



The first Japanese nationwide multicenter study of *BRCA* mutation testing in ovarian cancer: CHARacterizing the cross-sectional approach to Ovarian cancer geneTic TEsting of *BRCA* (CHARLOTTE)

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HIGHLIGHTS

- The overall prevalence of germline *BRCA1/2* mutations was 14.7% in Japanese patients with ovarian cancer.
- Our data suggest that germline *BRCA* testing should be carried out in all patients with ovarian cancer.
- Most patients were satisfied with pre-test counseling, irrespective of the provider's profession.

ABSTRACT

Introduction *BRCA* gene mutations are associated with hereditary ovarian cancer. *BRCA* plays a key role in genome integrity, and mutations result in an increased risk for ovarian cancer. Although various guidelines recommend *BRCA* testing in patients with ovarian cancer, data on germline *BRCA* (*gBRCA*) mutation frequency in ovarian cancer in Japan are scarce.

Objective This study aimed to determine *gBRCA1/2* mutations in Japanese patients with ovarian cancer, stratified by clinicopathological characteristics, and to assess patients' satisfaction with pre-test genetic counseling.

Methods The CHARLOTTE study (CHARacterizing the cross-sectional approach to Ovarian cancer: geneTic TEsting of *BRCA*; UMIN000025597) is the first large multicenter epidemiological survey of Japanese women, aged ≥ 20 , with newly diagnosed ovarian cancer (epithelial, primary peritoneal, or fallopian tube cancer), with histologically confirmed specimens. Patients were enrolled sequentially and underwent pre-test genetic counseling for *BRCA* testing. Blood samples were centrally tested for the presence or absence of known *gBRCA* mutations. A questionnaire was used to assess patient satisfaction with pre-test genetic counseling.

Results A total of 634 patients with a mean age of 56.9 years were included. Most patients (84.2%) had epithelial ovarian cancer, and 51.1% had FIGO stage III–IV cancer. Nearly all patients (99.5%) received genetic counseling before the *BRCA* testing, either by an obstetrician-gynecologist (42.0%) or a clinical geneticist (42.0%). The overall prevalence of *gBRCA1/2* mutations was 14.7% (93/634), with *gBRCA1* mutations (9.9%) more common than *gBRCA2* mutations (4.7%). High-grade serous carcinoma showed a prevalence of *gBRCA* mutations of 28.5%. Most patients were satisfied with pre-test counseling, irrespective of the service provider's professional position.

Discussion Patients with high-grade serous carcinoma and family history of ovarian cancer had a slightly higher prevalence of *gBRCA* mutations, but none of the subgroups had considerably high *gBRCA* mutation prevalence. These data suggest that *gBRCA* testing should be carried out in all patients with ovarian cancer.

INTRODUCTION

Among breast and ovarian cancers, between 5% and 10% are hereditary.^{1–3} These hereditary cancers are associated with mutations in the *BRCA1* or *BRCA2* genes, which are germline breast cancer susceptibility genes with autosomal dominant inheritance.^{3,4} Functional *BRCA1* and *BRCA2* proteins are present in normal breast and ovarian tissue and are involved in homologous recombination mediated DNA repair with wide-ranging functions in cells, and play a key role in genome integrity.^{5–7} Mutations that interfere with the critical *BRCA* function lead to increased susceptibility and progression of breast and ovarian cancers.⁷

BRCA is a biomarker with clinical significance and has implications for therapy outcomes, drug susceptibility (including that to platinum agents), and prognosis.^{7–11} Various guidelines worldwide, including National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology and the American College of Obstetricians and Gynecologists Guidelines, recommend testing for germline *BRCA* (*gBRCA*) mutations in patients with ovarian cancer.^{12,13}

Data on the frequency of *gBRCA1* and *gBRCA2* mutations in Japanese patients with ovarian cancer are scarce, largely because of the lack of financial coverage for *BRCA* genetic testing by the National Health Insurance system. Research data are also limited in Japan; a few studies have been published,

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but no nationwide large-scale study has been conducted. Sekine et al reported that 45 of 82 Japanese families with a history of ovarian cancer had *gBRCA1/2* mutations.¹⁴ Hirasawa et al reported that among 230 patients with ovarian, fallopian tube, or peritoneal cancer, only 27 patients (11.7%) had *gBRCA1/2* mutations.⁴

This study, CHARLOTTE (CHARacterizing the cross-sectional approach to Ovarian cancer: geneTic TEsting of BRCA), was the first multicenter epidemiological survey conducted to investigate *gBRCA1/2* mutations in Japanese patients with ovarian cancer. The primary objective was to examine the frequency of *gBRCA1/2* mutations in patients with newly diagnosed ovarian cancer. As pre-test explanation and proper genetic counseling are important aspects of patient care, we evaluated patient understanding and satisfaction with this counseling.

METHODS

Study design

This was a collaborative multicenter, large-scale, cross-sectional study conducted across 63 eligible institutions that provided a pre-test genetic counseling service, in all regions of Japan. Study registration occurred between December 2016 and June 2018.

Ethical approval was obtained from the institutional review boards of all participating institutions. The study was conducted in accordance with the principles of the Helsinki Declaration. All patients provided written informed consent to participate in the study and approved the submission and analysis of histopathological specimens. All patient data were anonymized by the investigator. This study was registered at the University hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000025597).

Patients

Eligible patients were registered in serial order (to avoid selection bias) by the respective attending physicians throughout the study period. The inclusion criteria were as follows: Japanese women aged ≥ 20 years, newly diagnosed with ovarian cancer, with histologically confirmed diagnosis, based on surgically resected specimens, and with histological specimens evaluated by central pathological review. Patients were excluded if they had an acute or chronic disease, a mental illness that could affect the study results as determined by their physician, or if their participation in the study was judged to be inappropriate by their physician. Patients were also excluded based on the centrally assessed histological classification of the surgically resected specimen.

Data sources and measurements

Patients' medical charts were reviewed for demographic data, medical history, and information about ovarian cancer. Family history of cancer was obtained during pre-test genetic counseling at the first visit. Data collected included patient demographic and clinical characteristics (date of birth, age), medical history, medications, menopausal status, obstetric history, and blood biochemical testing (cancer antigen 125). Data were also collected regarding ovarian cancer, including date of diagnosis, pathological and histological type, and grade on diagnosis and International Federation of Gynecology and Obstetrics (FIGO) classification. Blood samples from all eligible patients were collected in 10 mL ethylenediaminetetraacetic acid tubes and centrally tested for the presence

or absence of known *gBRCA* mutations (*gBRCA1* and *gBRCA2*) by Myriad Genetics, Inc (Salt Lake City, Utah, USA).

Confirmation of the histological diagnosis was performed centrally by a pathologist assigned by the Japanese Gynecologic Oncology Group using hematoxylin and eosin slide specimens from tumor tissues. The central histological evaluation and diagnosis of ovarian cancer was based on the WHO classification of tumors of female reproductive organs.¹⁵

All patients underwent pre-test genetic counseling, which was provided by a trained obstetrician-gynecologist or oncologist, clinical geneticist, or certified genetic counselor. If the test was positive or indicated a variant of uncertain significance, the patient received further genetic counseling. A genetic specialist revised the document used to provide counseling for *gBRCA* testing.

To assess patient satisfaction with the pre-test explanation of *gBRCA* testing, a written questionnaire, including eight questions, was administered to all patients after receiving the pre-test counseling, but before they received their results. Responses were given on a scale of 1 to 5, with 5 indicating the highest satisfaction. Questionnaires were sent to CMIC Healthcare Co, Ltd (Tokyo, Japan), in a pre-specified reply envelope.

Study endpoints

The primary endpoint of the study was the prevalence of *gBRCA1/2* mutations in patients with newly diagnosed ovarian cancer in Japan. A positive *BRCA* mutation was defined as a deleterious or suspected deleterious mutation.

Secondary endpoints were the prevalence of *gBRCA1/2* mutations in subgroups stratified by histological classification, FIGO stage, and family history of cancer, and the evaluation of patient satisfaction with pre-test genetic counseling.

Statistical methods

Details of the sample size calculation are given in online supplementary text 1, supplemental digital content 2. Descriptive statistics were used for baseline demographic and clinical characteristics, with *n* (%) for categorical variables and mean \pm SD for continuous variables. The full analysis set consisted of all patients who underwent *gBRCA* mutation testing and had histological specimens available for central pathology confirmation.

The prevalence of *gBRCA1/2* mutations was calculated, together with 95% CIs, for all patients, and was stratified by patient background factors, diagnosis, histological classification, staging presence, or absence of family history of cancer in close relatives, and by type of cancer in the family history. All statistical analyses were performed using statistical analysis software (SAS) 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patients

Patient disposition is shown in online supplementary figure 1, supplemental digital content 1. A total of 666 patients were enrolled, but three patients withdrew and 29 were excluded from the full analysis set, based on centralized pathological results. A total of 634 patients were thus included in the final analysis.

Patient characteristics are described in online supplementary table 1, supplemental digital content 2. Patients in the full analysis

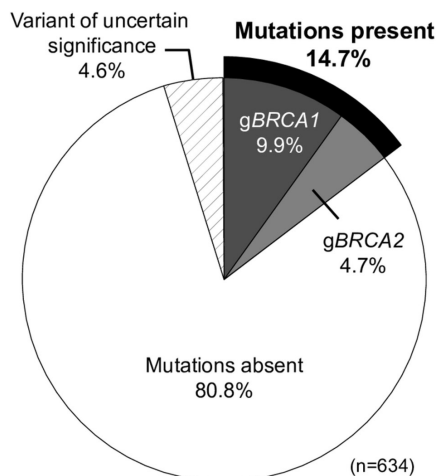


Figure 1 Prevalence of *gBRCA1/2* mutations. **gBRCA* mutations were interpreted using the Myriad Database. CI, confidence interval; *gBRCA*, germline *BRCA*.

had a mean age of 56.9 years; 72.9% of patients were postmenopausal. Epithelial ovarian cancer was the most common diagnosis (84.2%), 48.4% of the ovarian cancers were FIGO stage I–II, and 51.1% were FIGO stage III–IV.

Primary outcomes

The overall prevalence of *gBRCA1/2* mutations in the study population was 14.7% (93/634) (Figure 1). The prevalence of *gBRCA1* mutations (9.9%) was higher than that of *gBRCA2* mutations (4.7%). Test results for 29 (4.6%) patients were variants of uncertain significance. No patients had both *gBRCA1* and *gBRCA2* mutations.

Secondary outcomes

Overall, stratification by patient background factors did not disclose any subgroup with a considerably high prevalence of *gBRCA* mutations, except for those with a family history of cancers (Table 1 and Figures 2A and 2B). The prevalence of *gBRCA* mutations was 9.8% in patients under 41 years of age and 15.0% in those over 41 years of age. Patients under 40 years old with *gBRCA* mutations comprised 0.5% of the study population (see online supplementary figure 2, supplemental digital content 1, which shows the prevalence of *gBRCA* mutations in the study population by age). No notable trend was observed in the prevalence of *gBRCA* mutations according to menopausal status.

The prevalence of *gBRCA* mutations was highest in fallopian tube carcinoma (29.2%) and lowest in epithelial ovarian cancer (12.7%) (see online supplementary figure 3, supplemental digital content 1, which shows the prevalence of *gBRCA* mutations by cancer diagnosis). For epithelial ovarian and primary peritoneal cancers, the prevalence of *gBRCA1* mutations was higher than that of *gBRCA2*, whereas for fallopian tube carcinomas, the prevalence of both *gBRCA1* and *gBRCA2* mutations was the same at 14.6% (online supplementary figure 3, supplemental digital content 1). The age distribution for epithelial ovarian cancer, primary peritoneal cancer, and fallopian tube cancer is shown in online supplementary figure 4, supplemental digital content 1. Patients with epithelial ovarian cancer, primary peritoneal cancer, and fallopian tube cancer were diagnosed as FIGO stage IV in 11.4%, 25.0%, and 12.5% of cases, respectively (online supplementary figure 5, supplemental digital content 1, which shows FIGO stage distribution by carcinoma

<i>gBRCA</i> *	n=634 n (%) [95% CI]
Mutations present	93 (14.7) [12.0–17.7]
<i>gBRCA1</i> only	63 (9.9)
<i>gBRCA2</i> only	30 (4.7)
<i>gBRCA1/2</i>	0
Mutations absent	512 (80.8)
Variant of uncertain significance	29 (4.6)

type). The prevalence of *gBRCA1/2* mutations by histological type is presented in Table 1. In patients with high-grade serous carcinoma the prevalence of *gBRCA1/2* mutations was 28.5%, followed by low-grade serous carcinoma which had a prevalence of 20.0%. In endometrioid and clear-cell types the prevalence was 6.7% and 2.1%, respectively, while in mucinous ovarian cancer the prevalence was 0.0%.

FIGO stages showed a general increasing pattern in the prevalence of *gBRCA* mutations. The prevalence of *gBRCA* mutations in patients diagnosed with FIGO stage I was 3.4% compared with 20.0% in those with FIGO IV (Table 1). When grouped into stage I–II and stage III–IV, the prevalence of *gBRCA* mutations was 4.9% and 24.1%, respectively (Figure 2A). High-grade serous ovarian cancer accounted for 69.8% of those diagnosed with FIGO III or IV and 14.7% of those with stage I or II (online supplementary figure 6, supplemental digital content 1, which shows cancer histological sub-types by FIGO stage). The prevalence of *gBRCA* mutation in high-grade serous cancers was generally high compared with other histological types. Further, *gBRCA* mutation was also observed in patients with early-stage non-serous ovarian cancer (Figure 3). None of the patients with mucinous cancers had *gBRCA* mutation (Table 1).

When cancer history in first- or second-degree relatives was grouped by type of *BRCA*-related cancer, the prevalence of *gBRCA* mutations was highest for patients with a family history of ovarian cancer (63.9%) and breast cancer (31.4%) (see Figure 2B and supplementary table 2, supplemental digital content 2, which shows relatives' cancer sites and prevalence of patient *BRCA* mutations).

During the informed consent process, 99.5% of patients received pre-test genetic counseling (Table 2). Most of the pre-test genetic counseling was provided by either an obstetrician-gynecologist (42.0%) or a clinical geneticist (42.0%). Follow-up genetic counseling was provided in 91.8% of the 122 patients with a positive or variant of uncertain significance *BRCA* test result, which in most cases (80.4%) was done by a clinical geneticist. Twenty-two (3.5%) patients were not notified of the results of genetic testing. Reasons for non-notification included disclosure not wanted (13 patients), death of patient (four patients), transferred to a different hospital or difficulty in visiting

Table 1 Prevalence of germline *BRCA1/2* (*gBRCA1/2*) mutation classified by patient background and ovarian factors

Classification factors	n	<i>gBRCA</i> mutation prevalence					Variant of uncertain significance
		Present	<i>gBRCA1</i> mutation only	<i>gBRCA2</i> mutation only	<i>gBRCA1</i> and <i>gBRCA2</i> mutations	Absent	
Patient factors							
Age (years)							
<41	41	4 (9.8)	4 (9.8)	0 (0.0)	0 (0.0)	36 (87.8)	1 (2.4)
≥41	593	89 (15.0)	59 (9.9)	30 (5.1)	0 (0.0)	476 (80.3)	28 (4.7)
Menopausal status							
Post-menopausal	462	70 (15.2)	47 (10.2)	23 (5.0)	0 (0.0)	369 (79.9)	23 (5.0)
Pre-menopausal	169	22 (13.0)	15 (8.9)	7 (4.1)	0 (0.0)	141 (83.4)	6 (3.6)
Unknown	3	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)
Ovarian cancer factors							
Cancer type (diagnosis by attending physician)							
Epithelial ovarian cancer	534	68 (12.7)	47 (8.8)	21 (3.9)	0 (0.0)	440 (82.4)	26 (4.9)
Primary peritoneal cancer	52	11 (21.2)	9 (17.3)	2 (3.8)	0 (0.0)	40 (76.9)	1 (1.9)
Fallopian tube carcinoma	48	14 (29.2)	7 (14.6)	7 (14.6)	0 (0.0)	32 (66.7)	2 (4.2)
Histological category, atypia (centralized pathological diagnosis)							
All serous cancers	279	79 (28.3)	54 (19.4)	25 (9.0)	0 (0.0)	185 (66.3)	15 (5.4)
High-grade serous cancer	274	78 (28.5)	53 (19.3)	25 (9.1)	0 (0.0)	181 (66.1)	15 (5.5)
Low-grade serous cancer	5	1 (20.0)	1 (20.0)	0 (0.0)	0 (0.0)	4 (80.0)	0 (0.0)
All mucinous cancers	19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (100.0)	0 (0.0)
All endometrioid cancers	120	8 (6.7)	7 (5.8)	1 (0.8)	0 (0.0)	104 (86.7)	8 (6.7)
Clear-cell carcinoma	187	4 (2.1)	2 (1.1)	2 (1.1)	0 (0.0)	178 (95.2)	5 (2.7)
Seromucinous cancer	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)
Other	25	2 (8.0)	0 (0.0)	2 (8.0)	0 (0.0)	22 (88.0)	1 (4.0)
FIGO stage							
I	236	8 (3.4)	3 (1.3)	5 (2.1)	0 (0.0)	221 (93.6)	7 (3.0)
II	71	7 (9.9)	7 (9.9)	0 (0.0)	0 (0.0)	60 (84.5)	4 (5.6)
III	244	62 (25.4)	42 (17.2)	20 (8.2)	0 (0.0)	170 (69.7)	12 (4.9)
IV	80	16 (20.0)	11 (13.8)	5 (6.3)	0 (0.0)	58 (72.5)	6 (7.5)
Other	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)

Values are n (%).

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; *gBRCA*, germline *BRCA*.

the hospital (three patients), or notification scheduled after database lock (two patients).

The level of patient satisfaction with pre-test genetic counseling and their level of satisfaction depending on the provider was high overall (see online supplementary table 3, supplemental digital content 2). For each question, irrespective of the provider, over 96% provided satisfaction.

DISCUSSION

The CHARLOTTE study is the first multicenter, epidemiological, prospective survey to investigate the frequency of *gBRCA1/2* mutations among Japanese patients with newly diagnosed ovarian cancer, focusing on relevant sub-populations. Current

findings show that the overall prevalence of *gBRCA1/2* mutations in the sample population was 14.7%, with a higher prevalence of *gBRCA1* than *gBRCA2*. When categorized by patient factors, no subgroup had a considerably higher prevalence of *gBRCA* mutations.

The *gBRCA1/2* mutation prevalence found in this study is consistent with that previously reported in Japan and other countries. Hirasawa et al conducted a single-center study and reported a *gBRCA* mutation prevalence of 11.7%.⁴ International studies also reported similar findings; 13.8% in a European and US multicenter study and 12.1% in a Taiwanese study.^{16,17} Ovarian cancer includes hereditary breast and ovarian cancers at a similar rate regardless of race or ethnicity; a consideration important to bear in mind when conducting medical examinations.

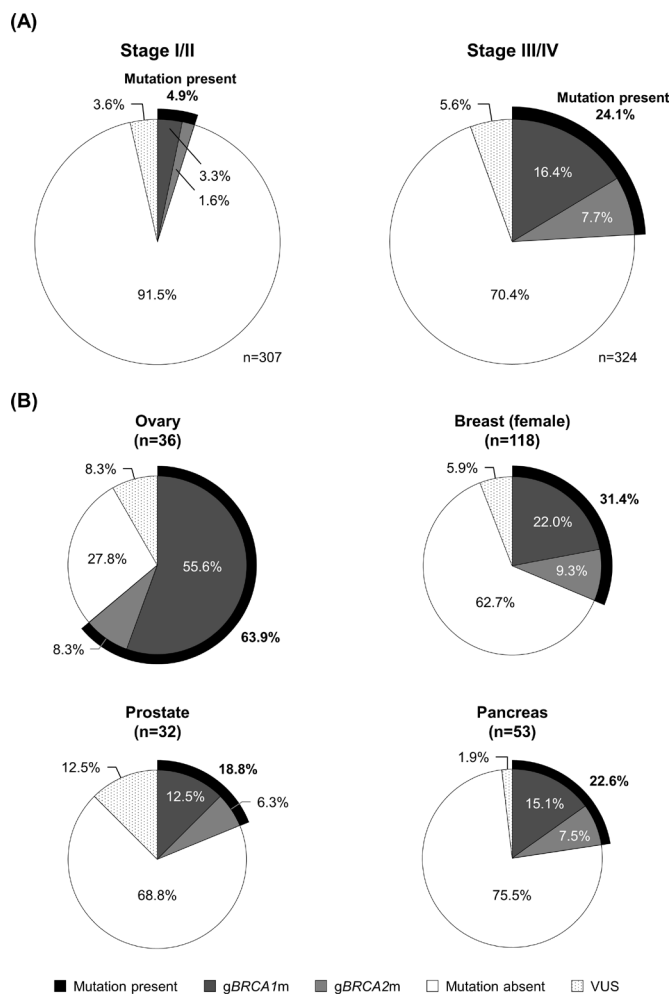


Figure 2 Prevalence of *gBRCA1/2* mutations stratified by (A) FIGO stage, and (B) family history of cancer. In panel (A), three patients with a FIGO stage of 'other' were not included in the analysis. FIGO, International Federation of Gynecology and Obstetrics; *gBRCA*, germline *BRCA*.

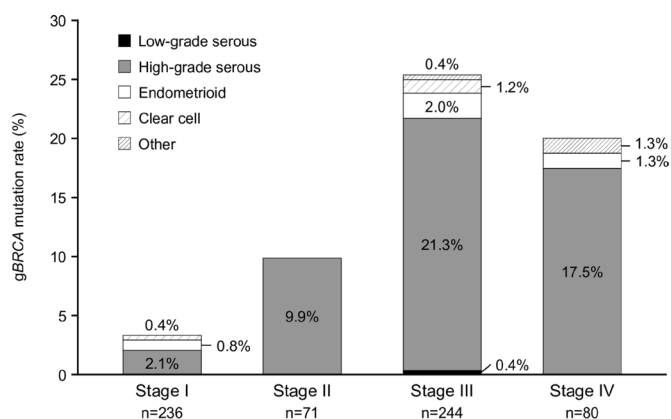


Figure 3 Prevalence of *gBRCA* mutation by histological sub-type and FIGO stage. Three patients with a FIGO stage of 'other' were not included in the analysis. FIGO, International Federation of Gynecology and Obstetrics; *gBRCA*, germline *BRCA*.

The prevalence of *gBRCA* mutations varied by histology (mucinous, clear-cell, endometrioid, low-grade serous, and high-grade serous carcinoma: 0%, 2.1%, 6.7%, 20.0%, and 28.5%, respectively). The ratio of histologic types differs between Japan, Europe, and North America, with a lower prevalence of high-grade serous carcinoma in Japanese populations than in Caucasians, which might have affected the prevalence of *gBRCA* mutations.¹⁸ However, we should note that in the present study the prevalence of *gBRCA1/2* mutations in patients with high-grade serous carcinoma was slightly higher (28.5%) than that reported in previous studies.^{8,19} Alsop et al (Australia) reported a *gBRCA* mutation prevalence of 17.1% in patients with high-grade serous carcinoma, and Norquist et al (USA) found a combined *gBRCA1* and *gBRCA2* prevalence of 16.0%.^{8,19} Nonetheless, the results of our study are consistent with a recent study in Japan that reported a *gBRCA* prevalence of 29.7% in patients with high-grade serous carcinoma.⁴ In this study, patients with mucinous cancers did not have *gBRCA* mutations, which is consistent with the statement of the NCCN guidelines.¹² The prevalence of *gBRCA* mutations generally increased with increasing FIGO stage; the prevalence was higher among high-grade, FIGO stage III–IV serous ovarian cancers than stage I–II cancers. Additionally, there was a generally higher prevalence of *gBRCA* mutations in high-grade serous carcinoma than in other histological types. Thus, the increasing prevalence of *gBRCA* mutations in FIGO III–IV cancers correlated with the prevalence of high-grade serous ovarian cancer. In both serous and non-serous ovarian cancers, *gBRCA* mutations were noted in the earlier disease stages. Therefore, it is difficult to speculate about the presence of *gBRCA* mutations according to the histological types and stages, and we consider that *gBRCA* testing should be conducted at all stages of ovarian cancer.

Mutations in the *BRCA* genes can also occur without a positive family history of *BRCA*-related cancers. In this study, a family history of cancer was associated with a slightly higher prevalence of *gBRCA* mutations. The prevalence of *gBRCA* mutations was highest with a family history of ovarian (63.9%) or breast cancer (31.4%). These findings are consistent with the results of other studies, with a higher prevalence in those with a family history of ovarian cancer.^{4,8,20,21} Lee et al also reported a higher standardized incidence ratio of ovarian cancer in all first-degree relatives of patients with ovarian cancer (2.5, 95% CI 1.6 to 4.0) compared with the standardized incidence ratio of ovarian cancer in all first-degree relatives of patients with breast cancer (1.0, 95% CI 0.7 to 1.4).²² Nonetheless, a *gBRCA* prevalence of 7.4% was observed in patients without a family history (first- or second-degree relatives) of cancer in our study. Overall, our results suggest that genetic testing is warranted for all patients with ovarian cancer, regardless of family history or cancer risk factors, which is in line with NCCN guidelines.¹² Results of genetic testing will encourage other family members to consider undergoing the same testing before the onset of ovarian cancer and allow for regular check-ups and prophylactic removal for risk reduction.^{23,24}

Genetic counseling before genetic testing is necessary to promote the correct understanding of results and genetic risk of cancer among family members. The proportion of patients satisfied with pre-test genetic counseling was high (>96%), irrespective of who provided the *gBRCA* test information. These results indicate that trained clinicians, cancer specialists, and other health professionals

Table 2 Provision of genetic counseling

Professional position of the service provider	Genetic counseling		
	Pre-test genetic counseling (at time of informed consent explanation) (n=631)	If result of <i>BRCA</i> test was positive or variant of uncertain significance (n=112)	<i>gBRCA</i> test result disclosed (n=612)
Gynecologist/obstetrician	265 (42.0)	3 (2.7)	354 (57.8)
Oncologist	4 (0.6)	0 (0.0)	3 (0.5)
Clinical geneticist	265 (42.0)	90 (80.4)	211 (34.5)
Certified genetic counselor	92 (14.6)	19 (17.0)	30 (4.9)
Other	5 (0.8)	0 (0.0)	14 (2.3)
Genetic counseling not provided/not notified of results	3 (0.5 [†])	10 (8.2 [†])	22 (3.5 [†])

Values are n (%). [†]Percentages are calculated using the total number of patients (n=634) as a denominator. [†]The percentage is calculated using the number of patients with a positive *gBRCA* mutation or variant of uncertain significance (n=122) as a denominator. *gBRCA*, germline *BRCA*.

can effectively conduct pre-test genetic counseling in a dedicated setting.²⁵ Given that the pre-test genetic counseling framework is undergoing further development in Japan, the best option might be to provide genetic counseling through multidisciplinary collaboration among different healthcare professionals.

These findings were based on Japanese clinical practices, and their application may be limited in other countries with different clinical practices. The varying number of patients included from different sites (online supplementary table 4, supplemental digital content 2) was another limitation; no upper limit was set for the registration of patients at individual sites, and only a few patients were registered at some sites.

CONCLUSIONS

The overall prevalence of *gBRCA1/2* mutations in patients with ovarian cancer was 14.7%, with a higher prevalence of *gBRCA1* than of *gBRCA2*. While high-grade serous carcinoma and family history, particularly of ovarian cancer, showed a somewhat higher prevalence of *gBRCA* mutations, none of the subgroups had considerably high *gBRCA* mutation prevalence overall. These findings indicate that *gBRCA* testing should be performed in all patients with ovarian cancer. Most patients were satisfied with the pre-test counseling provided, irrespective of the professional position of the service provider.

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Contributors TE, DA, YW, JK, NT, TS, and HT conceived and designed the study. KH was involved in data acquisition. KY and KH analyzed the data. All authors were involved in the interpretation of data, drafting of the manuscript, and provided critical feedback. All authors approved the final manuscript.

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