



## Original Article

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# Different Patterns of Risk Reducing Decisions in Affected or Unaffected *BRCA* Pathogenic Variant Carriers

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## Purpose

The purpose of this study was to investigate decision patterns to reduce the risks of *BRCA*-related breast and gynecologic cancers in carriers of *BRCA* pathogenic variants. We found a change in risk-reducing (RR) management patterns after December 2012, when the National Health Insurance System (NHIS) of Korea began to pay for *BRCA* testing and risk-reducing salpingo-oophorectomy (RRSO) in pathogenic-variant carriers.

## Materials and Methods

The study group consisted of 992 patients, including 705 with breast cancer (BC), 23 with ovarian cancer (OC), 10 with both, and 254 relatives of high-risk patients who underwent *BRCA* testing at the National Cancer Center of Korea from January 2008 to December 2016. We analyzed patterns of and factors in RR management.

## Results

Of the 992 patients, 220 (22.2%) were carriers of *BRCA* pathogenic variants. About 92.3% (203/220) had a family history of BC and/or OC, which significantly differed between *BRCA1* and *BRCA2* carriers ( $p < 0.001$ ). All 41 male carriers chose surveillance. Of the 179 female carriers, 59 of the 83 carriers (71.1%) with BC and the 39 of 79 unaffected carriers (49.4%) underwent RR management. None of the carriers affected with OC underwent RR management. Of the management types, RRSO had the highest rate (42.5%) of patient choice. The rate of RR surgery was significantly higher after 2013 than before 2013 (46.3% [74/160] vs. 31.6% [6/19],  $p < 0.001$ ).

## Conclusion

RRSO was the preferred management for carriers of *BRCA* pathogenic variants. The most important factors in treatment choice were NHIS reimbursement and/or the severity of illness.

## Key words

*BRCA1*, *BRCA2*, Familial breast cancer, Ovarian neoplasms, Prophylactic surgical procedure

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## Introduction

Pathogenic variants of *BRCA1* and *BRCA2* result in hereditary breast-ovarian cancer syndrome (HBO) in affected persons [1]. Activating mutations in *BRCA1* and *BRCA2* are present in approximately 16%-25% of hereditary breast cancers (BCs) [2,3], 5%-10% of all BCs [4], and 15% of ovarian cancers (OC) [5]. *BRCA* pathogenic variants are also associated with an increased risk of developing any invasive cancer [6]. Risk-reducing mastectomy (RRM) reduces the lifetime risk of BC diagnosis [7]; and salpingo-oophorectomy is the single most effective method to prevent ovarian and fallopian tube cancer in women with a *BRCA* pathogenic variant [8,9]. Current National Comprehensive Cancer Network (NCCN) guidelines recommend risk-reducing salpingo-oophorectomy (RRSO) at age 35-45 years and after completion of child bearing. Patients who undergo RRM can select from various procedural options, each associated with a different risk of subsequently developing BC, and reconstruction options [10]. In Western countries, RRSO was the approach of choice to reduce the OC risk in about 50%-70% of patients with pathogenic variants of *BRCA1* and *BRCA2* undergoing risk-reducing (RR) management [3,11]. However, there are few reports about RR management in Asia. In December 2012, the National Health Insurance System (NHIS) of Korea approved reimbursement of *BRCA* testing and RRSO in patients suspected of having a *BRCA1/2* mutation. The patterns of RR management began changing after NHIS instituted its new policy. However, RR management decision-making remains difficult because of various individual factors.

A recent retrospective study revealed that the rate of RRSO among female carriers of *BRCA* mutations in Korea was affected by the presence of amenorrhea and consultation with gynecologic oncologists [12]. To date, the types of RR management in Korean carriers of *BRCA* pathogenic variants, including unaffected pathogenic variant carriers, have not been evaluated. To address this gap in research, this study was designed to identify RR management patterns in Korean carriers of *BRCA1* and *BRCA2* pathogenic variants.

## Materials and Methods

### 1. Study population

This study was designed as a retrospective cohort study. We evaluated the medical records of 992 consecutive patients, including those with breast and/or OC as well as

relatives of high-risk patients, who underwent *BRCA* testing from January 2008 to December 2016 at the National Cancer Center of Korea (Goyang, Korea). Based on the standards of the National Medical Insurance Reimbursement in Korea, patients with BC and OC and a family history of BC or OC, early onset BC (diagnosed at age  $\leq 40$  years), bilateral BC, both BC and OC, male BC, or multi-organ cancer are recommended to undergo testing for *BRCA1/2* pathogenic variants.

### 2. Genetic testing and RR management

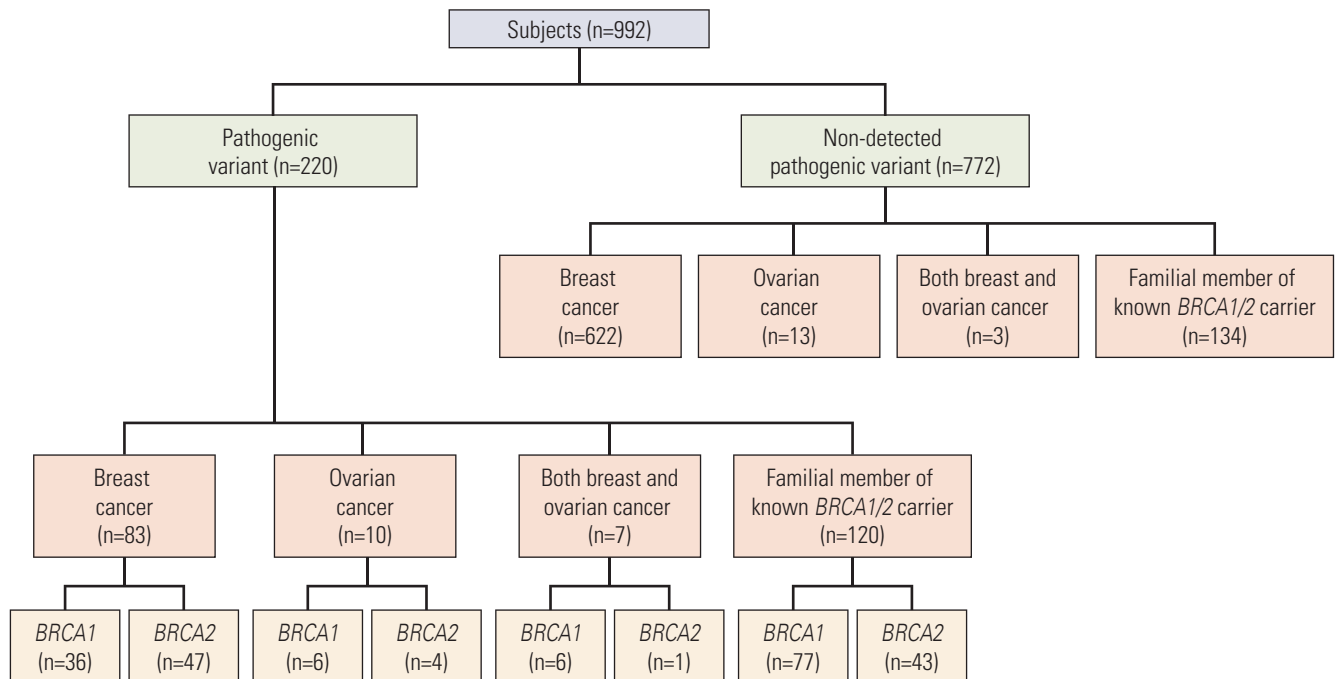
*BRCA* mutations were determined by direct gene sequencing. Some patients without pathogenic variants who agreed to additional testing were further evaluated by *BRCA* deletion/duplication analysis using multiplex ligation-dependent probe amplification (MLPA) kits. Of the 992 individuals who underwent *BRCA* testing, 220 (22.2%) had *BRCA* pathogenic variants, including 125 (12.6%) with *BRCA1* variants and 95 (9.6%) with *BRCA2* variants (Fig. 1).

After patients with *BRCA1/2* pathogenic variants were identified by genetic testing, the carriers met with a genetic counselor or various clinical experts, such as surgeons, oncologists specializing in BC, or gynecologic oncologists. Carriers were advised about appropriate risk reduction options according to carriers' preference, disease severity, and expert advice on RR management.

RR management methods presented to carriers included RR surgery and chemoprevention. Chemoprevention included oral contraceptives, olaparib for patients with OC, and tamoxifen for hormone-receptor positive patients with BC. RR surgery included RRM and RRSO. For carriers who elected surveillance, BC and OC screening at 6-month intervals was recommended. Of the 220 *BRCA* pathogenic-variant carriers, 98 (44.5%) underwent RR management.

### 3. Statistical analysis

Statistical analysis was performed using SAS 9.4 software (SAS Institute Inc., Cary, NC). The distribution of clinicopathological characteristics in *BRCA1* and *BRCA2* pathogenic-variant carriers were compared, and the factors affecting RR management in the female carriers were assessed appropriately, depending on the characteristics of each variable. Male carrier patients were excluded from the analysis of RR management patterns. Continuous variables were analyzed using Student's *t* test and represented as the mean  $\pm$  standard deviation, whereas categorical variables were analyzed using Pearson's chi-square test or Fisher exact test, as appropriate, and represented as frequency and percentages. Statistical significance was defined as  $p < 0.05$ .



**Fig. 1.** Flow diagram of study subjects. Genetic testing included direct sequencing and multiple ligation-dependent probe amplification analysis. A total of 220 carriers of pathogenic variants, including 125 with *BRCA1* gene variants and 95 with *BRCA2* gene variants, were identified.

#### 4. Ethical statement

The informed consent was waived and this study was approved by the Institutional Review Board of the Korean National Cancer Center (Goyang, Korea; approval no. NCC-2017-0219).

## Results

### 1. Comparison of *BRCA1* vs. *BRCA2*

Of the 220 carriers of *BRCA* pathogenic variants, 125 had *BRCA1* mutations, and 95 had *BRCA2* mutations. Table 1 shows the clinical and pathological characteristics of these patients. The mean ages of these two groups were 39.3 and 43.7 years, respectively ( $p=0.009$ ). The 220 carriers included 179 women and 41 men ( $p=0.100$ ). None of these carriers had mutations in both the *BRCA1* and *BRCA2* genes.

The 220 individuals consisted of 83 patients with BC, 10 with OC, and seven with both, as well as 120 unaffected carriers ( $p=0.010$ ). Approximately 92.3% (203/220) had a family

history of BC and/or OC, including 117 (93.6%) of the 125 with *BRCA1* mutations and 86 (90.5%) of the 95 with *BRCA2* mutations ( $p < 0.001$ ). The rate of family OC history was significantly higher (50.4% vs. 22.1%) and the rate of family BC history significantly lower (19.2% vs. 56.8%) in carriers of *BRCA1* than in carriers of *BRCA2* pathogenic variants. The rate of family BC history was also significantly lower in carriers of *BRCA1* than in carriers of *BRCA2* pathogenic variants with BC (44.4% vs. 78.7%,  $p=0.003$ ). However, rates of early onset and bilateral BC, as well as stage of BC, did not differ significantly in carriers of *BRCA1* and *BRCA2* pathogenic variants. The most common BC subtypes in carriers of *BRCA1* and *BRCA2* mutations were basal-like (72.2% vs. 21.3%) and luminal A type (19.4% vs. 70.2%), respectively ( $p < 0.001$ ). The percentages of carriers of *BRCA1* and *BRCA2* pathogenic variants did not differ significantly in patients with OC. In unaffected carriers of *BRCA* pathogenic variants, the rate of family BC history was significantly higher in carriers of *BRCA2* than in carriers of *BRCA1* pathogenic variants (3.9% vs. 39.5%), whereas the rate of familial OC history was significantly higher in *BRCA1* than in *BRCA2* variants (68.8% vs. 37.2%,  $p < 0.001$ ).

**Table 1.** Overall characteristics of *BRCA* pathogenic variant carriers

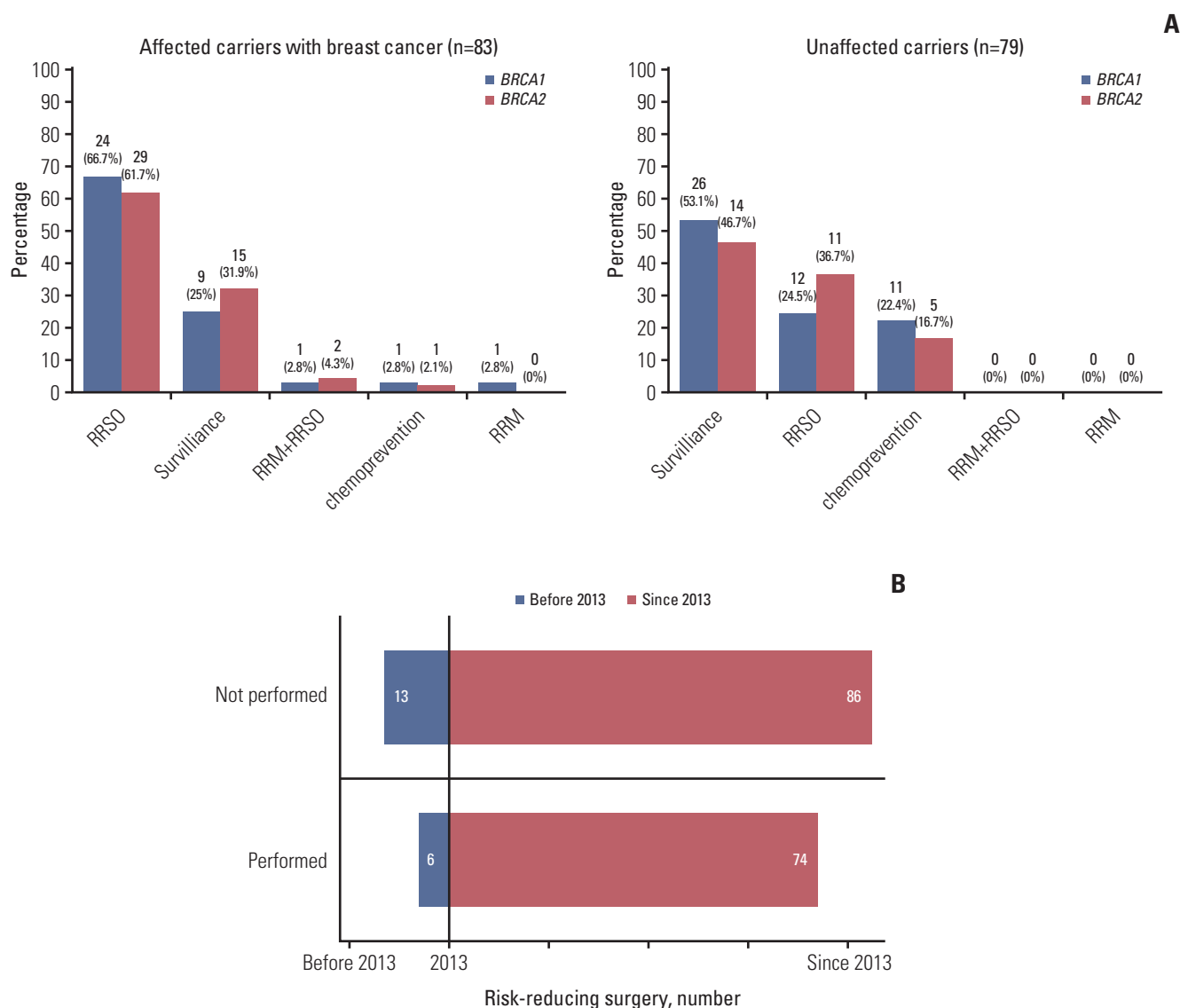
Clinicopathological characteristic	Total	<i>BRCA1</i>	<i>BRCA2</i>	p-value
<b><i>BRCA</i> pathogenic variant carriers</b>	220	125	95	
Age (yr)	41.23±12.59	39.32±12.83	43.75±11.86	0.010
Sex				
Male	41	28 (22.4)	13 (13.7)	0.100
Female	179	97 (77.6)	82 (86.3)	
Familial history				
None	17	8 (6.4)	9 (9.5)	< 0.001
Breast cancer	78	24 (19.2)	54 (56.8)	
Ovarian cancer	84	63 (50.4)	21 (22.1)	
Both breast and ovarian cancer	41	30 (24.0)	11 (11.6)	
<b>Affected carriers with breast cancer</b>	83	36	47	
Age (yr)	45.01±8.92	43.78±8.61	45.96±9.14	0.273
Familial history				
None	14	7 (19.4)	7 (14.9)	0.003
Breast cancer	53	16 (44.4)	37 (78.7)	
Ovarian cancer	8	6 (16.7)	2 (4.3)	
Both breast and ovarian cancer	8	7 (19.4)	1 (2.1)	
Early onset breast cancer				
No	69	28 (77.8)	41 (87.2)	0.254
Yes	14	8 (22.2)	6 (12.8)	
Bilaterality of breast cancer				
No	70	33 (91.7)	37 (78.7)	0.108
Yes	13	3 (8.3)	10 (21.3)	
Stage of breast cancer				
Tis	3	2 (5.6)	1 (2.1)	0.602
I	32	14 (38.9)	18 (38.3)	
II	41	16 (44.4)	25 (53.2)	
III	6	4 (11.1)	2 (4.3)	
IV	1	0	1 (2.1)	
Subtypes of breast cancer				
Luminal A	40	7 (19.4)	33 (70.2)	< 0.001
Luminal B	5	2 (5.6)	3 (6.4)	
HER2	2	1 (2.8)	1 (2.1)	
Basal	36	26 (72.2)	10 (21.3)	
<b>Affected carriers with ovary cancer</b>	10	6	4	
Age (yr)	53±6.82	52.33±8.57	54±3.83	0.728
Stage of ovarian cancer				
I	2	1 (16.7)	1 (25.0)	0.886
II	2	1 (16.7)	1 (25.0)	
III	2	2 (33.3)	0	
IV	3	1 (16.7)	2 (50.0)	
Unknown	1	1 (16.7)	0	
Familial history				
None	2	0	2 (50.0)	0.333
Breast cancer	1	1 (16.7)	0	
Ovarian cancer	5	3 (50.0)	2 (50.0)	
Both breast and ovarian cancer	2	2 (33.3)	0	

(Continued to the next page)

**Table 1.** Continued

Clinicopathological characteristic	Total	BRCA1	BRCA2	p-value
<b>Unaffected carriers</b>	120	77	43	
Age (yr)	37±13.6	35.23±13.22	40.16±13.84	0.057
<b>Familial history</b>				
Breast cancer	20	3 (3.9)	17 (39.5)	< 0.001
Ovarian cancer	70	53 (68.8)	16 (37.2)	
Both breast and ovarian cancer	30	21 (27.3)	9 (20.9)	

Values are presented as the mean±standard deviation or the number (%).



**Fig. 2.** Types of risk-reducing management applied to female *BRCA1/2* pathogenic variant carriers over time. (A) Types of risk-reducing management chosen by affected female *BRCA1/2* pathogenic-variant carriers with breast cancer and by unaffected carriers. (B) Numbers of women who underwent risk-reducing surgery before and after 2013, the year National Health Insurance System began reimbursing for *BRCA* testing and risk-reducing salpingo-oophorectomy in pathogenic-variant carriers. RRSO, risk-reducing salpingo-oophorectomy; RRM, risk-reducing mastectomy.

**Table 2.** Factors affecting risk-reducing management patterns in female *BRCA1/2* pathogenic-variant carriers

Factor	Total number	Not performed RR management	Performed RR management	p-value
<b><i>BRCA1/2</i> pathogenic variant carriers</b>	179	81	98	
Age (yr)	43.15±12.26	43.58±13.32	42.79±11.37	0.667
<i>BRCA</i> mutation				
<i>BRCA 1</i>	97	47 (58.0)	50 (51.0)	0.349
<i>BRCA 2</i>	82	34 (42.0)	48 (49.0)	
Type of carriers				
Affected carriers with breast cancer	83	24 (29.6)	59 (60.2)	< 0.001
Affected carriers with ovary cancer	10	10 (12.4)	0	
Affected carriers with both cancer	7	7 (8.6)	0	
Unaffected carriers	79	40 (49.4)	39 (39.8)	
Familial history				
None	17	8 (9.9)	9 (9.2)	0.249
Breast cancer	72	27 (33.3)	45 (45.9)	
Ovarian cancer	60	33 (40.7)	27 (27.6)	
Both breast and ovarian cancer	30	13 (16.1)	17 (17.3)	
<b>Affected carriers with breast cancer</b>	83	24	59	
Age (yr)	45.01±8.92	41.13±7.80	46.59±8.93	0.011
Familial history				
None	14	5 (20.8)	9 (15.3)	0.853
Breast cancer	53	14 (58.3)	39 (66.1)	
Ovarian cancer	8	3 (12.5)	5 (8.5)	
Both breast and ovarian cancer	8	2 (8.3)	6 (10.2)	
Early onset breast cancer				
No	69	16 (66.7)	53 (89.8)	0.020
Yes	14	8 (33.3)	6 (10.2)	
Bilaterality of breast cancer				
No	70	21 (87.5)	49 (83.1)	0.748
Yes	13	3 (12.5)	10 (17)	
Stage of breast cancer				
Tis	3	0	3 (5.1)	0.489
I	32	9 (37.5)	23 (39)	
II	41	13 (54.2)	28 (47.5)	
III	6	1 (4.2)	5 (8.5)	
IV	1	1 (4.2)	0	
Subtypes of breast cancer				
Luminal A	40	11 (45.8)	29 (49.2)	0.930
Luminal B	5	1 (4.2)	4 (6.8)	
HER2	2	0	2 (3.4)	
Basal	36	12 (50)	24 (40.7)	
<b>Unaffected carriers</b>	79	40	39	
Age (yr)	39.14±14.56	41.20±16.34	37.03±12.33	0.205
Familial history				
Breast cancer	14	8 (20.0)	6 (15.4)	0.659
Ovarian cancer	46	24 (60.0)	22 (56.4)	
Both breast and ovarian cancer	19	8 (20.0)	11 (28.2)	

Values are presented as the mean±standard deviation or the number (%). RR, risk-reducing.

## 2. RR management of female carriers of *BRCA1/2* pathogenic variants

All 41 male carriers chose surveillance. RR management patterns in female carriers of *BRCA1/2* pathogenic variants are presented in Fig. 2. Of these 179 women, 98 (54.7%) underwent RR management, including 18 (10.1%) who received chemoprevention and 80 (44.7%) who underwent risk-reducing surgery (RRS), including RRSO in 76 patients, RRM in one, and both in three. The remaining 81 patients (45.3%) chose intensive surveillance, including both BC and OC patients. Of the female *BRCA1/2* pathogenic-variant carriers with BC, 59 (71.1%) underwent RR management, including RRSO in 53 patients, contralateral RRM in one, both in three, and chemoprevention in two ( $p=0.8497$ ). The distribution of BC subtype in the 56 affected carriers with BC who underwent RRSO was 51.8% luminal A type, 7.1% luminal B type, 3.6% HER-2 type, and 37.5% basal type.

None of the affected carriers with OC underwent RR management for BC. Of the 79 unaffected female carriers, 39 (49.4%) received RR management, including 23 (29.1%) who underwent RRSO and 16 (20.3%) who received chemoprevention ( $p=0.495$ ).

Insurance reimbursement started in 2013. The numbers of carriers of pathogenic variants detected (160 vs. 19) and the percentage who underwent RRS (46.3% [74/160] vs. 31.6% [6/19],  $p < 0.001$ ) were significantly higher after 2013 than before 2013 (Fig. 2B).

## 3. Factors affecting RR management of female carriers of *BRCA1/2* pathogenic variants

The type of female carriers was significantly associated with RR management ( $p < 0.001$ ) (Table 2). In affected female carriers with BC, older age was significantly associated with RR management ( $p=0.011$ ). However, in unaffected carriers, age, type of *BRCA* pathogenic variant, and family history were not significantly associated with RR management.

## Discussion

In the current study, we investigated RR management patterns in *BRCA1* and *BRCA2* pathogenic-variant carriers, including both affected and unaffected carriers. The prevalence of these pathogenic variants was associated with both familial and personal factors. Carriers of pathogenic variants with both familial and personal factors were at much higher risk of cancer [13]. RR management in carriers of *BRCA* mutations has been studied more in Western than in Asian

populations [3,14]. To our knowledge, this study involved the largest number of Asian *BRCA* pathogenic-variant carriers managed by RR approaches.

We found that older age of affected carriers with BC was significantly associated with RR management. Interestingly, in unaffected carriers, age, family history, and type of *BRCA* pathogenic variant were not associated with the decision to undergo RR management. The results showed that carriers may consider whether to undergo RR management differently depending on the type of carrier. Although a high percentage of *BRCA* carriers in a population-based health system underwent RRSO, these women did not undergo RRSO by the age recommended by the NCCN [14]. Older age was found to be significantly associated with an increase in RRSO rate [12]. According to the World Health Organization, the fertility rates of Korean women are lower than in other populations. As the average age at the first marriage increased in Korea, so has the age at the first childbirth. This may explain the association we found between age and decision to undergo RR management.

The prevalence of OC in our population was low. However, OC tends to be diagnosed at an advanced stage and has a poorer survival rate than BC [15]. Moreover, carriers of *BRCA* pathogenic variants were found to worry about developing OC [16,17]. Our findings were similar: the mean age of RR management in carriers with BC was 46 years, and the frequency of RR management was lower in patients with early onset BC. The rate of RRSO was higher in unaffected carriers with a family history of OC than in those with a familial history of BC. Assessment of survival in our population showed that four (4.8%) affected carriers with BC, one (10.0%) affected carrier with OC, and one (14.3%) affected carrier with both died. Most affected carriers with OC had advanced stage disease and were being treated with adjuvant chemotherapy. A review of pathologic reports of patients who underwent RR surgery showed that no woman who underwent RRM was diagnosed with BC, whereas three women who underwent RRSO were diagnosed with ovarian, fallopian tube, or peritoneal cancer and required additional treatment.

BC has a better prognosis than OC. BC screening is easier and can detect early cancerous lesions. With recent advancements, reconstructive surgery after mastectomy has a low rate of complications and increases patient satisfaction [18,19]. However, RRM may destroy body image and be costly, as it may not be reimbursed by insurance. A study of women carriers of *BRCA* pathogenic variants showed that those who opted for RRM were significantly more satisfied with their decision than those who did not undergo surgery [20]. A previous study showed RRM performed within 5 years was not cost effective when compared with BC screening for most *BRCA* pathogenic-variant carriers with OC [21].

Interestingly, we found that RRM was less preferred by these carriers, indicating that RRM must be chosen by patients.

In Korea, the detection of pathogenic variants and the performance of RRSs have changed over time. Since 2013, the annual number of individuals with *BRCA* pathogenic variants has increased, as has the percentage undergoing surgery. These increases are largely due to insurance reimbursement for RRSO and genetic testing of family members by the NHIS in Korea. Since October 2017, in carriers with BC, RRM of the contralateral breast and reconstruction are also covered. Future insurance coverage changes may further affect the patterns of RRSs in *BRCA* pathogenic-variant carriers. Another possible factor in the change of RR management patterns is the “Angelina Jolie effect” after the movie star Angelina Jolie, who is a *BRCA* pathogenic-variant carrier, underwent RRM despite being unaffected [22,23]. This increased public attention to HBOS and RR management [24]. In RR management, RRSO is a safe and simple surgery. Recently, embryonic natural orifice transumbilical endoscopic surgery is performed efficiently with good cosmetic outcome [25]. A meta-analysis of other studies on the efficacy of RRSO reported hazard ratios of 0.21 (95% confidence interval [CI], 0.12 to 0.39) for onset of ovarian and fallopian tube cancer and 0.49 (95% CI, 0.37 to 0.65) for onset of BC, indicating that the risk of developing these cancers was reduced following RRSO [26]. A third reason for the increase was the opening of genetic counseling clinics, with active counselors and researchers [27,28]. Our study showed that genetic testing and consulting have grown rapidly since 2013. Nevertheless, in this study, unaffected carriers paid less attention to RR management, with about 36% lost to follow-up. Decisions on RR management may depend on the various factors, including family history, awareness of disease, the individual’s environment, insurance reimbursement, and age at detection of a *BRCA* mutation [29]. Improved education and genetic counseling support throughout the decision-making process have been found to enhance carriers’ overall levels of satisfaction [30].

Our study had several limitations, despite assessing a greater number of patients with RR management than in pre-

viously published studies. First, this study was a single-center retrospective study. Second, we could not perform MLPA tests on all non-carriers of *BRCA* pathogenic variants. Third, this study examined a heterogeneous cohort. Future multi-center studies are needed to provide more information on patterns of RR management.

In this study, the older affected carriers with BC underwent more RR management, and RRSO was preferred to RRM by both affected carriers with BC and unaffected carriers. This may have been due to the severity of illness and to RRSO being the only RR strategy reimbursed by the NHIS. Further long-term follow-up prospective studies of RR management are needed, including investigations into the effects of genetic counseling, insurance payments, and social media marketing.

#### Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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