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ORIGINAL ARTICLE

Clinical background and outcomes of risk-reducing salpingo-oophorectomy for hereditary breast and ovarian cancers in Japan

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Abstract

Background This study aimed to identify the clinical background and treatment outcomes of risk-reducing salpingo-oophorectomy (RRSO) in Japan for women with hereditary breast and ovarian cancer (HBOC).

Methods In the present retrospective observational study, we examined the Japanese HBOC Consortium's (JHC) database. This database contains 11,711 probands who received *BRCA* genetic testing, or their relatives, with any cancer in 2433 pedigrees. This study was supported by the registration committee of the JHC.

Results We analyzed 488 individuals diagnosed with HBOC, of which 153 (31.4%) underwent RRSO. Of the latter patients, 88 carried *BRCA1* mutation (B1); 62 carried *BRCA2* mutation (B2); and 3 carried both mutations. During a mean follow-up period of 2.6 years (range 0–12.6), one patient developed a primary peritoneal cancer (PPC). Clinical background comparison for individuals who underwent RRSO vs. those > 45 years of age who did not undergo RRSO revealed that significant factors were represented by B1 ($p < 0.0001$); child bearing ($p < 0.00001$); and breast cancer history ($p < 0.01$). However, family history of ovarian cancer and menopause status were not significantly different.

Conclusion Over 30% HBOC's in Japan underwent RRSO. In Japan, individuals with breast cancer history and B1 generally underwent RRSO, whereas those who did not bear a child mostly avoided RRSO.

Keywords BRCA · Hereditary breast and ovarian cancers · Risk-reducing salpingo-oophorectomy

Introduction

Women with inherited mutations in the *BRCA1* or *BRCA2* (*BRCA1/2*) genes have elevated risks of breast and ovarian cancers; specifically, the lifetime risk of breast cancer ranges between 56 and 84%. The estimated ovarian cancer (OC) risk ranges between 36 and 63% for *BRCA1*-positive individuals and between 10 and 27% for *BRCA2* mutation carriers [1–5]. Of the OC diagnosed in *BRCA1/2*-positive subjects, 80–90% are advanced stage [6]. Women with an elevated OC risk have been offered OC screening with periodic transvaginal ultrasound and serum CA-125 measurements. However, this approach has not been shown to be effective [7–11]. As a consequence, many high-risk women choose risk-reducing salpingo-oophorectomy (RRSO) [12–16]. This procedure lowers OC's risk by 80–96% [12, 17, 18], accompanied by a low surgical morbidity [19]. According to the National Comprehensive Cancer Network's (NCCN) guidelines, RRSO is generally recommended to women between 35 and 40 years old, following completion of child bearing. OC onset in patients with *BRCA2* mutations occurs an average of 8–10 years later than in those positive for *BRCA1*. As a consequence, in patients with *BRCA2* mutations, RRSO for OC risk's management is reasonably delayed until 40–45 years of age [20].

It has been shown in the Netherlands that most mutation carriers (74%) are reported to choose preventive surgery

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[21]. On the contrary, in Japan not so many mutation carriers are thought to have undergone RRSO. Such occurrence is due to the fact that both RRSO and genetic testing are not covered by the national health insurance system. Additionally, aside from patients' economic problems, some individuals have a psychological aversion to removing healthy organs [22, 23]. Furthermore, some patients with no children may refuse to lose their fertility despite having passed reproductive age. Therefore, when proposing RRSO for individuals who are *BRCA1/2* mutation carriers, we must understand patients' background and accordingly manage their various circumstances.

This study aimed to identify the clinical background and treatment outcomes of RRSO for Japanese women. To this end, information was gathered in a nation-wide database. We clarified both the treatment outcome and difference in the patients' clinical background for those who underwent RRSO vs. those who did not.

Materials and methods

The registration system

In this a retrospective observational study, the database of the Japanese HBOC Consortium (JHC) was examined. The registration system received approval by the Ethical Review Board of JHC in December 2014. In the JHC database, 34 Japanese medical institutions registered 11,711 probands who received *BRCA* genetic testing, or their relatives, with any cancer in 2433 pedigrees. An earlier report by Arai et al. has outlined details of the registration procedures as well as database's items [24]. 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.

Clinical information

Clinical information was obtained from the JHC's database, wherein patient information was registered in the form of age at the time of RRSO. Hence, the observation period post-RRSO was calculated based on the patients' age (year) between the last visit and RRSO. We obtained a precise family history by interviewing up to second-degree relatives of probands. However, interviews were not performed in full for the extended family. Therefore, when comparing the family history of those who underwent RRSO with those who did not, we performed a statistical analysis exclusively for probands. We analyzed the background between individuals who underwent RRSO and those who did not. Specifically, the following parameters were analyzed: type of variant allele; mean age at genetic testing; mean age at RRSO; menstrual status; parity; breast cancer history; risk-reducing mastectomy; whether the patients were probands; OC family history; and BC family history BC. A univariate analysis using Chi-square test was used for individual categorical variables. When comparing the background of those individuals, failure to reach the recommended age for RRSO determined exclusion from the study. R (version 3.0.1) was used to perform data analysis.

Results

Of the 11,711 individuals registered with 2433 pedigrees, 2366 probands underwent *BRCA1/2* genetic testing in various clinical practices, after having received genetic counseling. Results showed that *BRCA1/2* mutations were positive in 476 (20.1%) cases; with uncertain variants in 171 (7.2%) cases; and negative in 1719 (72.7%) cases (Table 1). We evaluated 488 individuals, including the 12 individuals who have received genetic testing at the institution that does not belong to JHC. Diagnosed as HBOC who did not undergo bilateral salpingo-oophorectomy, of which 153 (31.4%) received RRSO. Table 2 describes these individuals' background. Of these 153 individuals, 88 carried *BRCA1* mutation, 62 carried *BRCA2* mutation, and 3 carried both mutations. For 11 individuals of the RRSO group and 35 individuals of the control group, the menopause status was unclear, and for 24 individuals of the RRSO group and 69 individuals of the control group, parity was unclear. The mean period between genetic testing and RRSO was 1 year (range 0–14 years). One hundred thirty-six individuals (88.8%) were probands. Thirty-three individuals (21.6%) had a family history of OC. The mean age of the individuals who had not undergone RRSO was 45.2 (range 21–80) years at the time of the last visit. The mean age of the individuals at the time of RRSO was 49.5 (range 34–69) years. Figure 1 shows the age distribution at the time of RRSO. The peak age of undertaking RRSO is 40–44 years in *BRCA1* mutation carriers and 45–49 years in *BRCA2* mutation carriers. The mean age of the individuals who had not undergone RRSO is

Table 1 Genetic mutations of patients ($n = 2366$)

Variant allele	Number (%)
Negative	1719 (72.7)
BRCA1-positive	262 (11.1)
BRCA2-positive	211 (8.9)
Both positive	3 (0.1)
BRCA1 uncertain	65 (2.7)
BRCA2 uncertain	101 (4.3)
Both uncertain	5 (0.2)

Table 2 Clinical background of HBOC

	RRSO ($n=153$)	Control ($n=335$)
Variant allele (total)	153	335
BRCA1	88 (35.9%)	165 (49.3%)
BRCA2	62 (40.5%)	170 (50.7%)
Both	3 (2.0%)	0
Mean age at genetic test (total)	48.5	42.9
BRCA1	48.1	41.1
BRCA2	49.1	44.7
Both	49.2	
Mean age at RRSO (total)	49.5	NA
BRCA1	49	NA
BRCA2	50.1	NA
Both	50.3	NA
Menopause (total)	89 (62.7%)	84 (28.0%)
BRCA1	48 (59.3%)	33 (21.3%)
BRCA2	40 (67.8%)	51 (34%)
Both	1 (50%)	0
Parity (total)	106 (82.2%)	159 (59.8%)
BRCA1	57 (77.0%)	77 (57.0%)
BRCA2	48 (88.9%)	82 (62.6%)
Both	1 (100%)	0
History of breast cancer (total)	138 (90.2%)	301 (89.9%)
BRCA1	79 (89.8%)	145 (87.9%)
BRCA2	56 (90.3%)	156 (91.8%)
Both	3 (100%)	0
Risk-reducing mastectomy (total)	40 (26.1%)	27 (8.1%)
BRCA1	29 (33.0%)	16 (9.7%)
BRCA2	12 (19.4%)	11 (6.5%)
Both	0	0
Proband (total)	136 (88.9%)	288 (86.0%)
BRCA1	81 (92.0%)	135 (81.8%)
BRCA2	52 (83.9%)	153 (90.0%)
Both	3 (100%)	0
Family history of OC (total)	33 (21.6%)	40 (11.9%)
BRCA1	20 (22.7%)	21 (12.7%)
BRCA2	11 (17.7%)	19 (30.6%)
Both	2 (66.7%)	0
Family history of BC (total)	72 (47.1%)	159 (47.5%)
BRCA1	38 (43.2%)	65 (39.4%)
BRCA2	32 (51.6%)	94 (55.3%)
Both	2 (66.7%)	0

naturally younger than those who had, due to the fact that the former were enrolled during their twenties and early thirties. Therefore, failure to reach the recommended age for RRSO determined exclusion from background comparison. Table 3 shows the clinical background comparison between the individuals who underwent RRSO and those aged > 45 years who did not undergo RRSO. The study selection schema

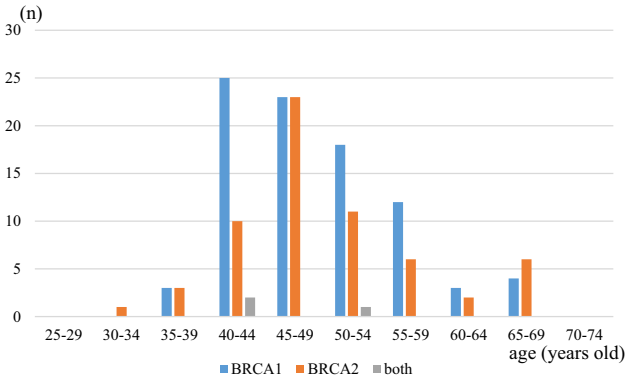

Fig. 1 Distribution of the age at RRSO

is shown in Fig. 2. We observed that breast cancer history ($p<0.01$), parity ($p<0.00001$), and carrying *BRCA1* mutation ($p<0.0001$) were significant factors for undergoing RRSO. However, family history of OC ($p=0.097$) and menopause status showed no significant difference. Among the patients who underwent RRSO, the proportion of those who also underwent RRM was significantly higher.

Discussion

To clarify the clinical background of individuals who underwent RRSO, we examined the nation-wide database of JHC. History of breast cancer, parity, and carrying *BRCA1* mutation were significant factors in performing RRSO. On the contrary, menopause status and family history of OC were not significant factors in their decision-making. Four occult cancers were identified within 153 RRSO specimens and PPC was observed in one individual during the mean follow-up period of 2.6 years.

According to the NCCN guidelines, RRSO is generally recommended to women between 35 and 40 years old, following completion of child bearing. OC onset in patients with *BRCA2* mutation occurs on an average of 8–10 years later than in those positive for *BRCA1*. As a consequence, in patients with *BRCA2* mutations, RRSO for OC risk's management is reasonably delayed until 40–45 years of age. In Japan the mean age of the individuals undergoing RRSO was older than the recommended age by the NCCN guidelines [11]. It has been reported that patients delay RRSO until after 40 years of age. Such an approach might be due to worries about the negative hormonal influence of bilateral oophorectomy. Specifically, the latter would lead to a dramatic and rapid decline in estrogen and androgen levels, with a possible negative influence on quality of life and health [25, 26]. However, in our case the main reason for delaying RRSO is not the fear for hormone deficiency. During genetic testing, the mean age of individuals was 48.5 years

Table 3 Univariate analysis of the factors for RRSO

	RRSO ($n=153$)	Observation ($n=145$)	p value
Variant allele			0.000074
BRCA1 (including both)	91 (59.5%)	52 (35.9%)	
BRCA2	62 (405%)	93 (64.1%)	
Menopause	89 (58.2%)	78 (53.7%)	0.48
Parity	126 (82.4%)	83 (57.2%)	0.0000041
History of breast cancer	138 (90.2%)	112 (77.2%)	0.0039
Risk-reducing mastectomy	41 (26.8%)	5 (3.4%)	0.000000061
Proband	136 (88.9%)	130 (89.7%)	0.98
Family history of OC (per proband)	33 (24.3%)	20 (15.4%)	0.097

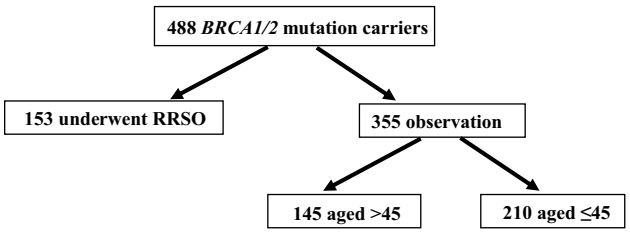

Fig. 2 Study selection schema

since most individuals were probands and received genetic testing after having developed breast cancer. As a consequence, in the future, the mean age at RRSO may decrease once their families undergo genetic testing. In our study, the proportion of parity was significantly low among those aged > 45 years who did not undergo RRSO. Nulliparae mostly avoided RRSO. This may be due to the emotional guilt of removing the ovaries unless they bear children. Such aspect needs to be considered when proposing RRSO to the nulliparas. The reason for carrying *BRCA1* mutation ($p<0.0001$), which was the significant factor for undergoing RRSO, is the difference for the risk of ovarian cancer. The risk of ovarian cancer is two to three times higher among *BRCA1* mutation carriers. Appropriate genetic counseling is believed to have been performed for those individuals. Studies have investigated the perioperative psychosocial aspects of RRSO [27]. RRSO has been reported to reduce worries about breast and OCs and cancer-specific distress, as well as contributing to a reduction in mortality from fallopian tube and ovarian-related cancers. Remarkably, our data has shown that a higher number of individuals with breast cancer history undergo RRSO versus those with a family history of OC. These individuals are believed to become anxious at developing OC once they experience breast cancer, rather than knowing of their family's OC experience. Such observation appears to be a characteristic of Japanese women, who are inclined to believe that they will not develop cancer. Specifically, it has been shown that OC's family history can increase the risk of OC. However, reports have demonstrated that it does not influence the detection rate of precursor lesions or occult cancer at RRSO [28]. RRSO should not be forced on patients only based on OC's family history. Their free will should be prioritized.

Globally, there is a large variability on the reported uptake of RRSO among women at high-risk of OC as follows: between 17 and 52.4% in Asia [16, 29]; between 17.3 and 38% in Australia [29]; between 40 and 89.5% in North America [29–31]; and between 21.4 and over 90% across European countries [29, 32]. In Japan, both RRSO and genetic testing are not covered by national insurance. This represents the main reason of the comparatively low uptake rate of RRSO. Since insurance does not cover RRSO, only a limited number of medical institutions can perform RRSO, following approval of institutional review boards. Additionally, the shortage of genetic counselors represents a problem as genetic testing in absence of suitable counseling should be avoided. A nation-wide system of training and education for genetic counselors is necessary. Importantly, nowadays more institutions are gradually preparing for RRSO and an increasing number of individuals with HBOC will be able to undergo RRSO in Japan.

In the present study, some limitations can be identified. First, since the medical staff that made this database was largely specialized in breast cancer, there is a lack of precise clinical data on OC (i.e., histology and FIGO stage). The rate of occult cancer is inadequate to evaluate owing to its retrospective nature. Pathological evaluation must be performed based on the SEE-FIM protocol, but we could not survey the accuracy of the evaluation. Second, 68% of individuals registered to this database belonged to an institute in Tokyo. Therefore, although we concluded that as much as 32.1% of the *BRCA1/2* pathogenic variant carriers received RRSO, our study may not reflect the current circumstances occurring elsewhere in Japan. Most individuals are believed to not have received RRSO in the suburbs.

We clarified the treatment outcome and the situation of RRSO for Japanese women using a Japanese nationwide database. Despite the fact that the national insurance does not cover RRSO, over 30% of HBOC have undergone

RRSO. Specifically, patients with *BRCA1* mutation and a history of breast cancer generally underwent RRSO, whereas those who did not bear a child mostly avoided RRSO. As a risk-reducing surgery, RRSO should be performed based on an individual's free will. It is the physician's role to provide patients with appropriate information about their cancer risk based on their clinical background.

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Compliance with ethical standards

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

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