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Original Article

Differences in age at diagnosis of ovarian cancer for each *BRCA* mutation type in Japan: optimal timing to carry out risk-reducing salpingo-oophorectomy

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ABSTRACT

Objective: *BRCA1* and *BRCA2* mutation carriers are recommended to undergo risk-reducing salpingo-oophorectomy (RRSO) by age 40 and 45, respectively. However, the carriers have a different way of thinking about their life plan. We aimed to investigate the distribution of age at diagnosis of ovarian cancer (OC) patients to examine the optimal timing of RRSO in the carriers.
Methods: We examined a correlation between age at diagnosis of OC and common mutation types in 3,517 probands that received *BRCA* genetic testing. Among them, germline *BRCA1* mutation (g*BRCA1*m), germline *BRCA2* mutation (g*BRCA2*m) and germline *BRCA* wild-type (g*BRCA*wt) were found in 185, 42 and 241 OC patients, respectively.
Results: The average age at diagnosis of OC in g*BRCA1*m and g*BRCA2*m was 51.3 and 58.3 years, respectively, and the difference from g*BRCA*wt (53.8 years) was significant. The g*BRCA2*m carriers did not develop OC under the age of 40. The average age was 50.1 years for L63X and 52.8 years for Q934X in *BRCA1*, and 55.1 years for R2318X and 61.1 years for STOP1861 in *BRCA2*. The age at diagnosis in L63X or R2318X carriers was relatively younger than other *BRCA1* or *BRCA2* carriers, however their differences were not significant. With L63X and R2318X carriers, 89.4% (42/47) and 100% (7/7) of women were able to prevent the development of OC, respectively, when RRSO was performed at age 40.
Conclusion: There appears to be no difference in the age at diagnosis of OC depending on the type of *BRCA* common mutation. Further analysis would be needed.

Keywords: *BRCA1*; *BRCA2*; Ovarian Neoplasms; Age at Diagnosis; Common Mutation; Risk-Reducing Salpingo-Oophorectomy

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Conflict of Interest
Masayuki Sekine received lecture fees from AstraZeneca. Takayuki Enomoto received lecture fees from AstraZeneca and Chugai Pharmaceutical. Seigo Nakamura received an honoraria for a seminar presentation from AstraZeneca and KONICA MINOLTA. The other authors declare no conflicts of interest.

Author Contributions
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Synopsis
This is the first report to present the optimal timing of risk-reducing salpingo-oophorectomy for each *BRCA* mutation type in Japan. The average age at diagnosis of ovarian cancer (OC) in germline *BRCA2* mutation (g*BRCA2*m) is higher than that in germline *BRCA* wild-type. The g*BRCA2*m carriers did not develop OC under the age of 40. The average age at diagnosis in L63X or R2318X carriers was relatively younger than other *BRCA* mutation carriers, though the differences were not significant.

INTRODUCTION

PARP inhibitors have become available as therapeutic agents for a variety of cancers, namely, ovarian cancer (OC), breast cancer (BC), prostate cancer and pancreatic cancer, and an increasing number of cancer patients are undergoing *BRCA1/2* genetic testing for companion diagnostics. Many patients with mutations in the *BRCA* genes have been found, and the number of *BRCA* mutation carriers has increased accordingly. For female *BRCA* mutation carriers, risk-reducing salpingo-oophorectomy (RRSO) has been shown to decrease OC-specific mortality and overall mortality by approximately 80% and 70%, respectively [1-4].

The National Comprehensive Cancer Network guideline recommends that female *BRCA* mutation carriers undergo RRSO between ages 35 to 40 or after childbearing is complete. For *BRCA2* mutation carriers, the guideline suggests that it is reasonable to delay RRSO until 40 to 45 years of age due to the later onset of OC [5]. These recommendations have been approved by many national societies including the Society of Gynecologic Oncology, the American College of Obstetrics and Gynecology, and the European Society for Medical Oncology [6-8]. However, in actual clinical practice, detailed genetic counseling is required for RRSO because each *BRCA* mutation carrier has a different way of thinking about the time of marriage and childbirth. In the current genetic counseling for the carriers, it seems that the explanation of RRSO is given by the counselor to distinguish between *BRCA1* and *BRCA2*, but personal counseling based on the mutation location and the mutation type is not performed [5]. Individual counseling that takes into account each *BRCA* mutation type and the age at diagnosis of OC in each family would be a great benefit to the carrier for life planning.

Regarding the difference in OC risk depending on the *BRCA* mutation location, *BRCA1* and *BRCA2* have the ovarian cancer cluster region (OCCR) in or near exon 11 and the breast cancer cluster region (BCCR) in multiple regions other than exon 11 so far [9-11]. However, there are few reports on the correlation between *BRCA* mutation location and age at diagnosis of OC. Therefore, we aimed to investigate the distribution of the age at diagnosis of OC with *BRCA* mutation in detail to examine the optimal timing of RRSO.

MATERIALS AND METHODS

We examined the database of the Japanese Organization of Hereditary Breast and Ovarian Cancer (JOHBOC) and analyzed the data registered by August 2019 in this analysis. The ethics review board approved the establishment of the database in 2014 to investigate the characteristics of Japanese HBOC patients. After obtaining further approval from the ethics review board or institutional review board of each of the Japanese medical institutions where

genetic testing of *BRCA1* and *BRCA2* and genetic counseling by certified specialists were available, we began this registration project. Previous reports have outlined details of the registration procedures [12,13].

In the JOHBOC database, 62 medical institutions registered 3,517 probands that received both *BRCA1* and *BRCA2* genetic testing or their relatives. Any purposes for genetic testing were acceptable, including clinical practice and translational research. Almost all genetic testing, including sequence and large rearrangement analysis, was performed at Myriad Genetic Laboratories or FALCO Biosystems. The detected variants were interpreted according to the criteria of Myriad Genetic Laboratories. The following data were registered: clinical information of ovarian, fallopian tube or peritoneal cancer (age at diagnosis, disease site, histological subtype, and FIGO stage), personal BC history, family history, and germline *BRCA1/2* variants. All first- and second-degree relatives and cousins with any cancer were included in the family history. Informed consent was obtained from the subjects. If informed consent could not be obtained face to face, such as for retrospective cases for whom medical treatment had been terminated or for patients who had died, the candidate or the candidate's family members were allowed to opt out on the homepages of JOHBOC and each participating institute. All patients underwent genetic counseling and genetic testing of their own free will. Statistical analyses were performed using R software ver4.0.2 (R Development Core Team, Vienna, Austria) for t-test, Fisher's exact test, χ^2 test, analysis of variance and Kruskal-Wallis test. A 2-sided p-value of <0.05 was considered to indicate statistically significant.

RESULTS

1. Clinical characteristics of the OC patients in the JOHBOC database

The clinical characteristics of OC patients were compared by dividing into germline *BRCA1* mutation (g*BRCA1*m: 185 patients), germline *BRCA2* mutation (g*BRCA2*m: 42 patients), and germline *BRCA* wild-type (g*BRCA*wt: 241 patients) according to the presence or absence of *BRCA* mutation (**Table 1**). There was no case of non-epithelial OC among the registered cases. The clinical features of a high frequency of serous carcinoma and advanced stage in patients with *BRCA1/2* mutation are similar to previous reports. Among OC patients with serous carcinoma, the patients with low-grade carcinoma were 1 case (1/138), 0 case (0/32), and 4 cases (4/125) in g*BRCA1*m, g*BRCA2*m and g*BRCA*wt, respectively. Regarding personal BC history, OC patients with g*BRCA2*m tended to have BC more often than g*BRCA1*m or g*BRCA*wt. As expected, the average age at diagnosis of OC in g*BRCA1*m was 51.3 years (median: 50 years), which was significantly younger than that in g*BRCA2*m (mean: 58.3 years, median: 57.5 years) and g*BRCA*wt (mean: 53.8 years, median: 54 years). Reflecting the results, it was also shown that the frequency of premenopausal or nulliparous women tended to be high in g*BRCA1*m. On the other hand, the age at diagnosis of OC in g*BRCA2*m is higher than that in g*BRCA*wt. **Fig. 1** shows the distribution of age at diagnosis for OC among different age groups. The peak age at diagnosis of OC was in the late 40s with g*BRCA1*m and in the late 50s with g*BRCA2*m. The general statistical data for comparison were data from the Japanese cancer statistics in 2017 [14].

We analyzed whether the age at diagnosis of OC differs depending on the prior history of BC (**Table S1**). As a result, there was no significant difference of the age at diagnosis by the presence or absence of BC history. In addition, we performed subgroup analyses among the nulliparous women. The results showed that the average age at diagnosis of OC in g*BRCA1*m

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Table 1. Clinical characteristics of OC patients in the JOHBOC database

Characteristics	g*BRCA1*m (n=185)	g*BRCA2*m (n=42)	g*BRCA*wt (n=241)	p-value
Histological subtype				<0.001†
Serous carcinoma	138 (74.6)	32 (76.2)	125 (51.9)	
Endomerioid carcinoma	14 (7.6)	1 (2.4)	25 (10.4)	
Clearcell carcinoma	1 (0.5)	1 (2.4)	43 (17.8)	
Mucinous carcinoma	1 (0.5)	1 (2.4)	10 (4.1)	
Others	10 (5.4)	2 (4.8)	11 (4.6)	
Unknown	21 (11.4)	5 (11.9)	27 (11.2)	
FIGO stage				0.018†
I	19 (10.3)	5 (11.9)	52 (21.6)	
II	16 (8.6)	2 (4.8)	17 (7.1)	
III	102 (55.1)	23 (54.8)	99 (41.1)	
IV	26 (14.1)	6 (14.3)	42 (17.4)	
Unknown	22 (11.9)	6 (14.3)	31 (12.9)	
Personal breast cancer history				0.180‡
Yes	54 (29.2)	16 (38.1)	60 (24.9)	
No	131 (70.8)	26 (61.9)	181 (75.1)	
Menopausal status				0.001†
Premenopause	54 (29.2)	6 (14.3)	45 (18.7)	
Postmenopause	90 (48.6)	31 (73.8)	181 (75.1)	
Unknown	41 (22.2)	5 (11.9)	15 (6.2)	
Parity				0.062†
0	23 (12.4)	5 (11.9)	60 (24.9)	
1	16 (8.6)	5 (11.9)	30 (12.4)	
2	21 (11.4)	18 (42.9)	77 (32.0)	
>3	18 (9.7)	3 (7.1)	27 (11.2)	
Unknown	107 (57.8)	11 (26.2)	47 (19.5)	
Age at diagnosis of OC				
Mean ± standard deviation	51.3±9.8	58.3±9.3	53.8±13.2	
Median	50	57.5	54	
Minimum	28	41	12	
Maximum	83	77	81	
p-value*	0.039	0.034	Ref.	

Values are presented as number (%) or mean ± standard deviation.
g*BRCA1*m, germline *BRCA1* mutation; g*BRCA2*m, germline *BRCA2* mutation; g*BRCA*wt, germline *BRCA* wild-type; JOHBOC, Japanese Organization of Hereditary Breast and Ovarian Cancer; OC, ovarian cancer.
*The t-test (vs. g*BRCA*wt); †Fisher's exact test (excluding unknown cases); ‡χ^2 test.

and g*BRCA2*m was 44.9 and 54.4 years, respectively, and their differences from g*BRCA*wt (47.4 years) was significant in the nulliparous women (**Table S2**).

There were 6 families with both *BRCA1* and *BRCA2* germline mutations. We have shown the detailed information in **Table S3**. All probands with both *BRCA1* and *BRCA2* germline mutations were BC patients and there was no *BRCA* mutation carrier developed OC in the families.

2. Common mutations in the JOHBOC database

Among the *BRCA* mutation types in this analysis, the common mutations found in more than 10 families are shown in **Fig. 2**. The most common mutation in *BRCA1* was L63X in 103 families, followed by Q934 X, STOP799, and Y1853C, in 37, 16 and 10 families, respectively. L63X and Y1853C are located in BCCR, on the other hand, Q934 X and STOP799 are located in OCCR. The most common *BRCA2* mutation was R2318X in 33 families, followed by STOP1861, Q3026X, S1882X, P3039P, STOP613, S2835X, and STOP2868, in 26, 17, 13, 12, 11, 11, and 10 families, respectively. R2318X, STOP1861, and S1882X are located in OCCR, on the other hand, S2835X and STOP2868 are located in BCCR. Q3026X, P3039P and STOP613 are not located in either the OCCR or BCCR region.

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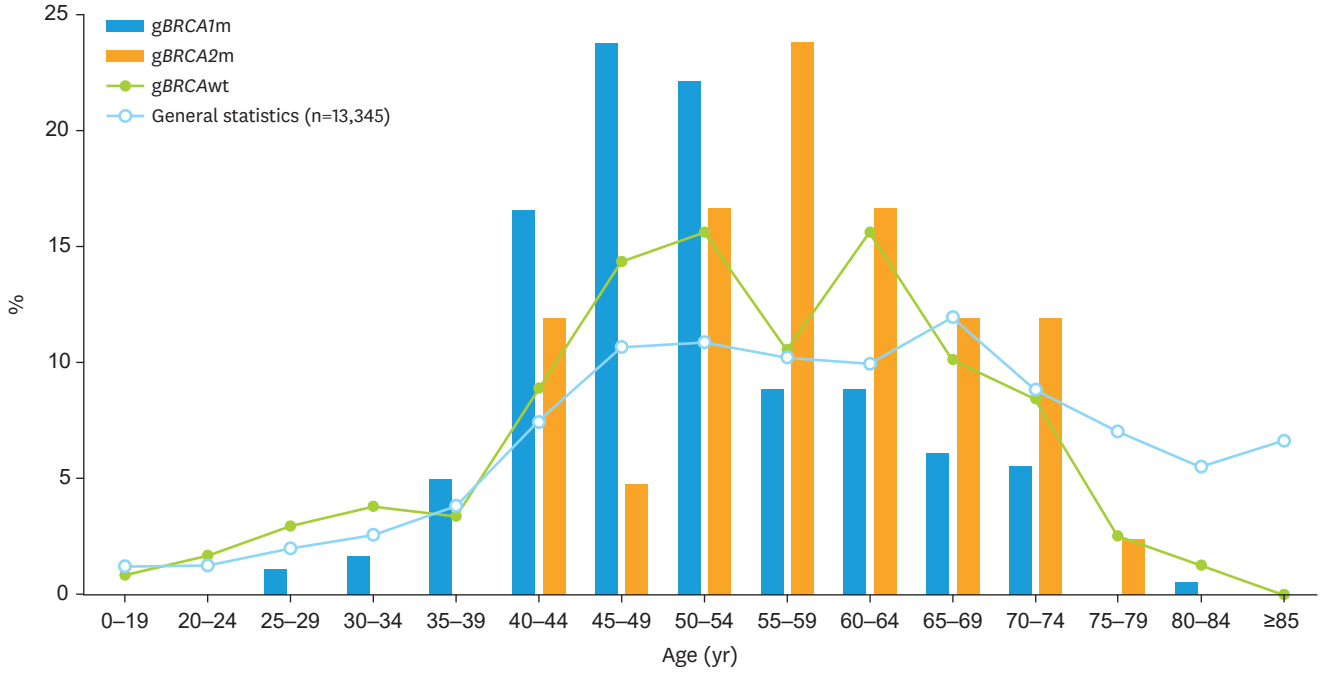

Fig. 1. Age distribution of OC diagnosis by *BRCA1/2* mutaiton status. The peak age at diagnosis of OC was in the late 40s with g*BRCA1*m and in the late 50s with g*BRCA2*m. The general statistical data for comparison were data from the Japanese cancer statistics in 2017 [14].
g*BRCA1*m, germline *BRCA1* mutation; g*BRCA2*m, germline *BRCA2* mutation; g*BRCA*wt, germline *BRCA* wild-type; OC, ovarian cancer.

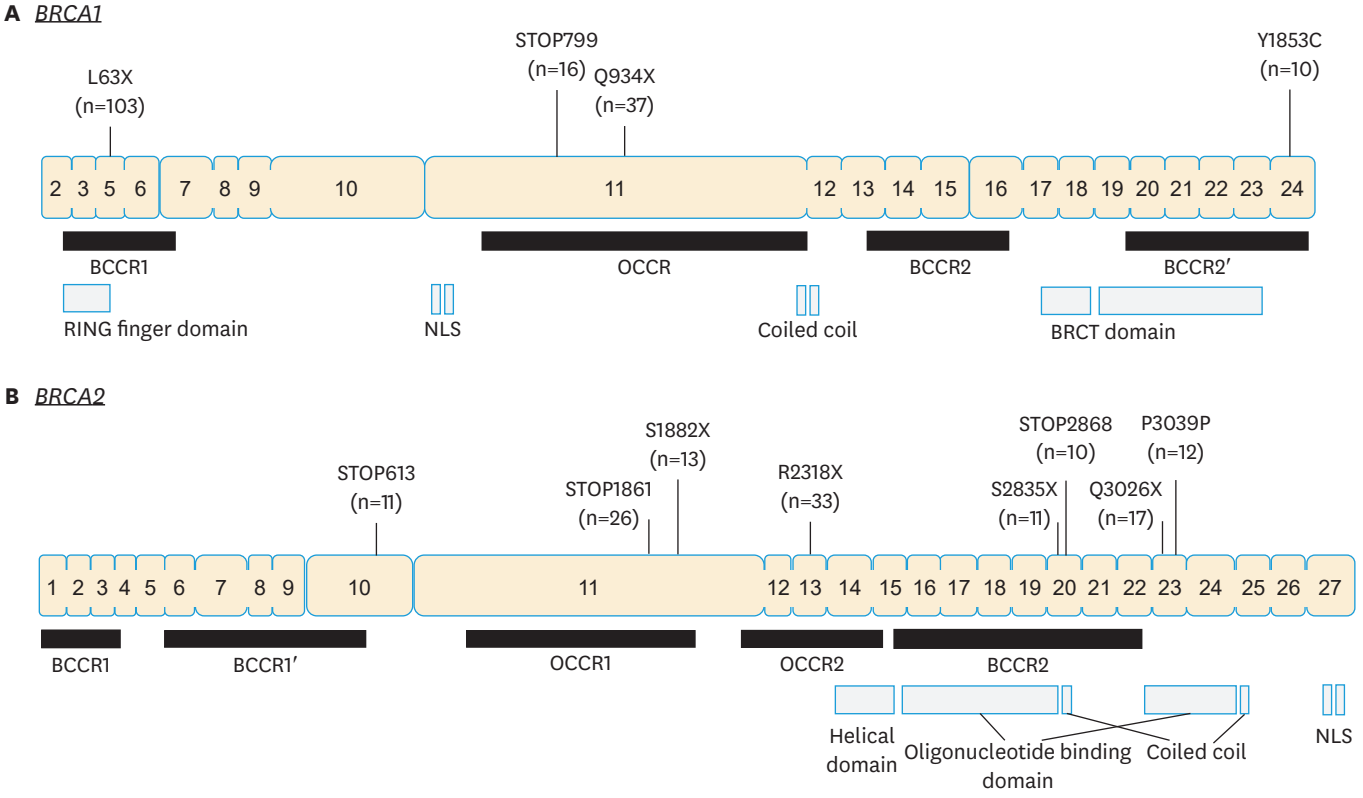

Fig. 2. Prevalence of (A) *BRCA1* and (B) *BRCA2* common mutations by location. Regions inferred to be OCCR and BCCR are shown in the middle. Putative functional domains are shown at the bottom.
BCCR, breast cancer cluster region; NLS, nuclear localization signal; OCCR, ovarian cancer cluster region.

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3. Differences in age at diagnosis of OC among *BRCA* mutation types

The average age at diagnosis of OC was 50.1 years for L63X and 52.8 years for Q934X in *BRCA1*, on the other hand, 55.1 years for R2318X and 61.1 years for STOP1861 in *BRCA2*. The L63X or R2318X mutation carriers appeared to develop OC at a relatively younger age than carriers with other *BRCA1* or *BRCA2* mutations, though the differences were not statistically significant. There was no difference in the age at diagnosis of OC depending on the type of *BRCA* common mutation. Moreover, we analyzed the difference of age between each mutation involved in *BRCA1* (L63X vs. Q934X vs. STOP799 vs. Y1853C vs. others) or *BRCA2* (L63X vs. Q934X vs. STOP799 vs. Y1853C vs. others), separately. The results demonstrated no significant difference of age between each mutation type (**Table 2**).

4. Optimal timing for RRSO

In order to consider the optimal age for performing RRSO, the age distribution of OC diagnosis is summarized by *BRCA* mutation type in **Table 3** and **Fig. 3**. In L63X mutation carriers, who are presumed to develop OC at a younger age, 97.9% (46/47) of women can be prevented from developing OC if RRSO is performed at the age of 35. When performed at age 40, it was possible to prevent the development of OC in 89.4% (42/47) of the carriers. On the other hand, although the number of women with STOP799 or Y1853C is small, there are no OC patients under the age of 40. It should be noted that there are 2 women with g*BRCA1*m who developed OC under the age of 30. Women with g*BRCA2*m did not develop OC under the age of 40, and 83.4% (35/42) of women developed OC after age 50. In women with R2318X of *BRCA2*, all women could prevent the development of OC if RRSO was performed until age 40, however, 28.6% (2/7) of women developed OC if RRSO was not performed until age 45.

Table 2. Differences in age at diagnosis of OC among *BRCA1* and *BRCA2* mutation types

Characteristics	*BRCA1*				*BRCA2*							
	L63X	Q934X	STOP799	Y1853C	R2318X	STOP1861	Q3026X	S1882X	P3039P	STOP613	S2835X	STOP2868
No. of families	103	37	16	10	33	24	16	13	12	11	12	10
No. of carriers	153	60	22	13	38	30	17	13	14	16	14	10
No. of OC patients	47	23	7	3	7	7	0	1	3	1	0	1
Age at diagnosis of OC												
Mean ± standard deviation	50.1±10.1*	52.8±12.1*	54.4±9.8*	50.0±1.7*	55.1±10.2†	61.1±11.0†	-	56	63.3±13.1†	56	-	61
Minimum	32	28	44	49	42	41	-	56	51	56	-	61
Maximum	83	72	74	52	67	73	-	56	77	56	-	61
OCCR or BCCR	BCCR	OCCR	OCCR	BCCR	OCCR	OCCR	Outside	OCCR	Outside	Outside	BCCR	BCCR

BCCR, breast cancer cluster region; OC, ovarian cancer; OCCR, ovarian cancer cluster region; Outside, outside of OCCR or BCCR.
*Not significant (Kruskal-Wallis test, p=0.54) (vs. *BRCA1* mutations excluding the mutation type); †Not significant (Kruskal-Wallis test, p=0.52) (vs. *BRCA2* mutations excluding the mutation type).

Table 3. Distribution of age at diagnosis of OC by *BRCA1* and *BRCA2* common mutations

Characteristics	*BRCA1*					*BRCA2*			
	L63X	Q934X	STOP799	Y1853C	All	R2318X	STOP1861	P3039P	All
No. of OC patients	47	23	7	3	185	7	7	3	42
Age at diagnosis (No. of patients)									
<30	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
30–34	1 (2.1)	1 (4.5)	0 (0.0)	0 (0.0)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
35–39	4 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
40–44	10 (21.3)	4 (18.2)	1 (14.3)	0 (0.0)	30 (16.6)	2 (28.6)	1 (14.3)	0 (0.0)	5 (11.9)
45–49	12 (25.5)	2 (9.1)	1 (14.3)	2 (66.7)	43 (23.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)
50–54	10 (21.3)	5 (22.7)	2 (28.6)	1 (33.3)	40 (22.1)	2 (28.6)	0 (0.0)	1 (33.3)	7 (16.7)
≥55	10 (21.3)	9 (40.9)	3 (42.9)	0 (0.0)	54 (29.8)	3 (42.9)	6 (85.7)	2 (66.7)	28 (66.7)
Unknown	0 (-)	1 (-)	0 (-)	0 (-)	4 (-)	0 (-)	0 (-)	0 (-)	0 (-)
Mean (yr)	50.1	52.8	54.4	50.0	51.3	55.1	61.1	63.3	58.3
Median (yr)	49.0	52.5	52.0	49.0	50.0	54.0	60.0	62.0	57.5

Values are presented as number (%).
OC, ovarian cancer.

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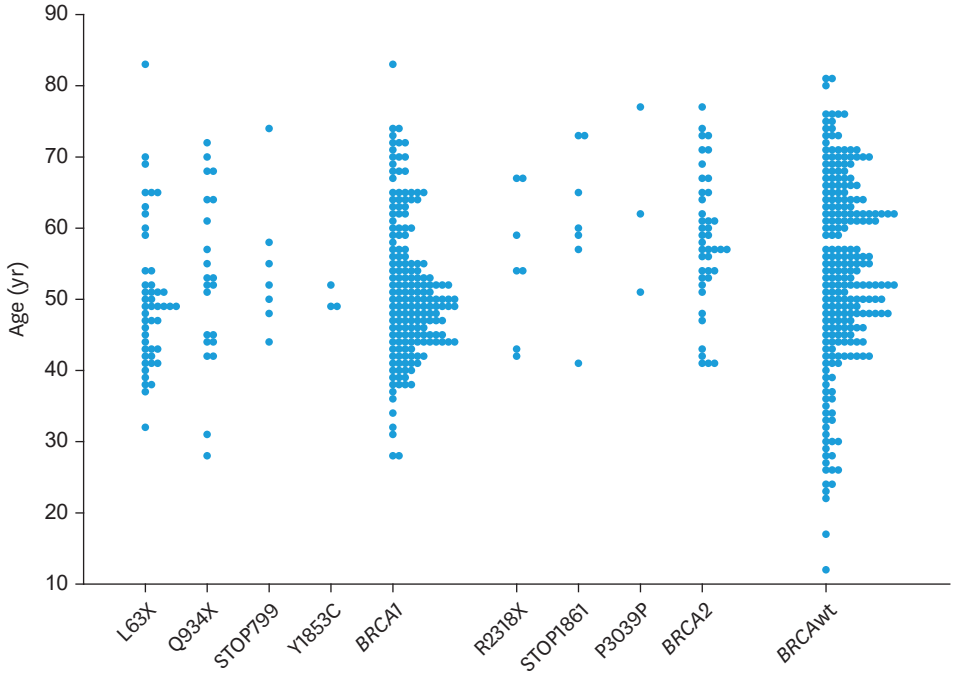

Fig. 3. Age distribution of OC diagnosis by common mutation type of *BRCA1/2*. In *BRCA1* mutation carriers, cases of OC were observed from the late 20s, however, no cases of OC were found until the age of 40 in *BRCA2* mutation carriers. OC, ovarian cancer.

There were 5 women who developed OC in their 20s and early 30s. **Table S4** shows clinical characteristics of early-onset OC patients and her family members. Interestingly, there was an aunt who developed OC in her 30s in Q934X family.

DISCUSSION

This is the first report to present the distribution of the age at diagnosis of OC with *BRCA* mutation in detail and analyze the age by each common mutation type in the Japanese population. The age at diagnosis in L63X or R2318X carriers was relatively younger than other *BRCA1* or *BRCA2* carriers, however their differences were not significant. The results need to be interpreted carefully, thus we examined the age distribution of OC patients and discussed the optimal timing of RRSO in detail.

For all *BRCA1* carriers, the preventive effect was 97% or 92%, if RRSO was given by age 35 or 40, respectively. As expected, no women with *BRCA2* mutation carriers developed OC under the age of 40, but there were women in their late 20s who developed OC in *BRCA1* mutation carriers. From the results, we recognized that it is reasonable for Japanese women to determine the timing of RRSO with reference to the age of the women who developed OC at a young age in her family. Although there is a woman who developed OC at the age of 32 in the L63X carrier, it was found that 98% of OC preventive effect can be obtained by performing RRSO by the age of 35. If the timing of RRSO is delayed to 40 years, the preventive effect is reduced to 89%.

We previously reported that the average age at diagnosis of Japanese OC patients with g*BRCA1*m, g*BRCA2*m, and g*BRCA*wt are 52.1, 58.4, and 54.2 years, respectively [15,16].

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Our current results are almost the same as that of previous reports. Interestingly, the age at diagnosis of OC in g*BRCA2*m was significantly higher than that in g*BRCA*wt. On the other hand, the age at diagnosis in Japanese BC patients with *BRCA2* mutations was significantly lower than that in g*BRCA*wt [17]. In Western countries, the mean age at diagnosis of OC in g*BRCA1*m and g*BRCA2*m was 51.3 years (ranges 33–84) and 61.4 years (ranges 44–80), respectively [18]. The highest OC incidence rate for *BRCA1* and *BRCA2* mutation carriers was observed the ages of 50–59 years and 60–69 years, respectively [2]. The prevalence of OC has been reported to be lower in Japan than in the Western countries, but no clear difference has been pointed out in the mean age in *BRCA* mutation carriers between Japan and the Western countries.

Antoniou et al. [19] reported the relative risk of developing BC and OC in American women compared to the general population by age group. For both *BRCA1* and *BRCA2* mutation carriers, the risk of BC increases from the 20s, but the risk of OC increases from the 30s in the *BRCA1* mutation carriers, and the risk begins to increase from the 40s in the *BRCA2* mutation carriers. Yoshihara et al. [20] reported that there was no significant difference in the age at diagnosis between mutation carriers within OCCR and outside of OCCR in 93 Japanese patients with OC. They have also analyzed the age at diagnosis in 16 OC patients with L63X, but could not discuss the conclusions due to the small number of cases. Yoshida et al. [21] reported that there was no significant difference in the age at diagnosis and the status of BC between L63X (n=25) and other *BRCA1* mutations (n=59).

Regarding the age at which RRSO was performed on Japanese *BRCA* carriers, Nomura et al. [12] analyzed the Japanese HBOC consortium database and reported the following in 2019. Of the 488 *BRCA* mutation carriers, 31% (153/488) have RRSO, and the most common age group of *BRCA1* mutation carriers who underwent RRSO was 40–44 years, and 3.4% (3/88) had RRSO under 40 years of age. On the other hand, the age of *BRCA2* mutation carriers who underwent RRSO was most often 45–49 years, and the carriers under 40 years of age who underwent RRSO was 6.4% (4/62). There are few carriers who received RRSO by the age of 40 according to the guidelines. Smith et al. [22] reported that the most common reason for the delay in RRSO was delayed identification of *BRCA* mutation, thus timely genetic testing for eligible patients can increase appropriately timed RRSO for prevention of OC and reduction of mortality in *BRCA* mutation carriers.

Recently, the JOHBOC Breast Cancer Group reported on the onset age of 3,891 BC cases in Japan. In the analysis, the mean age of onset was 43.6, 45.2, and 48.8 years in the *BRCA1, BRCA2*, and *BRCA*wt groups, respectively. They showed that BC cases with *BRCA1/2* mutation were diagnosed at a younger age in a Japanese cohort, and particularly those with *BRCA1* mutations had a younger age at onset. Although *BRCA2* carriers did not have OC under the age of 40 in our analysis, the JOHBOC Breast Cancer Group reported that 162 of 473 *BRCA2* carriers (34.2%) had BC under the age of 40. Therefore, if the preventive effect on BC is also taken into consideration, further discussion is needed on the optimal timing of RRSO for *BRCA2* carriers. In Japan, risk-reducing surgery has been covered by insurance since April 2020 for *BRCA* mutation carriers with BC and/or OC [23-25]. Since the data by Nomura et al. [12] was before the insurance coverage, the age distribution of *BRCA* carriers who received RRSO may now be changing.

Our retrospective analysis has several limitations. First, we obtained information of 917 OC cases within second-degree relatives from the database, but not all OC cases have undergone a *BRCA* genetic testing, therefore, we performed this analysis only on 468 OC patients who

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underwent the test. Second, in carriers with mutations other than L63X and R2318X, the conclusion regarding the age at diagnosis of OC could not be discussed due to the small number of cases. A more accurate analysis would have been possible if the genetic and clinical information of OC patients up to the second-degree relatives could be collected more accurately. Third, this database is supposed to enter the age at which the cancer was diagnosed, however, OC might have actually occurred earlier than the date of diagnosis.

In conclusion, with the widespread use of companion diagnostics for PARP inhibitors, a large number of *BRCA* mutation families are found, and it is expected that genetic counseling regarding surveillance and risk-reducing surgery for healthy individuals in family members will increase rapidly. In that situation, precise data on cancer risk is needed for genetic counseling. Currently, genetic counseling in Japan is based on Western data regarding the optimal timing for RRSO. However, genetic counseling should be based on Japanese data as much as possible. We hope that our results on the age at diagnosis of OC in *BRCA* mutation carriers will be helpful in the field of actual genetic counseling. Especially in our results, it is very important that no Japanese *BRCA2* mutation carrier developed OC before the age of 40. Personalized counseling that takes into account *BRCA* mutation type and the age at diagnosis of OC in the family would be of great benefit to *BRCA* mutation carriers.

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SUPPLEMENTARY MATERIALS

Table S1
Differences in age at diagnosis of OC due to prior history of BC

Click here to view

Table S2
Clinical characteristics of the nulliparous patients with OC

Click here to view

Table S3
Characteristics of the families with both *BRCA1* and *BRCA2* germline mutation

Click here to view

Table S4
Clinical characteristics of early-onset OC patient and her family members

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