Uptake Rate of Risk-reducing Salpingo-oophorectomy and Surgical Outcomes of Female Germline BRCA1/2 Mutation Carriers: A Retrospective Cohort Study at a Tertiary Institutional Hospital in Korea

Hyunji Lim

Seoul National University College of Medicine

Se Ik Kim

Seoul National University College of Medicine

Sowoon Hyun

Seoul National University College of Medicine

Gwang Bin Lee

Seoul National University College of Medicine

Aeran Seol

Seoul National University College of Medicine

Maria Lee (✉ marialeemd@gmail.com)

Seoul National University College of Medicine

Research

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Abstract

Background: This study investigated the uptake rate of risk-reducing salpingo-oophorectomy (RRSO) and surgical outcomes of germline *BRCA1/2* mutation carriers at Seoul National University Hospital (SNUH). We examined records of 824 women who underwent germline *BRCA1/2* gene testing at SNUH between 2005 and 2020. Among them, we identified women with a pathogenic mutation on either the *BRCA1* or the *BRCA2* gene and excluded ovarian cancer patients. Characteristics of participants who underwent RRSO (RRSO group) were compared to those who did not (non-RRSO group). Surgical outcomes and pathologic results were investigated in the RRSO group.

Results: There were 117 *BRCA1/2* mutation carriers included in this analysis. The uptake rate of RRSO was 70.1% (82/117). Older age (mean: 48.8 vs. 42.1 years; $P = 0.002$) and higher employment rate (65.9% vs. 14.3%; $P < 0.001$) were observed in the RRSO group than in the non-RRSO group. However, no differences in other factors such as personal and family history of breast cancer were observed between the two groups. In the RRSO group, the median time interval between the genetic test and RRSO was 10.0 months, and there were three (3.7%) incidental cases of high-grade serous carcinoma. However, one patient in the non-RRSO group developed primary peritoneal cancer after 103.8 months of surveillance.

Conclusions: The uptake rate of RRSO in *BRCA1/2* mutation carriers was about 70%. Considering incidental cancer cases in women without abnormal findings on preoperative evaluation, it would be recommended to perform RRSO soon after the genetic test.

Background

Ovarian cancer, one of the most lethal gynaecological malignancies, is a global burden, with 313,959 new cases and 207,252 deaths estimated in 2020 (1). Due to a lack of appropriate screening tools for ovarian cancer, most patients are diagnosed at an advanced stage. Accordingly, the prognosis of ovarian cancer is poor—the likelihood of 5-year survival is 23% in stage III and only 11% in stage IV. Many efforts have been focused on diagnosing ovarian cancer at an early stage through risk prediction and prevention. Identifying genetic predisposition offers opportunities for cancer prevention.

The *BRCA1* and *BRCA2* genes are the most commonly mutated genes in ovarian cancer patients. These autosomal dominant mutations account for approximately 90% of hereditary ovarian cancers and 30–70% of hereditary breast cancers (2). People with these genetic mutations have a higher chance of developing breast and ovarian cancer. The cumulative risk of breast cancer at age 70 is 45–85% in individuals with the *BRCA1/2* gene mutation compared to the 11% risk of the general population. In addition, the cumulative risk of ovarian cancer at age 70 is 39–46% for the *BRCA1* mutation and 10–27% for the *BRCA2* mutation, compared to the 1.3%–1.9% risk of the general population (3) (4). These cancers develop 10 years earlier than non-hereditary cancers, and the most common histologic type in ovarian cancer is high-grade serous carcinoma (HGSC).

Risk-reducing salpingo-oophorectomy (RRSO) is currently regarded as one of the most protective tools for *BRCA1/2* mutation carriers. Typically, RRSO is recommended between the ages of 35 and 40 for the *BRCA1* mutation, between ages 40 and 45 for the *BRCA2* mutation, and upon completion of child-bearing (5). Otherwise, intensive screening for ovarian cancer is recommended: transvaginal ultrasonography combined with serum CA-125 may be considered from age 30 to 35, although benefits of this are uncertain. It is known that there are many factors that affect patients' decisions to undergo RRSO, such as personal or family history of breast cancer, individual family plan, social atmosphere, and so on.

At our hospital, the *BRCA1/2* gene tests on high-risk patients have been conducted since 2005. This study presents a 15-year experience of RRSO in female germline *BRCA1/2* mutation carriers at a tertiary institutional hospital in Korea. We also investigated significant factors that might affect the carriers' decisions.

Materials And Methods

Study population

Between September 2005 and August 2020, a total of 824 women underwent germline *BRCA1/2* gene testing at our institution. We included women aged 20 or older who had a pathogenic or a likely pathogenic variant on either the *BRCA1* or the *BRCA2* gene. We excluded women with the following conditions: (1) those diagnosed with peritoneal, ovarian, or tubal cancers, or received bilateral salpingo-oophorectomy before the time of the genetic test; (2) had not been referred to the OB/GYN clinic; or (3) were lost to follow-up checks after visiting the OB/GYN clinic once.

Overall, 117 *BRCA1/2* mutation carriers who met these inclusion criteria were included in this analysis (Fig. 1). They were divided into two groups based on whether they received RRSO after *BRCA1/2* gene testing or not. Thereafter, we compared the baseline characteristics of the RRSO and non-RRSO (surveillance only) groups.

Data collection

We reviewed the women's medical records and pathologic reports, retrospectively, and collected their clinicopathologic data, including age at *BRCA1/2* gene testing, menopausal status, parity, marital status, educational status, occupational status, comorbidity, prior abdominopelvic surgery, and personal history of breast and other cancers. Family history of breast, ovarian, and other cancers were also collected up to the women's second-degree relatives. Germline *BRCA1/2* gene testing methods at SNUH were described in our previous study (6). As of February 2016, the method changed from direct sequencing (Sanger sequencing) to next-generation sequencing (NGS) of *BRCA1/2* genes. Pathogenic or like-pathogenic variants found in NGS were confirmed by direct sequencing.

In the non-RRSO group, patients received regular examinations with transvaginal ultrasonography, serum CA-125, or both every 6–12 months. In the RRSO group, the patients also received regular examinations until the date of RRSO, and we collected their detailed surgical information and pathological results. Observation period was defined as intervals between the *BRCA1/2* gene test and date of gynecologic cancer diagnosis or last visit in the non-RRSO group, while it was defined as intervals between the *BRCA* gene test and date of RRSO in the RRSO group.

Statistical analysis

First, we calculated the total uptake rate of RRSO in *BRCA1/2* mutation carriers. Next, regarding *BRCA1/2* mutation carriers aged ≥ 35 years at the time of genetic testing and receiving RRSO within 12 months as having intentions to receive RRSO, we assigned them to the RRSO strategy group. In contrast, the remaining participants were assigned to the surveillance strategy group. We calculated the intentional uptake rate of RRSO, which was the proportion of patients receiving RRSO within a year among *BRCA1/2* mutated patients aged ≥ 35 .

We compared women's clinicopathologic characteristics between the two groups using Student's t- or Mann-Whitney U-tests for continuous variables and Pearson's chi-squared or Fisher's exact tests for categorical variables. In multivariate analysis, we used a logistic regression model to calculate adjusted odds ratio (aOR) and 95% confidence interval (CI) for each variable. All these statistical analyses were performed using SPSS statistical software (version 25.0; IBM Corp., Armonk, NY, USA). A *P* value of less than 0.05 was considered statistically significant.

Results

During 18.8 months of the median observation periods, 82 of the 117 *BRCA1/2* mutation carriers received RRSO; therefore, the total uptake rate of RRSO was calculated as 70.1%. The women's characteristics at the time of the *BRCA1/2* gene test are shown in Table 1. Women in the RRSO group were significantly older ($P = 0.002$) and had higher employment rate ($P < 0.001$), compared to those in the non-RRSO group. However, other characteristics, such as parity, comorbidity, menopausal and educational status, prior abdominopelvic surgery, type of mutated gene (*BRCA1* or *BRCA2*), personal history of cancer other than breast/ovarian cancers, and family history of cancers, were similar between the two groups.

Table 1
Characteristics of the study population at the time of the BRCA1/2 gene test

Characteristics	All (n = 117, %)	Surveillance only (n = 35, %)	RRSO (n = 82, %)	P
Age at <i>BRCA</i> test, years				0.002
Mean $\pm$ SD	46.8 $\pm$ 11.2	42.1 $\pm$ 13.0	48.8 $\pm$ 9.8	
Menopausal status				0.083
Premenopause	66 (56.4)	24 (68.6)	42 (51.2)	
Menopause*	51 (43.6)	11 (31.4)	40 (48.8)	
Parity				0.129
Mean $\pm$ SD	1.7 $\pm$ 1.1	1.5 $\pm$ 1.1	1.8 $\pm$ 1.1	
Median (range)	2.0 (0–5)	2.0 (0–4)	2.0 (0–5)	
Null	19 (16.2)	8 (22.9)	11 (13.4)	0.205
Marital status				0.106
Single	17 (14.5)	6 (17.1)	11 (13.4)	
Married	96 (82.1)	26 (74.3)	70 (85.4)	
Divorced/Bereavement	4 (3.4)	3 (8.6)	1 (1.2)	
Educational status				0.546
$\leq$ High school	38 (32.5)	10 (28.6)	28 (34.1)	
$\geq$ College	50 (42.7)	14 (40.0)	36 (43.9)	
Unknown	29 (24.8)	11 (31.4)	18 (22.0)	
Occupational status				< 0.001
No	47 (40.2)	22 (62.9)	25 (30.5)	
Yes	59 (50.4)	5 (14.3)	54 (65.9)	
Unknown	11 (9.4)	8 (22.9)	3 (3.7)	
Comorbidity				
Hypertension	12 (10.3)	2 (5.7)	10 (12.2)	0.506
Diabetes	9 (7.7)	2 (5.7)	7 (8.5)	0.723
Dyslipidemia	13 (11.1)	2 (5.7)	11 (13.4)	0.339
Prior abdominopelvic surgery				0.775
No	78 (66.7)	24 (68.6)	54 (65.9)	
Yes	39 (33.3)	11 (31.4)	28 (34.1)	
Hx of BC	101 (86.3)	30 (85.7)	71 (86.6)	> 0.999
Age at diagnosis of BC				
Mean $\pm$ SD	44.9 $\pm$ 10.9	41.7 $\pm$ 12.6	46.3 $\pm$ 10.0	0.027
Young-age BC [†]	44 (37.6)	17 (48.6)	27 (32.9)	0.084
Bilateral BC	20 (17.1)	2 (5.7)	18 (22.0)	0.031
Synchronous	8 (6.8)	0	8 (9.8)	0.495
Metachronous	12 (10.3)	2 (5.7)	10 (12.2)	
Recurrent BC	14 (12.0)	3 (8.6)	11 (13.4)	0.546
Hx of other cancer	5 (4.3)	2 (5.7)	3 (3.7)	0.635
Family Hx of BC [‡]	77 (65.8)	21 (60.0)	56 (68.3)	0.387
No. of relatives				
Mean $\pm$ SD	0.9 $\pm$ 0.9	0.8 $\pm$ 0.8	1.0 $\pm$ 0.9	0.198

Characteristics	All (n = 117, %)	Surveillance only (n = 35, %)	RRSO (n = 82, %)	P
Family Hx of ovarian cancer [‡]	27 (23.1)	7 (20.0)	20 (24.4)	0.606
No. of relatives				
Mean ± SD	0.3 ± 0.6	0.2 ± 0.5	0.3 ± 0.6	0.565
Family Hx of other cancer [‡]	28 (23.9)	5 (14.3)	23 (28.0)	0.110
No. of relatives				
Mean ± SD	0.4 ± 0.8	0.2 ± 0.5	0.4 ± 0.8	0.087
Germline <i>BRCA</i> mutational status				0.586
<i>BRCA1</i> mutation	58 (49.6)	16 (45.7)	42 (51.2)	
<i>BRCA2</i> mutation	59 (50.4)	19 (54.3)	40 (48.8)	
Both gene mutation	0	0	0	
Abbreviations: BC, breast cancer; Hx, history; RRSO, risk-reducing salpingo-oophorectomy; SD, standard deviation.				
*Menopause was defined when a woman has missed menstruation for 12 consecutive months.				
†Breast cancer diagnosed before the age of 40 years.				
‡According to the pedigree up to second degree relatives.				

Overall, 101 (86.3%) of the study population had been diagnosed with breast cancer before the genetic test, and this proportion did not differ between the RRSO and non-RRSO groups ($P > 0.999$) (Table 1). However, the age at breast cancer diagnosis was significantly older in the RRSO group than the non-RRSO group (mean, 46.3 vs. 41.7 years, $P = 0.027$). Regarding history of breast cancer, significantly more patients in the RRSO group had been diagnosed with bilateral breast cancer ($P = 0.031$), while no differences in the proportions of young-age breast cancer (diagnosed before the age of 40 years) ($P = 0.084$) and recurrent breast cancer cases ($P = 0.546$) were observed between the two groups.

In the RRSO group, the median time interval between the *BRCA1/2* gene test and RRSO was 10.0 months. During the observation period, 11 of the 71 (15.5%) breast cancer patients experienced disease recurrence, while one of the 11 (9.1%) non-breast cancer patients developed *de novo* breast cancer (Table 2). Surgical details of the RRSO group are presented in **Supplementary Table 1**. Of 82 women, 58 (70.7%) received RRSO only, while eight (9.8%) received RRSO plus hysterectomy. The reasons for hysterectomy were uterine myoma ($n = 4$), adenomyosis ($n = 1$), endometrial hyperplasia ($n = 1$), endometrial polyp ($n = 1$), and cervical intraepithelial neoplasia 3 ($n = 1$). One postmenopausal woman opted to received hysterectomy without any cause. Breast cancer surgery was conducted on the same day of RRSO in 11 (13.4%) patients, of which one also received simultaneous risk-reducing mastectomy (RRM). Among the rest, three (3.7%), one (1.2%), and one (1.25%) received RRM, myomectomy, and breast augmentation surgery, respectively, concomitantly with RRSO. In terms of the surgical approach for RRSO, laparoscopic surgery was the dominant method that accounted for 95.1% of the cases, while open surgery was conducted in 4.9%.

Table 2
Development of breast and gynecologic cancers after the BRCA1/2 gene test

Characteristics	<i>Surveillance only</i> (n = 35, %)	<i>RRSO</i> (n = 82, %)
Observational period, months*		
Median (range)	96.6 (2.4-175.9)	10.0 (1.1-162.6)
Baseline BC	30 (85.7%)	71 (86.6%)
Recurrence of BC		
No	17 (48.6%)	60 (73.2%)
Yes	13 (37.1%)	11 (13.4%)
Contralateral breast	4	4
Other sites	9	6
Both	0	1
Development of ovarian cancer	0	1 [†]
Development of tubal cancer	0	1 [†]
Development of peritoneal cancer	1	0
Development of other cancer	1 (cervix)	0
Baseline no BC	5 (14.3)	11 (13.4)
Development of BC	0	1
Development of ovarian cancer	0	1 [†]
Abbreviations: BC, breast cancer; RRSO, risk-reducing salpingo-oophorectomy.		
*Observation period was defined as intervals between the <i>BRCA</i> gene test and date of gynecologic cancer diagnosis or last visit in the surveillance-only group, while it was defined as intervals between the <i>BRCA1/2</i> gene test and date of RRSO in the RRSO group.		
[†] Incidental case (diagnosed after RRSO).		

The final pathologic diagnosis was reported with no abnormality in 46.3% of the salpingo-oophorectomy specimens (**Supplementary Table 2**). Approximately, one-third of patients (31.7%) were diagnosed with paratubal cysts, and other benign lesions were identified in 18 (22.0%) patients. Three (3.7%) patients were incidentally diagnosed with ovarian/tubal cancers; HGSCs were identified in their single ovary (n = 1), both ovaries (n = 1), and single tube (n = 1). All patients underwent subsequent laparoscopic staging operations. Regarding the observation periods of these three incidental ovaria/tubal cancer patients, one received RRSO 1.9 months after *BRCA1/2* gene testing, and the other two took 14.3 months and 69.0 months.

In the non-RRSO group, the median observation period was 96.6 months, during which 13 of the 30 (43.3%) breast cancer patients experienced disease recurrence, while none of the five non-breast cancer patients developed *de novo* breast cancer. Following *BRCA1/2* gene testing, one patient was diagnosed with cervical cancer at 26.3 months and another developed primary peritoneal cancer at 103.8 months (Table 2).

The follow-up of the study population focusing on the development of breast and gynecologic cancers after *BRCA1/2* gene testing are depicted in Fig. 2. In addition, details of three incidental ovarian/tubal cancer cases in the RRSO group and newly developed primary peritoneal cancer and cervical cancer cases are shown in Table 3.

Table 3
Detailed characteristics of patients who developed gynecologic cancers

No.	Age, years	Mutated gene	Parity/MP	Comorbidity	Family Hx of BC	Family Hx of OC	BC (age, years)	Strategy	Time interval, months	Preoperative findings	Surgeon
#1.	55.6	<i>BRCA2</i> c.5722_5723delCT	3/MP	No	Mother	No	Yes, bilateral (55.6)	RRSO	1.9	Unilateral ovarian cyst, 3 cm	SPL BSO
#2.	41.4	<i>BRCA1</i> c.3746dupA	0/No	No	Sister	No	No	Surveillance ◇ RRSO	69.0	Newly diagnosed BC; Normal uterus and ovaries	SPL BSO and BC surgery
#3.	70.2	<i>BRCA2</i> c.3744_3747delTGAG	2/MP	HTN	Sister	No	Yes (70.2)	Surveillance ◇ RRSO	14.3	Bilateral ovarian cysts	SPL BSO
#4.	54.8	<i>BRCA2</i> c.1399A > T	2/MP	HTN	Mother, Sister 2	No	Yes (47.7)	Surveillance	103.8	Development of peritoneal carcinomatosis and ascites	
#5.	47.7	<i>BRCA1</i> c.911_918dupTCTGTAAT	2/No	DM	Mother	Mother	Yes (47.7)	Surveillance	26.3	LEEP due to Pap abnormality (ASC-H)	
Abbreviations: ASC-H, atypical squamous cells cannot exclude HSIL; BC, breast cancer; BSO, bilateral salpingo-oophorectomy; DM, diabetes; FIGO, International Gynaecology and Obstetrics; HGSC, high-grade serous carcinoma; HTN, hypertension; MP, menopause; OC, ovarian cancer; RH, radical hysterectomy; RRSO, risk-reducing salpingo-oophorectomy; SCC, squamous cell carcinoma; SPL, single-port laparoscopy.											

Lastly, we re-assigned the study population to the RRSO strategy and surveillance strategy groups based on the women's age at the time of the *BRCA1/2* gene test and time interval between the test and actual date of RRSO (12 months). After excluding 14 women aged < 35 years, we identified that 44 of the 103 women received RRSO within 12 months after genetic testing; therefore, the intentional uptake rate of RRSO was 42.7%. Multivariate analysis was conducted to identify the factors affecting the *BRCA1/2* mutation carrier's decision on taking RRSO strategy rather than surveillance. Results showed that an age of ≥ 50 years (aOR, 5.060; 95% CI, 1.639–15.623; $P = 0.005$) and employed status (aOR, 3.402; 95% CI, 1.104–10.484; $P = 0.033$) were positive factors towards RRSO strategy (Table 4).

Table 4
Factors associated with taking risk-reducing salpingo-oophorectomy strategy rather than surveillance

Characteristics	Comparison	Univariate analysis			Multivariate analysis		
		OR	95% CI	<i>P</i>	aOR	95% CI	<i>P</i>
Age at <i>BRCA</i> test, years	≥ 50 vs. <50	2.770	1.234–6.219	0.014	5.060	1.639–15.623	0.005
Menopausal status*	Menopause vs. Premenopause	1.964	0.889–4.339	0.095			
Parity	Parous vs. Null	1.346	0.368–4.919	0.653			
Educational status	$\geq$ College vs. $\leq$ High school	0.711	0.292–1.727	0.451	0.735	0.238–2.270	0.593
Occupational status	Yes vs. No	2.677	1.153–6.216	0.022	3.402	1.104–10.484	0.033
Prior abdominopelvic surgery	Yes vs. No	0.936	0.415–2.125	0.874			
Family Hx of breast cancer [†]	Yes vs. No	1.041	0.463–2.338	0.923			
Family Hx of ovarian cancer [†]	Yes vs. No	1.469	0.587–3.677	0.412	1.948	0.596–6.367	0.270
Mutated gene	<i>BRCA1</i> vs. <i>BRCA2</i>	0.753	0.344–1.647	0.477			
Abbreviations: Hx, history; OR, odds ratio; aOR, adjusted OR; CI, confidence interval.							
*Menopause was defined as when a woman has missed menstruation for 12 consecutive months.							
[†] According to the pedigree up to second degree relatives.							

Discussion

In this retrospective cohort study, we presented our real-world experience on management of female germline *BRCA1/2* mutation carriers in relation to RRSO strategy. The total and intentional uptake rates of RRSO were 70.1% and 42.7%, respectively. Despite RRSO, incidental ovarian/tubal cancers were identified in 3.7% of the women. *BRCA1/2* mutation carriers' age and occupational status affected their decision on taking RRSO strategy rather than surveillance.

The ovary is an essential organ for maintaining fertility and secreting female sex hormones, especially estrogen. Therefore, women with premature surgical menopause may suffer from an increased risk of bone loss, cardiovascular disease, and decreased cognitive function (7). In addition, they may experience a lower quality of life due to vasomotor symptoms, such as hot flashes, sweating, etc. Moreover, women who experience early menopause may feel that they have lost their femininity. In this aspect, older women, particularly those who have already experienced menopause, are more inclined to undergo RRSO, compared to young, premenopausal women (8).

Women who are employed also tended to choose RRSO strategy, rather than surveillance, possibly because it is more difficult for them to take regular screening tests, compared with unemployed women. Previous studies have shown that family history of cancer and personal history of breast cancer were important factors for *BRCA1/2* mutation carriers to undergo RRSO (9, 10). In addition, the type of mutated *BRCA* gene and menopausal status were significantly associated with RRSO (11). However, we observed inconsistent results, which might originate from the uniqueness of our study population; 86.3% of the mutation carriers had been diagnosed with breast cancer before genetic testing in this study. In general, people who have no personal cancer history are known to be reluctant to undergo *BRCA1/2* gene testing, even if they have high-risk factors such as a family history of cancer.

The total uptake rate of RRSO in this study was at the upper end of the range described in previous studies, who reported it as 50–70% with inter-center and inter-country variations (11–13). These variations are due to differences in the characteristics of the study population, sociocultural atmosphere, follow-up period, follow-up strategy, counselling by gynecologists, and so on. In Korea, the tendency to receive RRSO is highly influenced by the policy of the National Health Insurance Service (NHIS). The NHIS started to cover the *BRCA1/2* gene test in epithelial ovarian and breast cancer patients with a family history of cancer in April 2012, and RRSO in *BRCA1/2* mutated cancer patients in December 2012. Thereafter, the annual number of female cancer patients undergoing *BRCA1/2* gene testing and RRSO increased rapidly. Furthermore, in 2017, the NHIS began to cover the *BRCA1/2* gene test not only for ovarian and breast cancer patients but also for first-degree families of *BRCA*-mutated cancer patients.

The intentional uptake rate of RRSO was only 42.7%, which was quite low. We could infer that about half of the patients in the RRSO group wanted to take intensive screening at first, considering the finding that 3.7% of women in the RRSO group were incidentally diagnosed with ovarian/tubal cancers despite no abnormal findings on preoperative evaluation. In literature, the occult ovarian/tubal cancer rate in *BRCA1/2* mutation carriers undergoing RRSO was described as 0.6–17% (14–18). Therefore, it is recommended that *BRCA1/2* mutation carriers, especially those who completed childbearing, undergo RRSO soon after genetic testing to prevent development of ovarian/tubal cancer and microscopic cancer progression. Nevertheless, neglecting cancer screening after RRSO should be avoided, as risks of developing primary peritoneal cancer and breast cancer still remain (19).

With accumulated evidence that the fallopian tube plays a principal role in the development of ovarian/tubal cancer, some researchers have proposed a risk-reducing early salpingectomy and delayed oophorectomy (RRESDO) strategy for premenopausal women to resolve problems with premature menopause (20, 21). RRESDO is a two-stage surgical alternative to RRSO. In a pilot study, early salpingectomy was done for premenopausal women just after detection of a *BRCA1/2* gene mutation. Then, delayed oophorectomy was recommended for patients at age 40 with the *BRCA1* gene mutation and age 45 with the *BRCA2* gene mutation (22). Most patients who underwent RRESDO, particularly women concerned about sexual dysfunction, were satisfied with their choice of surgery. However, the RRESDO strategy still remains investigational and a clinical trial is required to make this strategy routine (23).

For *BRCA1/2* mutation carriers who are reluctant to undergo RRSO, the Korean Society of Gynecologic Oncology (KSOG) recommends transvaginal sonography or serum CA-125 tests every 4 months (24). Such intense screening might offer a better chance for early detection of ovarian cancer, however, robust scientific evidence on this issue is needed.

The current study had several limitations. First, there was bias in the study population towards breast cancer patients. Second, not all possible confounding factors were included. In particular, the causes of amenorrhea, such as natural menopause, surgical menopause, and medication-induced menopause (e.g., tamoxifen, aromatase inhibitor), were not considered. Third, the trend of undergoing RRSO with time was not analyzed. Further prospective cohort studies are warranted in a larger population.

In conclusion, the total uptake rate of RRSO in female germline *BRCA1/2* mutation carriers was 70.1%, but the intentional uptake rate was much lower at 42.7%. The uptake rate of RRSO was affected by the carriers' age and occupational status. Considering the 3.7% of incidental cancer cases in women who underwent RRSO despite no abnormal findings on preoperative evaluation, it is recommended to perform RRSO soon after the confirmation of germline *BRCA1/2* mutations.

Abbreviations

aOR, adjusted odds ratio; CI, confidence interval; HGSC, high-grade serous carcinoma; KSOG, Korean Society of Gynecologic Oncology; NGS, next-generation sequencing; NHIS, National Health Insurance Service; RRESDO, risk-reducing early salpingectomy and delayed oophorectomy; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy; SNUH, Seoul National University Hospital

Declarations

ACKNOWLEDGMENTS

Not applicable

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective cohort study was approved by the Institutional Review Board of Seoul National University Hospital (SNUH; No. H-2011-040-1170) and conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived.

AUTHORS' CONTRIBUTIONS

ML and SIK conceived the concept for the manuscript. SH and GBL collected the data. HL wrote the initial draft of the manuscript. All authors contributed to edit the manuscript. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Not applicable

CONSENT FOR PUBLICATION

The requirement for informed consent was waived.

COMPETING INTERESTS

The authors declare no conflicts of interest relevant to this study.

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Figures

Figure 1

A flow diagram depicting the selection of the study population.

Figure 2

Follow-up of study population after the BRCA1/2 gene test.

Supplementary Files

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