Original Article
Yonsei Med J 2021 Dec;62(12):1090-1097
https://doi.org/10.3349/ymj.2021.62.12.1090
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

# Uptake Rate of Risk-Reducing Salpingo-Oophorectomy and Surgical Outcomes of Female Germline *BRCA1/2* Mutation Carriers: A Retrospective Cohort Study

Hyunji Lim[1], Se Ik Kim[1,2], Sowoon Hyun[1], Gwang Bin Lee[1], Aeran Seol[1], and Maria Lee[1,3]

[1]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul;
[2]Seoul National University Hospital Biomedical Research Institute, Seoul;
[3]Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea.

**Purpose:** 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).

**Materials and Methods:** We examined the 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 the analysis. The uptake rate of RRSO was 70.1% (82/117). Older age (mean: 48.8 years 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 compared to 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.

**Conclusion:** 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, *BRCA1/2*-mutated women might refrain from the delayed implementation of RRSO after the genetic test.

**Key Words:** Ovarian cancer, hereditary breast and ovarian cancer syndrome, *BRCA1* gene, *BRCA2* gene

## INTRODUCTION

Ovarian cancer, one of the most lethal gynaecological malignancies, is a global burden, with 313959 new cases and 207252 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, with the likelihood of 5-year survival reported to be 23% in stage III and only 11% in stage IV. Various efforts have 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 cancers. The cumulative risk of breast cancer at age 70 is 45%–85% in individuals with the

**Received:** July 14, 2021 **Revised:** September 2, 2021
**Accepted:** September 27, 2021
**Corresponding author:** Maria Lee, MD, PhD, Department of Obstetrics and Gynecology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Tel: 82-2-2072-2842, Fax: 82-2-762-3599, E-mail: marialeemd@gmail.com

•The authors have no potential conflicts of interest to disclose.

*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 childbearing.[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. Many factors affecting the patients' decisions are known 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

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

### 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 years 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) 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 the inclusion criteria were included in our 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.

All *BRCA1/2* mutation carriers included in this study visited the OB/GYN clinic and underwent comprehensive counseling with 13 faculty from the Department of Obstetrics and Gynecology; nine were gynecologic oncology faculty, and four were non-gynecologic oncology faculty. They provided the following information to the *BRCA1/2* mutated women per the contemporary clinical practice guidelines[5,7]: 1) lifetime risk of breast and ovarian cancers; 2) screening methods; 3) methods of prophylactic surgery, complications, and the extent of risks

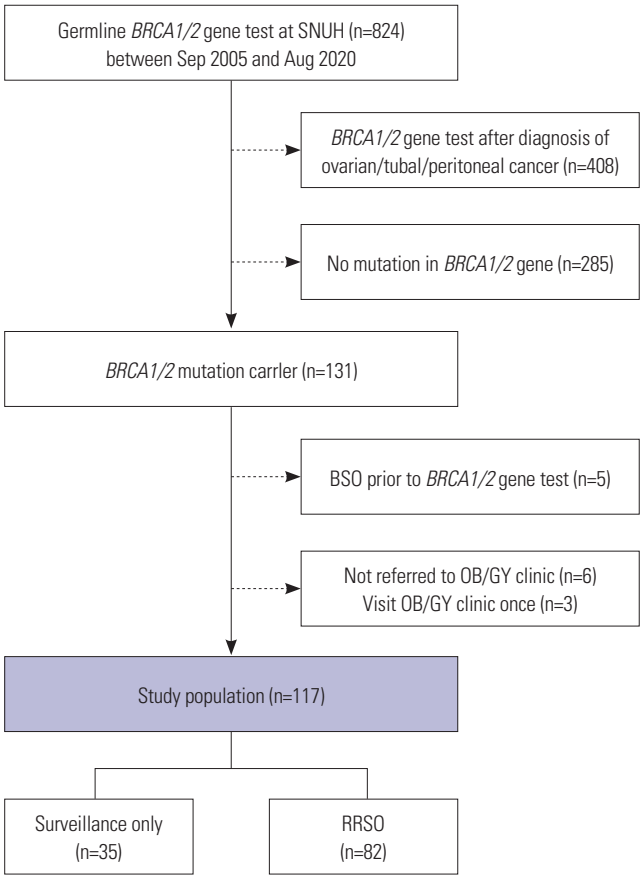


**Fig. 1.** Flow diagram depicting the selection of study population. SNUH, Seoul National University Hospital; BSO, bilateral salpingo-oophorectomy; RRSO, risk-reducing salpingo-oophorectomy.

decreased by surgery; 4) other alternative options; and 5) the need for family screening. Based on the women's marital status, marriage plan, and whether they completed childbearing, the adequate age of RRSO was also discussed. For the breast cancer survivors and breast cancer patients on active treatment, their attending breast surgeons and medical oncologists provided additional counseling in breast cancer.

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 their detailed surgical information and pathological results were collected. 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 the *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 years.

We compared the 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, a logistic regression model was used to calculate adjusted odds ratio (aOR) and 95% confidence interval (CI) for each variable. All statistical analyses were performed using SPSS statistical software (version 25.0; IBM Corp., Armonk, NY, USA). A $p$ value<0.05 was considered statistically significant.

## RESULTS

Among the study population (n=117), 111 and 6 women consulted with gynecologic oncology faculty and non-gynecologic oncology faculty, respectively. During a median observation period of 18.8 months, 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. The mean age for the gene test was 46.8 years, and more than half (53.0%) of the study participants received the gene testing at ≥45 years of age. 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.

Overall, 101 (86.3%) of the study population had been diagnosed with breast cancer before the genetic test was performed, 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 in the non-RRSO group (mean, 46.3 years 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). The mean age at the time of RRSO was 48.8 years and 52.9 years for the *BRCA1* and *BRCA2* mutation carriers, respectively (Supplementary Table 1, only online). In accordance with the current practice guidelines,[5] six out of 42 *BRCA1*-mutated women and six out of 40 *BRCA2*-mutated women received RRSO between the ages of 35 and 40 years and between the ages of 40 and 45 years, respectively. None of these 12 patients were diagnosed with ovarian/tubal cancers.

Surgical details of the RRSO group are also presented in Supplementary Table 1 (only online). Of 82 women, 58 (70.7%) received RRSO only, while 8 (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, 3 (3.7%), 1 (1.2%), and 1 (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%.

The final pathologic diagnosis was reported with no abnormality in 46.3% of the salpingo-oophorectomy specimens (Supplementary Table 2, only online). 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 ovari-


https://doi.org/10.3349/ymj.2021.62.12.1090

**Table 1.** Characteristics of the Study Population at the Time of *BRCA1/2* Gene Test

| Characteristics | All (n=117) | Surveillance only (n=35) | RRSO (n=82) | *p* |
|---|---|---|---|---|
| Age at *BRCA* test (yr) | 46.8±11.2 | 42.1±13.0 | 48.8±9.8 | 0.002 |
| <35 | 17 (14.5) | 14 (40.0) | 3 (3.7) | <0.001 |
| 35–40 | 25 (21.4) | 5 (14.3) | 20 (24.4) | |
| 40–45 | 13 (11.1) | 3 (8.6) | 10 (12.2) | |
| 45–50 | 18 (15.4) | 5 (14.3) | 13 (15.9) | |
| ≥50 | 44 (37.6) | 8 (22.9) | 36 (43.9) | |
| 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 | 1.7±1.1 | 1.5±1.1 | 1.8±1.1 | 0.129 |
| 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 |
| ≤High school | 38 (32.5) | 10 (28.6) | 28 (34.1) | |
| ≥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 (yr) | 44.9±10.9 | 41.7±12.6 | 46.3±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 | 0.9±0.9 | 0.8±0.8 | 1.0±0.9 | 0.198 |
| Family Hx of ovarian cancer‡ | 27 (23.1) | 7 (20.0) | 20 (24.4) | 0.606 |
| No. of relatives | 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 | 0.4±0.8 | 0.2±0.5 | 0.4±0.8 | 0.087 |
| Germline *BRCA* mutational status | | | | 0.586 |
| *BRCA1* mutation | 58 (49.6) | 16 (45.7) | 42 (51.2) | |
| *BRCA2* mutation | 59 (50.4) | 19 (54.3) | 40 (48.8) | |
| Both gene mutation | 0 | 0 | 0 | |

BC, breast cancer; Hx, history; RRSO, risk-reducing salpingo-oophorectomy.
Data are presented as mean±standard deviation or n (%).
*Menopause was defined as 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.

**Table 2.** Development of Breast and Gynecologic Cancers after *BRCA1/2* Gene Test

| Characteristics | Surveillance only (n=35) | RRSO (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† |

BC, breast cancer; RRSO, risk-reducing salpingo-oophorectomy.
Data are presented as n (%).
*Observation period was defined as intervals between the *BRCA* gene test and date of gynecologic cancer diagnosis or last visit in the surveillance-only group, while it was defined as intervals between the *BRCA1/2* gene test and date of RRSO in the RRSO group, †Incidental case (diagnosed after RRSO).

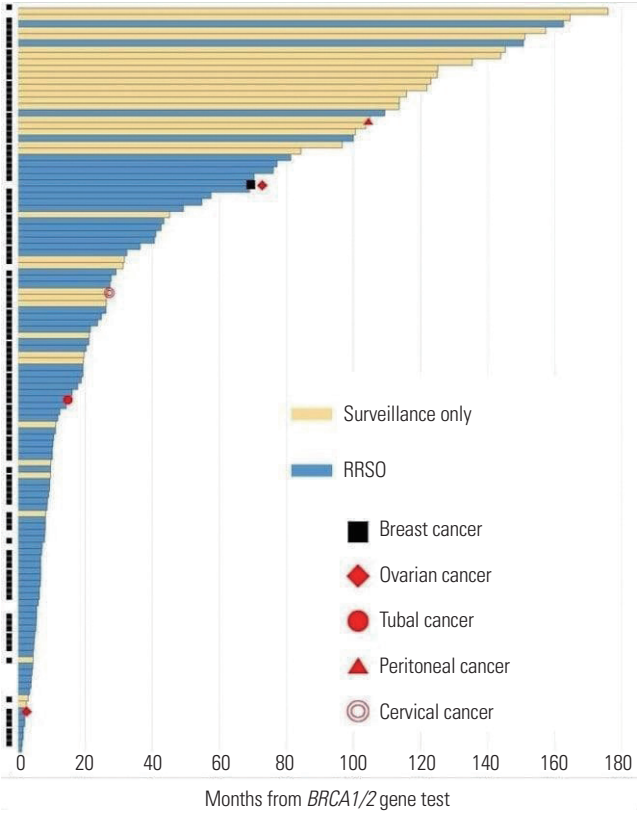


**Fig. 2.** Follow-up of study population after the *BRCA1/2* gene test. RRSO, risk-reducing salpingo-oophorectomy.

**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 | Surgery | Pathology | FIGO stage |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| #1. | 55.6 | *BRCA2* c.5722_5723delCT | 3/MP | No | Mother | No | Yes, bilateral (55.6) | RRSO | 1.9 | Unilateral ovarian cyst, 3 cm | SPL BSO | HGSC in both ovaries | Staging op → IIA |
| #2. | 41.4 | *BRCA1* c.3746dupA | 0/No | No | Sister | No | No | Surveillance → RRSO | 69.0 | Newly diagnosed BC; Normal uterus and ovaries | SPL BSO and BC surgery | HGSC in one ovary | Staging op → IC3 |
| #3. | 70.2 | *BRCA2* c.3744_3747delTGAG | 2/MP | HTN | Sister | No | Yes (70.2) | Surveillance → RRSO | 14.3 | Bilateral ovarian cysts | SPL BSO | HGSC in one tube | Staging op → IIIB |
| #4. | 54.8 | *BRCA2* c.1399A>T | 2/MP | HTN | Mother, Sister 2 | No | Yes (47.7) | Surveillance | 103.8 | Development of peritoneal carcinomatosis and ascites | | HGSC in peritoneum | Staging op → IIIC |
| #5. | 47.7 | *BRCA1* c.911_918dupTCTGTAAT | 2/No | DM | Mother | Mother | Yes (47.7) | Surveillance | 26.3 | LEEP due to Pap abnormality (ASC-H) | | SCC in the cervix | RH → IA1 |

ASC-H, atypical squamous cells cannot exclude HSIL; BC, breast cancer; BSO, bilateral salpingo-oophorectomy; DM, diabetes; FIGO, International Federation of Gynaecology and Obstetrics; HGSC, high-grade serous carcinoma; HTN, hypertension; Hx, history; LEEP, Loop Electrosurgical Excision Procedure; MP, menopause; OC, ovarian cancer; RH, radical hysterectomy; RRSO, risk-reducing salpingo-oophorectomy; SCC, squamous cell carcinoma; SPL, single-port laparoscopy.


https://doi.org/10.3349/ymj.2021.62.12.1090

**Table 4.** Factors Associated with Taking Risk-Reducing Salpingo-Oophorectomy Strategy Rather Than Surveillance

| Characteristics | Comparison | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | *p* | aOR | 95% CI | *p* |
| Age at *BRCA* 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 | ≥College vs. ≤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 | *BRCA1* vs. *BRCA2* | 0.753 | 0.344–1.647 | 0.477 | | | |

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.

an/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 shown 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.

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 age ≥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).

## DISCUSSION

In this retrospective cohort study, we presented our real-world experience on the 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.[8] 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.[9]

Women who are employed also tended to choose RRSO strategy over surveillance, possibly since it is more difficult for them to take regular screening tests compared to unemployed women. Previous studies have shown that the type of mutated *BRCA* gene, family history of cancer, and personal history of breast cancer were important factors for *BRCA1/2* mutation carriers to undergo RRSO.[10-12] However, we observed inconsistent results, which might originate from the uniqueness of our study population; all *BRCA1/2* mutation carriers had either or both personal history of breast cancer and family history of breast or ovarian cancer. Especially, the proportions of the mutation carriers who had been diagnosed with breast cancer before genetic testing and those who had at least one family member of breast cancer were exceptionally high (86.3% and 65.8%, respectively). Such a unique study population, reflecting the reality of a tertiary institutional hospital in Korea, might result in no association between personal and familial cancer histories and the uptake rate of RRSO.

The total uptake rate of RRSO in this study was at the upper end of the range described in previous studies, which was re-

ported to be 50%–70% with inter-center and inter-country variations.[12-14] These variations are due to differences in the characteristics of the study population, sociocultural atmosphere, follow-up period, follow-up strategy, counseling 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 began 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. Also, only about 20% of the patients underwent RRSO at the age suggested by the guidelines. 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 having no abnormal findings on preoperative evaluation. They were reluctant to receive RRSO at the ages of 30–40s, probably in their premenopausal state. In literature, the occult ovarian/tubal cancer rate in *BRCA1/2* mutation carriers undergoing RRSO has been reported to be 0.6%–17%.[15-19] Therefore, it is recommended that *BRCA1/2* mutation carriers, especially those who completed childbearing, undergo RRSO soon after genetic testing to prevent the development of ovarian/tubal cancer and microscopic cancer progression. Nevertheless, neglecting cancer screening after RRSO should be avoided, as the risks of developing primary peritoneal cancer and breast cancer still remain.[20]

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.[21,22] RRESDO is a two-stage surgical alternative to RRSO. In a pilot study, early salpingectomy was performed for premenopausal women immediately after the detection of a *BRCA1/2* gene mutation. Then, delayed oophorectomy was recommended for patients aged 40 years with the *BRCA1* gene mutation and those aged 45 years with the *BRCA2* gene mutation.[23] 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.[24]

For *BRCA1/2* mutation carriers who are reluctant to undergo RRSO, the Korean Society of Gynecologic Oncology recommends transvaginal sonography or serum CA-125 tests every 4 months.[7] Although such intense screening might offer a better chance for early detection of ovarian cancer, robust scientific evidence on this issue is still 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, there was a significant difference in the follow-up period between the RRSO and non-RRSO groups (median, 10.0 months vs. 96.6 months; $p<0.001$). As our institution is a tertiary hospital, most patients who underwent RRSO without any diagnostic abnormalities were referred out to the local OB/GYN clinics for further surveillance. Fourth, we could not investigate whether or not the counselor-related factors affected the uptake rate of RRSO, owing to a relatively higher number of faculty who participated in the counseling than the small study population. Moreover, due to the retrospective design of this study, we were unable to know the women's exact reasons for accepting or refusing RRSO and the quality of each counseling provided by the counselors. Lastly, the trend of undergoing RRSO with time was not analyzed. Further prospective cohort studies in a larger population are warranted.

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, women might refrain from the delayed implementation of RRSO after the confirmation of germline *BRCA1/2* mutations. Further prospective studies investigating long term health consequences of RRSO and alternative strategies to RRSO are warranted for the premenopausal *BRCA1/2* mutated women.

## ACKNOWLEDGEMENTS

This work was supported by grants from the Seoul National University Hospital Research Fund (No. 0320190260) and the National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT (No. 2020R1G1A1005711).

## AUTHOR CONTRIBUTIONS

Conceptualization: Maria Lee and Se Ik Kim. Data curation: Hyunji Lim, Sowoon Hyun, Gwang Bin Lee, and Aeran Seol. Formal analysis: Hyunji Lim and Se Ik Kim. Funding acquisition: Maria Lee. Investigation: Hyunji Lim, Sowoon Hyun, and Se Ik Kim. Methodology: Maria Lee and Se Ik Kim. Project administration: Maria Lee. Resources: Maria Lee and Se Ik Kim. Software: Maria Lee. Supervision: Maria Lee. Validation: Maria Lee and Se Ik Kim. Visualization: Hyunji Lim, Sowoon Hyun, Se Ik Kim, and Maria Lee. Writing—original draft: Hyunji Lim. Writing—review & editing: all authors. Approval of final


https://doi.org/10.3349/ymj.2021.62.12.1090

manuscript: all authors.

## ORCID iDs

Hyunji Lim https://orcid.org/0000-0003-4365-2079
Se Ik Kim https://orcid.org/0000-0002-9790-6735
Sowoon Hyun https://orcid.org/0000-0001-6094-6699
Gwang Bin Lee https://orcid.org/0000-0002-8020-3005
Aeran Seol https://orcid.org/0000-0003-4113-2280
Maria Lee https://orcid.org/0000-0002-8017-3176

## REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
2. Committee on Practice Bulletins–Gynecology, Committee on Genetics, Society of Gynecologic Oncology. Practice Bulletin No 182: hereditary breast and ovarian cancer syndrome. Obstet Gynecol 2017;130:e110-26.
3. Menon U, Karpinskyj C, Gentry-Maharaj A. Ovarian cancer prevention and screening. Obstet Gynecol 2018;131:909-27.
4. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-30.
5. Daly MB, Pilarski R, Yurgelun MB, Berry MP, Buys SS, Dickson P, et al. NCCN guidelines insights: genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 1.2020: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2020;18:380-91.
6. Kim SI, Lee M, Kim HS, Chung HH, Kim JW, Park NH, et al. Effect of BRCA mutational status on survival outcome in advanced-stage high-grade serous ovarian cancer. J Ovarian Res 2019;12:40.
7. Choi MC, Lim MC, Suh DH, Song YJ, Kim TJ, Chang SJ, et al. Position statements on genetic test for peritoneal, ovarian, and fallopian tubal cancers: Korean Society of Gynecologic Oncology (KSGO). J Gynecol Oncol 2016;27:e36.
8. Gordhandas S, Norquist BM, Pennington KP, Yung RL, Laya MB, Swisher EM. Hormone replacement therapy after risk reducing salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations; a systematic review of risks and benefits. Gynecol Oncol 2019;153:192-200.
9. Miller SM, Roussi P, Daly MB, Scarpato J. New strategies in ovarian cancer: uptake and experience of women at high risk of ovarian cancer who are considering risk-reducing salpingo-oophorectomy. Clin Cancer Res 2010;16:5094-106.
10. Bradbury AR, Ibe CN, Dignam JJ, Cummings SA, Verp M, White MA, et al. Uptake and timing of bilateral prophylactic salpingo-oophorectomy among BRCA1 and BRCA2 mutation carriers. Genet Med 2008;10:161-6.
11. Metcalfe KA, Foulkes WD, Kim-Sing C, Ainsworth P, Rosen B, Armel S, et al. Family history as a predictor of uptake of cancer preventive procedures by women with a BRCA1 or BRCA2 mutation. Clin Genet 2008;73:474-9.
12. Kim SI, Lim MC, Lee DO, Kong SY, Seo SS, Kang S, et al. Uptake of risk-reducing salpingo-oophorectomy among female BRCA mutation carriers: experience at the National Cancer Center of Korea. J Cancer Res Clin Oncol 2016;142:333-40.
13. Sidon L, Ingham S, Clancy T, Clayton R, Clarke A, Jones EA, et al. Uptake of risk-reducing salpingo-oophorectomy in women carrying a BRCA1 or BRCA2 mutation: evidence for lower uptake in women affected by breast cancer and older women. Br J Cancer 2012;106:775-9.
14. Chai X, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Use of risk-reducing surgeries in a prospective cohort of 1,499 BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 2014;148:397-406.
15. Piedimonte S, Frank C, Laprise C, Quaiattini A, Gotlieb WH. Occult tubal carcinoma after risk-reducing salpingo-oophorectomy: a systematic review. Obstet Gynecol 2020;135:498-508.
16. Palaiologos K, Ellaboudy A, Abdullah M, Karan S, Saha A. Prophylactic bilateral salpingo-oophorectomy in BRCA2 mutation with incidental finding of serous tubal intraepithelial carcinoma (STIC) and subsequent diagnosis of primary peritoneal carcinoma (PPC): a case report and review of current literature. Cureus 2020;12:e9301.
17. Colgan TJ, Murphy J, Cole DE, Narod S, Rosen B. Occult carcinoma in prophylactic oophorectomy specimens: prevalence and association with BRCA germline mutation status. Am J Surg Pathol 2001;25:1283-9.
18. Agoff SN, Garcia RL, Goff B, Swisher E. Follow-up of in situ and early-stage fallopian tube carcinoma in patients undergoing prophylactic surgery for proven or suspected BRCA-1 or BRCA-2 mutations. Am J Surg Pathol 2004;28:1112-4.
19. Vaughan MH, Modesitt SC, Mo Y, Trowbridge ER. Serous tubal intraepithelial carcinoma: an incidental finding at the time of prophylactic bilateral salpingo-oophorectomy. Case Rep Obstet Gynecol 2015;2015:760429.
20. Mavaddat N, Antoniou AC, Mooij TM, Hooning MJ, Heemskerk-Gerritsen BA, Noguès C, et al. Risk-reducing salpingo-oophorectomy, natural menopause, and breast cancer risk: an international prospective cohort of BRCA1 and BRCA2 mutation carriers. Breast Cancer Res 2020;22:8.
21. Gaba F, Blyuss O, Chandrasekaran D, Osman M, Goyal S, Gan C, et al. Attitudes towards risk-reducing early salpingectomy with delayed oophorectomy for ovarian cancer prevention: a cohort study. BJOG 2021;128:714-26.
22. Ghezelayagh TS, Stewart LE, Norquist BM, Bowen DJ, Yu V, Agnew KJ, et al. Perceptions of risk and reward in BRCA1 and BRCA2 mutation carriers choosing salpingectomy for ovarian cancer prevention. Fam Cancer 2020;19:143-51.
23. Nebgen DR, Hurteau J, Holman LL, Bradford A, Munsell MF, Soletsky BR, et al. Bilateral salpingectomy with delayed oophorectomy for ovarian cancer risk reduction: a pilot study in women with BRCA1/2 mutations. Gynecol Oncol 2018;150:79-84.
24. Gaba F, Piek J, Menon U, Manchanda R. Risk-reducing early salpingectomy and delayed oophorectomy as a two-staged alternative for primary prevention of ovarian cancer in women at increased risk: a commentary. BJOG 2019;126:831-9.