 (20.0)	2 (13.3)
≥50	66 (71.0)	41 (65.1)	25 (83.3)	366 (71.5)	19 (67.9)	9 (60.0)	9 (56.3)	12 (80.0)	13 (86.7)
≤64	63 (67.7)	46 (73.0)	17 (56.7)	368 (71.9)	21 (75.0)	11 (73.3)	11 (68.8)	8 (53.3)	9 (60.0)
≥65	30 (32.3)	17 (27.0)	13 (43.3)	144 (28.1)	7 (25.0)	4 (26.7)	5 (31.3)	7 (46.7)	6 (40.0)
History of childbirth									
Yes	72 (77.4)	50 (79.4)	22 (73.3)	351 (68.6)	22 (78.6)	13 (86.7)	11 (68.8)	9 (60.0)	13 (86.7)
No	3 (3.2)	2 (3.2)	1 (3.3)	12 (2.3)	1 (3.6)	0	1 (6.3)	1 (6.7)	0
Unknown	18 (19.4)	11 (17.5)	7 (23.3)	149 (29.1)	5 (17.9)	2 (13.3)	4 (25.0)	5 (33.3)	2 (13.3)
Histological classification									
Low-grade serous cancer	1 (1.1)	1 (1.6)	0	4 (0.8)	0	1 (6.7)	0	0	0
High-grade serous cancer	78 (83.9)	53 (84.1)	25 (83.3)	181 (35.4)	24 (85.7)	13 (86.7)	13 (81.3)	12 (80.0)	13 (86.7)
Mucinous cancer	0	0	0	19 (3.7)	0	0	0	0	0
Endometrioid cancer	8 (8.6)	7 (11.1)	1 (3.3)	104 (20.3)	4 (14.3)	1 (6.7)	1 (6.3)	1 (6.7)	0
Clear cell carcinoma	4 (4.3)	2 (3.2)	2 (6.7)	178 (34.8)	0	0	2 (12.5)	1 (6.7)	1 (6.7)
Others	2 (2.2)	0	2 (6.7)	22 (4.3)	0	0	0	1 (6.7)	1 (6.7)
Classification of advanced stage (FIGO 2014)									
I	8 (8.6)	3 (4.8)	5 (16.7)	221 (43.2)	2 (7.1)	0	0	4 (26.7)	1 (6.7)
II	7 (7.5)	7 (11.1)	0	60 (11.7)	3 (10.7)	1 (6.7)	3 (18.8)	0	0
III	62 (66.7)	42 (66.7)	20 (66.7)	170 (33.2)	16 (57.1)	13 (86.7)	11 (68.8)	8 (53.3)	12 (80.0)
IV	16 (17.2)	11 (17.5)	5 (16.7)	58 (11.3)	7 (25.0)	1 (6.7)	2 (12.5)	3 (20.0)	2 (13.3)
Others	0	0	0	3 (0.6)	0	0	0	0	0
Geographic location									
East	58 (62.4)	40 (63.5)	18 (60.0)	268 (52.3)	18 (64.3)	5 (33.3)	15 (93.8)	9 (60.0)	9 (60.0)
West	35 (37.6)	23 (36.5)	12 (40.0)	244 (47.7)	10 (35.7)	10 (66.7)	1 (6.3)	6 (40.0)	6 (40.0)
History of breast cancer									
Yes	14 (15.1)	11 (17.5)	3 (10.0)	16 (3.1)	3 (10.7)	1 (6.7)	6 (37.5)	2 (13.3)	1 (6.7)
No	79 (84.9)	52 (82.5)	27 (90.0)	496 (96.9)	25 (89.3)	14 (93.3)	10 (62.5)	13 (86.7)	14 (93.3)

Note: Data are given as n (%).

Abbreviations: BRCA, breast cancer susceptibility gene; FIGO, International Federation of Gynecology and Obstetrics; OCCR, ovarian cancer cluster region.

<sup>a</sup>Four patients with silent gBRCA1 mutations are not included.



**TABLE 2** Family history of cancer per subgroups stratified by gBRCA1/2 mutation locations

	gBRCA1 mutations <sup>a</sup>		gBRCA2 mutations	
	Inside the OCCR	Outside the OCCR	Inside the OCCR	Outside the OCCR
<b>n</b>	<b>27<sup>b</sup></b>	<b>15</b>	<b>15</b>	<b>15</b>
Family history				
Ovarian cancer				
Yes	11 (40.7)	2 (13.3)	1 (6.7)	2 (13.3)
No	16 (59.3)	13 (86.7)	14 (93.3)	13 (86.7)
Breast cancer				
Yes	9 (33.3)	9 (60.0)	5 (33.3)	6 (40.0)
No	18 (66.7)	6 (40.0)	10 (66.7)	9 (60.0)
Prostate cancer				
Yes	1 (3.7)	2 (13.3)	1 (6.7)	1 (6.7)
No	26 (96.3)	13 (86.7)	14 (93.3)	14 (93.3)
Pancreatic cancer				
Yes	2 (7.4)	2 (13.3)	3 (20.0)	1 (6.7)
No	25 (92.6)	13 (86.7)	12 (80.0)	14 (93.3)

Note: Data are given as n (%).

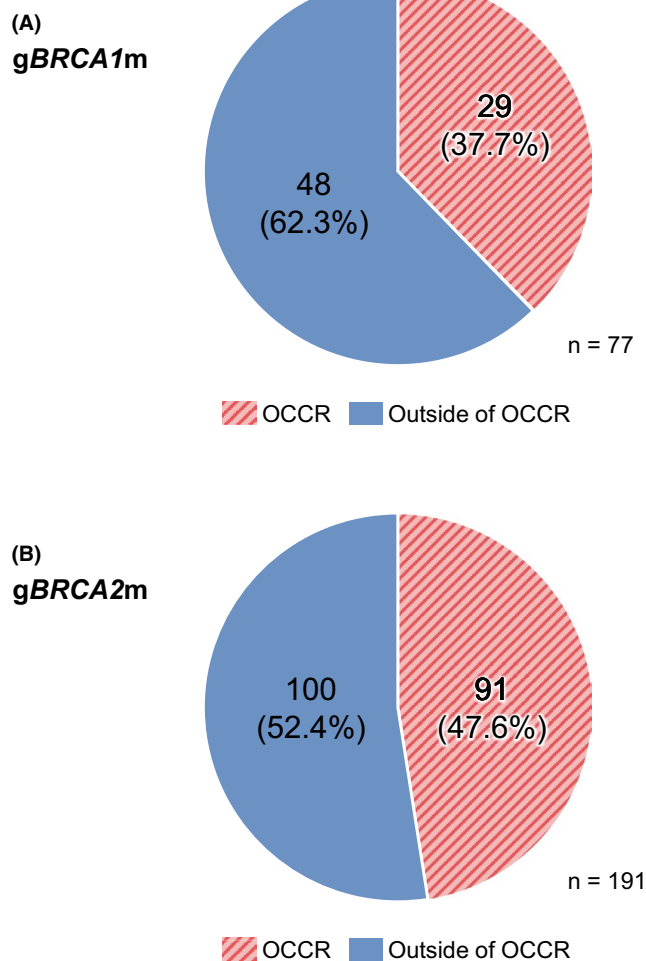
<sup>a</sup>Data of 16 patients with founder mutation (L63X) are not shown.

<sup>b</sup>One patient with unknown family history was excluded.

gBRCA2 mutations with respect to the location in and outside the OCCR<sup>8</sup> in Japanese ovarian cancer patients.

The present results show that gBRCA1 mutations, excluding the founder mutation and silent mutations, in this study cohort were more frequently found within the OCCR (65.1%) than outside the OCCR (34.9%). In the case of gBRCA2 mutations, the proportions were evenly split: 50.0% each for within and outside the OCCR. A previous study reported that 71% of gBRCA1 mutations of ovarian cancer patients with or without additional ovarian cancer family history were within the gBRCA1 OCCR, while 29% were located in non-BRCA1 OCCRs.<sup>19</sup> Interestingly, our analysis of the data from a recent large-scale Japanese study<sup>18</sup> showed that gBRCA1 mutations in breast cancer patients were more frequently located outside the OCCR (62.3%, 48/77). In the case of gBRCA2 mutations, the proportions were similar inside and outside the OCCR, but slightly more mutations were outside the OCCR (52.4%, 100/191).

In the present study, for gBRCA1 mutations, patients with mutations located within the OCCR had a higher frequency of family history of ovarian cancer compared with patients with mutations located outside of the OCCR. Furthermore, patients with gBRCA1 mutations outside the OCCR had a higher frequency of family history of breast cancer than patients with mutations within the OCCR. This finding is consistent with a previous report in which ovarian cancer patients with a family history of breast cancer had significantly fewer mutations located within the OCCR.<sup>19</sup> Conversely, there were no apparent differences between gBRCA2 mutations located inside or outside the OCCR for patients with either a family history of ovarian cancer or a family history of breast cancer. This

**FIGURE 4** Prevalence of (A) gBRCA1 and (B) gBRCA2 mutations by location in 7051 patients studied in Momozawa et al.<sup>18</sup> BRCA, breast cancer susceptibility gene; OCCR, ovarian cancer cluster region

finding is not consistent with previously reported results, as significant differences in patterns of distribution have been reported for patients with gBRCA2 mutations located within the OCCR.<sup>19</sup> Moreover, a study in a different population reported that gBRCA2 mutations located within the OCCR conferred different risks of developing breast, ovarian, and prostate cancer compared with other mutations.<sup>20</sup>

Based on the present results, no marked differences were observed in age, histopathological classification, stages, history of breast cancer, or family history of prostate or pancreatic cancers by mutation location. We did not expect the mutation location to affect factors such as stage or histopathological classification. Regarding the history of breast cancer and family history of prostate cancer, the small sample size may have precluded finding any differences according to the location of the mutation in relation to the OCCR. As the incidence of pancreatic cancer is generally low, it may be that family history of pancreatic cancer is not an influential factor in terms of the mutation location in relation to the OCCR.

When analyzed according to the geographic distribution, most patients with the L63X founder mutation were identified in testing centers located in eastern Japan. This tendency was similar to that reported in the study by Sekine et al.<sup>17</sup>

This ad hoc study had some limitations such as small sample size, limited power, and potential biases. As it is based on data from the main CHARLOTTE study,<sup>14</sup> the limitations pertaining to that study also apply here, including that Japanese clinical practices may have limited comparability with those in other countries, and that the varying levels of enrollment across the different sites may confound the regional analyses performed. Another important limitation of the study was the varying number of patients included from different sites; no upper limit was set for the number of patients registered at individual sites, whereas few patients were registered at some sites.

Among Japanese ovarian cancer patients, approximately half of the gBRCA1/2 mutations were located within the OCCR, with some regional differences in eastern vs western Japan. Patients with gBRCA1 mutations located within the OCCR had a higher frequency of family history of ovarian cancer, while those with gBRCA1 mutations located outside the OCCR had a higher frequency of family history of breast cancer. The analysis of gBRCA mutation location is important, as this information may contribute to more accurate risk assessments of susceptible individuals and early detection of ovarian cancer among gBRCA mutation carriers.

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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>.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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