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 (gBRCA1m), germline BRCA2 mutation (gBRCA2m) and germline BRCA wild-type (gBRCAwt) were found in 185, 42 and 241 OC patients, respectively.

Results: The average age at diagnosis of OC in gBRCA1m and gBRCA2m was 51.3 and 58.3 years, respectively, and the difference from gBRCAwt (53.8 years) was significant. The gBRCA2m 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
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
Differences in age at diagnosis of ovarian cancer for each BRCA mutation type

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, χ² 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 (gBRCA1m: 185 patients), germline BRCA2 mutation (gBRCA2m: 42 patients), and germline BRCA wild-type (gBRCAwt: 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 gBRCA1m, gBRCA2m and gBRCAwt, respectively. Regarding personal BC history, OC patients with gBRCA2m tended to have BC more often than gBRCA1m or gBRCAwt. As expected, the average age at diagnosis of OC in gBRCA1m was 51.3 years (median: 50 years), which was significantly younger than that in gBRCA2m (mean: 58.3 years, median: 57.5 years) and gBRCAwt (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 gBRCA1m. On the other hand, the age at diagnosis of OC in gBRCA2m is higher than that in gBRCAwt. 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 gBRCA1m and in the late 50s with gBRCA2m. 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 gBRCA1m
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Table 1. Clinical characteristics of OC patients in the JOHBOC database

| Characteristics                  | gBRCA1m (n=185) | gBRCA2m (n=42) | gBRCAwt (n=241) | p-value |
|----------------------------------|-----------------|----------------|-----------------|---------|
| **Histological subtype**         |                 |                |                 |         |
| Serous carcinoma                 | 138 (74.6)      | 32 (76.2)      | 125 (51.9)      | <0.001† |
| Endometrioid 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**                   |                 |                |                 |         |
| I                                | 19 (10.3)       | 5 (11.9)       | 52 (21.6)       | 0.018†  |
| 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.

*The t-test (vs. gBRCAwt); †Fisher’s exact test (excluding unknown cases); ‡χ² test.

and gBRCA2m was 44.9 and 54.4 years, respectively, and their differences from gBRCAwt (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 Q934X, STOP799, and Y1853C, in 37, 16 and 10 families, respectively. L63X and Y1853C are located in BCCR, on the other hand, Q934X 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.
Differences in age at diagnosis of ovarian cancer for each BRCA mutation type

**Fig. 1.** Age distribution of OC diagnosis by BRCA1/2 mutation status. The peak age at diagnosis of OC was in the late 40s with gBRCA1m and in the late 50s with gBRCA2m. The general statistical data for comparison were data from the Japanese cancer statistics in 2017 [14].

gBRCA1m, germline BRCA1 mutation; gBRCA2m, germline BRCA2 mutation; gBRCAwt, germline BRCA wild-type; OC, ovarian cancer.

A **BRCA1**

L63X (n=103) STOP799 (n=16) Q934X (n=37) Y1853C (n=10)

BCCRI

RING finger domain

STOP613 (n=11) STOP1861 (n=26) S1882X (n=13) STOP2688 (n=10)

BCCRI'

NLS

STOP1861 (n=26) R2318X (n=33) S2835X (n=11) P3039P (n=12)

OCCR

Coiled coil

BCCR2

BRCT domain

B **BRCA2**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27

BCCRI

BCCRI

OCCR1

OCCR2

BCCR2

NLS

Helical domain

Oligonucleotide binding domain

Coiled coil

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 gBRCA2m who developed OC under the age of 30. Women with gBRCA2m 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                                 |
|-----------------------------------------------|-----------------------------------------------|
| No. of families                           | 103                                      | 37                                     |
| No. of carriers                           | 153                                      | 60                                     |
| No. of OC patients                       | 47                                       | 23                                     |
| Age at diagnosis of OC                    |                                            |                                         |
| Mean ± standard deviation                 | 50.1±10.1*                               | 55.1±11.0*                             |
| Minimum                                   | 32                                       | 42                                     |
| Maximum                                   | 83                                       | 67                                     |
| OC patients under the age of 40            | 56                                       | 56                                     |
| OC patients under the age of 45            | 61                                       | 61                                     |

BRCA, 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                                 |
|-----------------------------------------------|-----------------------------------------------|
| No. of OC patients                       | 47                                      | 23                                     |
| Age at diagnosis (No. of patients)          |                                            |                                         |
| <30                                        | 0 (0.0)                                 | 1 (4.5)                                 |
| 30–34                                      | 1 (2.1)                                 | 1 (4.5)                                 |
| 35–39                                      | 4 (8.5)                                 | 0 (0.0)                                 |
| 40–44                                      | 10 (21.3)                               | 4 (18.2)                                |
| 45–49                                      | 12 (25.5)                               | 2 (9.1)                                 |
| 50–54                                      | 10 (21.3)                               | 5 (22.7)                                |
| >55                                       | 10 (21.3)                               | 9 (40.9)                                |
| Unknown                                   | 0 (-)                                   | 1 (-)                                   |
| Mean (yr)                                 | 50.1                                    | 52.8                                    |

Values are presented as number (%).
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 *gBRCA1m*, *gBRCA2m*, and *gBRCAwt* are 52.1, 58.4, and 54.2 years, respectively [15,16].
Our current results are almost the same as that of previous reports. Interestingly, the age at diagnosis of OC in gBRCA2m was significantly higher than that in gBRCAwt. On the other hand, the age at diagnosis in Japanese BC patients with BRCA2 mutations was significantly lower than that in gBRCA2m [17]. In Western countries, the mean age at diagnosis of OC in gBRCA1m and gBRCA2m 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 BRCA1 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 BRCAwt 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 BRCA4 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
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

Click here to view

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