

Original Article



Trends in Risk-Reducing Mastectomy and Risk-Reducing Salpingo-Oophorectomy in Korean Carriers of the *BRCA1/2* Mutation

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ABSTRACT

Purpose: *BRCA1/2* mutations are associated with risks of breast and ovarian cancer. In Korea, incidences of *BRCA1/2* genetic testing and risk-reducing surgery (RRS) have increased with insurance coverage and the Angelina Jolie effect. The aim of this study was to identify trends in RRS performed in Korean women with the *BRCA1/2* mutation.

Methods: We retrospectively reviewed the medical records of *BRCA1/2* mutation carriers with (affected carriers) and without (unaffected carriers) breast cancer until August 2018 from 25 Korean Hereditary Breast Cancer (KOHBRA)-affiliated hospitals.

Results: The numbers of contralateral risk-reducing mastectomy (RRM) and risk-reducing bilateral salpingo-oophorectomy (RRBSO) in affected carriers have increased 5.8- and 3.6-fold, respectively, since 2013. The numbers of RRBSO in unaffected carriers has increased 8-fold since 2013. The number of institutions that perform RRS has increased gradually. The number of hospitals that perform contralateral RRM on affected carriers increased from 3 in 2012 to 11 in 2018, and that of those that perform RRBSO increased from 7 to 17. The number of hospitals that perform bilateral RRM on unaffected carriers increased from 1 in 2012 to 2 in 2018, and that of those that perform RRBSO increased from 1 to 8. However, the hospitals showed differences in the rates of RRM or RRBSO performed.

Conclusion: The incidence of RRS increased each year throughout the study period. However, in Korea, the rate of RRS procedures depended on the hospital.

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Conflict of Interest

Lee HB is a member on the board of directors of, and has stock and ownership interests at DCGen, Co., Ltd., Seoul, South Korea, outside the current study. The other authors declare no conflict of interest.

Author Contributions

Conceptualization: Kim SW; Data curation: Park HS, Park JS, Kang E, Lee S, Lee HB, Youn HJ, Yoo TK, Kim J, Lee JE, Han SA; Investigation: Kim D; Writing - original draft: Jung SM; Writing - review & editing: Ryu JM, Lee JE, Kim SW.

Keywords: Breast neoplasms; Genes, *BRCA1*; Genes, *BRCA2*; Prophylactic mastectomy; Salpingo-oophorectomy

INTRODUCTION

The most common causative gene of hereditary breast cancer is *BRCA1/2*, with mutations in these genes accounting for almost 25% of families with a strong history of breast cancer [1]. The estimated lifetime risks are 56%–80% for breast cancer and 27%–45% for ovarian cancer in carriers of the *BRCA1* mutation, and 45%–84% for breast cancer and 10%–20% for ovarian cancer in carriers of the *BRCA2* mutation [2-4]. Results from the Korean Hereditary Breast Cancer (KOHBRA) study have helped improve clinicians' recognition of hereditary breast cancer, especially in Korea [5-7].

Carriers of the *BRCA1/2* mutation are recommended to undergo annual breast magnetic resonance imaging for screening or receive risk-reducing management procedures such as chemoprevention or risk-reducing surgery (RRS). In Korea, RRS for breast and ovarian cancer prevention was not widely performed before 2012. However, the National Health Insurance initiated insurance coverage of *BRCA1/2* genetic testing in May 2012. In addition, the actress Angelina Jolie—a carrier of the *BRCA1* mutation—announced her decision to undergo a bilateral risk-reducing mastectomy (RRM) in May 2013. Following these events, more women took interest in *BRCA1/2* mutations, and the frequency of RRS has increased over the past decade [8].

In a previous study, we reported the trends in RRS and *BRCA1/2* genetic testing from 2010 to 2015 [9]. Insurance for risk-reducing bilateral salpingo-oophorectomy (RRBSO) has been available since December 2012. Subsequently, insurance coverage of RRM with or without breast reconstruction was initiated in October 2017. The aim of this study was to investigate trends in RRS for the prevention of breast and ovarian cancer in Korean carriers of the *BRCA1/2* mutation until August 2018.

METHODS

Affected carriers were defined by *BRCA1/2* mutation with breast cancer, and unaffected carriers were defined by *BRCA1/2* mutation without breast cancer. Overall, 25 KOHBRA-affiliated hospitals agreed to participate in this study, with 18 hospitals subsequently providing data. The data were retrospectively collected from patients' medical records. In addition, the number of *BRCA1/2* genetic tests performed by the Health Insurance Review and Assessment Service was investigated. The numbers of genetic testing for *BRCA1/2* mutations and RRS were collected from January 2010 to August 2018.

The 25 KOHBRA-affiliated hospitals were Bunhongbit Hospital, Chonbuk National University Hospital, Daegu Catholic University Medical Center, Daejeon St. Mary's Hospital, Daerim Saint Mary's Hospital, Dankook University Hospital, Dongguk University Ilsan Hospital, Gangnam Severance Hospital, Gangwon National University Hospital, Inje University Ilsan Paik Hospital, Korea Cancer Center Hospital, Korea University Anam Hospital, Kwangju christian hospital, Kyunghee University Medical Center, Kyungpook National University Hospital, National Cancer Center, Samsung Medical Center, Seoul Asan Hospital, Seoul

National University Bundang Hospital, Seoul National University Hospital, Seoul St. Mary's Hospital, Severance Hospital, Soonchunhyang University Bucheon Hospital, Soonchunhyang University Cheonan Hospital, and Ulsan University Hospital.

Statistical analyses were performed using SPSS Statistics version 25 (IBM Corp., Armonk, USA). The χ^2 test and Fisher's exact test were conducted to compare categorical variables between the 2 groups. The categorical variables are reported here as number (percentage). The Wilcoxon signed rank test was used to analyze the difference in numbers of RRS performed among *BRCA1/2* mutation carriers before and after Angelina Jolie's announcement. Statistical significance was defined as $p < 0.05$ in all tests.

This study followed the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center (IRB file No. 2020-03-021-001). The need for informed consent was waived because of the low risk posed by this investigation.

RESULTS

In Korea, *BRCA1/2* genetic testing has rapidly increased 10-fold from 578 cases in 2010 to 5,880 cases in 2017 (**Figure 1**). Of 19,033 patients who underwent *BRCA1/2* genetic testing, 1,752 (9.2%) carriers of the *BRCA1/2* mutation were divided into two groups: 1238 affected carriers and 514 unaffected carriers (**Table 1**).

The numbers of RRM and RRBSO performed increased moderately during the period investigated. Among 1,238 affected carriers, contralateral RRM was performed in 122 (9.9%) patients, and RRBSO in 428 (34.6%) patients until August 2018. Among 514 unaffected

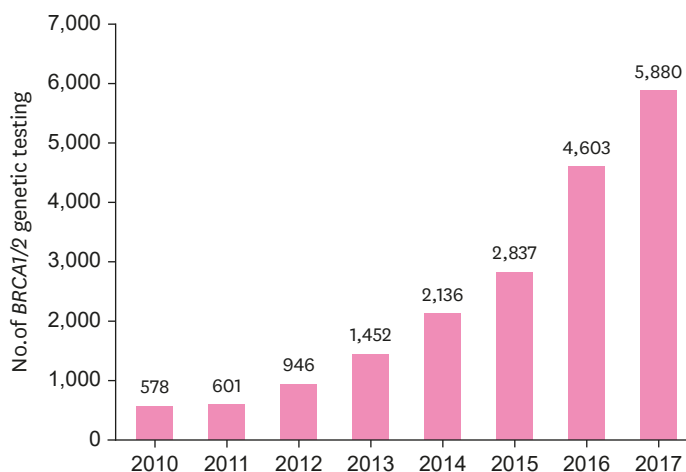


Figure 1. Annual trends in *BRCA1/2* genetic testing in South Korea.

Table 1. Number of RRS in *BRCA1/2* mutation carrier until August 2018

Variables	<i>BRCA1/2</i> mutation carrier with breast cancer	<i>BRCA1/2</i> mutation carrier without breast cancer
No. of <i>BRCA1/2</i> mutation carrier	1,238	514
RRM	122 (9.9%)	6 (1.2%)
RRBSO	428 (34.6%)	61 (11.9%)

RRS = risk-reducing surgery; RRM = risk-reducing mastectomy; RRBSO = risk-reducing bilateral salpingo-oophorectomy.

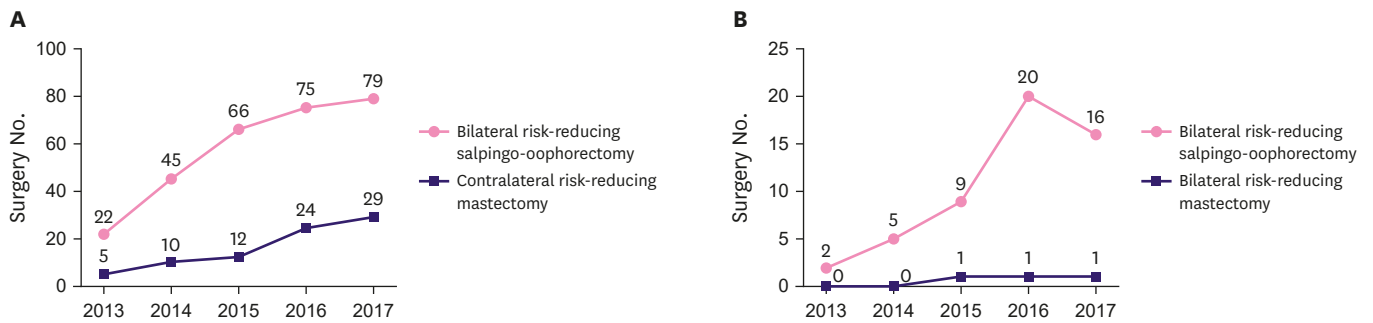


Figure 2. Annual trends for risk-reducing surgery in (A) affected carriers and (B) unaffected carriers.

Table 2. The Angelina Jolie effect on trends for RRS in *BRCA1/2* mutation carriers

Variables	Before 2012	After 2013	<i>p</i> -value
Contralateral RRM affected carrier	11 (9.0%)	111 (91.0%)	0.003
Bilateral RRM unaffected carrier	3 (50.0%)	3 (50.0%)	1.000
RRBSO affected carrier	43 (10.0%)	385 (90.0%)	<0.001
RRBSO unaffected carrier	4 (6.6%)	57 (93.4%)	0.007

RRS = risk-reducing surgery; RRM = risk-reducing mastectomy; RRBSO = risk-reducing bilateral salpingo-oophorectomy.

carriers, bilateral RRM and RRBSO were performed in 6 (1.2%) and 61 (11.9%) patients, respectively, until August 2018 (Table 1). Contralateral RRM among affected carriers increased approximately 5.8-fold, from 5 cases in 2013 to 29 cases in 2017. RRBSO among affected carriers also increased approximately 3.6-fold, from 22 cases in 2013 to 79 cases in 2017. Among unaffected carriers, bilateral RRM increased by 1 case in 2017, and RRBSO increased 8-fold from 2 cases in 2013 to 16 cases in 2017 (Figure 2). There were significant differences in the rate of contralateral RRM in affected carriers and RRBSO in *BRCA1/2* mutation carriers before and after Angelina Jolie's announcement ($p < 0.05$); however, there was no difference in the rate of bilateral RRM in unaffected carriers (Table 2).

The number of institutions that performed RRS increased gradually. The number of institutions performing contralateral RRM in affected carriers increased from 3 in 2012 to 11 in 2018, and that of those performing RRBSO increased from 7 to 17 in the same time frame. The number of institutions that performed bilateral RRM in unaffected carriers increased from 1 in 2012 to 2 in 2018, and that of those performing RRBSO increased from 1 in 2012 to 8 in 2018.

Hospitals in Korea showed differences in the rates of RRM and RRBSO. Among affected carriers treated at different hospitals, the highest and lowest rates of contralateral RRM were 44.4% and 2.9%, respectively, while those of RRBSO were 100% and 12.7%, respectively (Figures 3 and 4). Among unaffected carriers, the highest and lowest rates of RRS were 11.1% and 7.4% for bilateral RRM, and 80% and 2.0% for RRBSO, respectively (Figures 5 and 6). However, there was no significant difference in the rate of RRM or RRBSO by level of care. Of the 18 hospitals that provided data, 4 hospitals were secondary and 14 were tertiary. Among affected carriers treated at secondary and tertiary hospitals, the rates of contralateral RRM were 11.8% and 9.8%, and the rates of RRBSO were 23.5% and 34.9%, respectively. Among unaffected carriers treated at secondary and tertiary hospitals, the rates of bilateral RRM were 0.0% and 1.2%, and the rates of RRBSO were 3.4% and 12.4%, respectively (Tables 3 and 4).

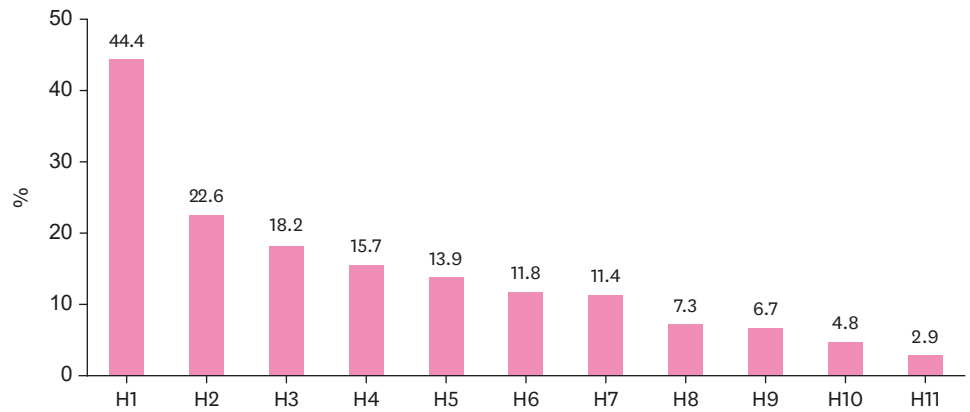


Figure 3. Rate of contralateral risk-reducing mastectomy in affected carriers by institution.



Figure 4. Rate of risk-reducing bilateral salpingo-oophorectomy in affected carriers by institution.

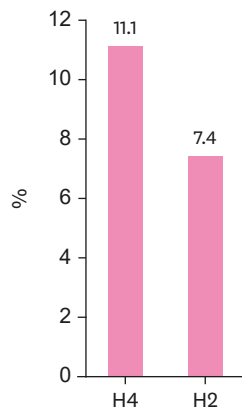


Figure 5. Rate of bilateral risk-reducing mastectomy in unaffected carriers by institution.

DISCUSSION

This study was conducted by collecting and analyzing data from multiple centers affiliated with the KOHBRA study that was conducted until May 2013. We retrospectively reviewed annual trends in *BRCA1/2* genetic testing and RRS in KOHBRA-affiliated hospitals until August

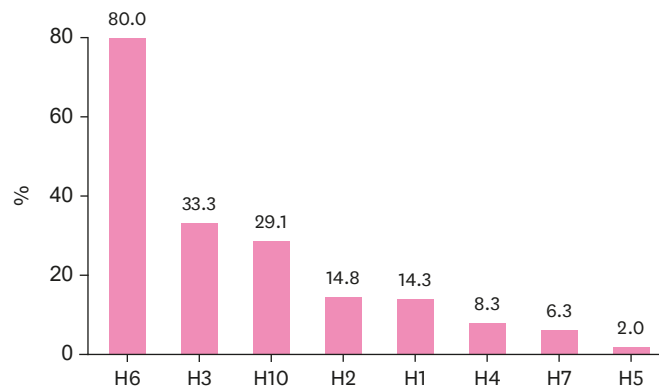


Figure 6. Rate of risk-reducing bilateral salpingo-oophorectomy in unaffected carriers by institution.

Table 3. Rate of RRS in affected carriers by level of care until August 2018

Variables	Secondary	Tertiary	p-value
No. of <i>BRCA1/2</i> mutation carrier	34	1,204	
Contralateral RRM	4 (11.8%)	118 (9.8%)	0.768
RRBSO	8 (23.5%)	420 (34.9%)	0.170

RRS = risk-reducing surgery; RRM = risk-reducing mastectomy; RRBSO = risk-reducing bilateral salpingo-oophorectomy.

Table 4. Rate of RRS in unaffected carriers by level of care until August 2018

Variables	Secondary	Tertiary	p-value
No. of <i>BRCA1/2</i> mutation carrier	29	485	
Bilateral RRM	0 (0.0%)	6 (1.2%)	1.000
RRBSO	1 (3.4%)	60 (12.4%)	0.234

RRS = risk-reducing surgery; RRM = risk-reducing mastectomy; RRBSO = risk-reducing bilateral salpingo-oophorectomy.

2018. Our study showed that while the rates of *BRCA1/2* genetic testing and RRS have increased rapidly, there are differences in the number of RRS performed among hospitals in Korea.

The prevalence of *BRCA1/2* genetic testing and RRS have continued to increase because of the global rise in numbers of laboratories offering genetic testing, expanding insurance coverage, celebrity endorsement, and evidence for the clinical benefits of known mutational status [3,9]. In Korea, the KOHBRA study (2007–2013) established a large cohort of *BRCA1/2* mutation carriers among Korean breast cancer patients [7], and has improved clinician awareness of the *BRCA 1/2* mutation. In addition, insurance reimbursement for hereditary breast cancer has been enacted in Korea over the past 10 years. Korea is the only Asian country that offers national insurance to patients with breast cancer for *BRCA1/2* genetic testing.

Moreover, the disclosure of Angelina Jolie's medical history was followed by increasing *BRCA1/2* genetic testing and RRS in Korea. Jolie underwent RRM in May 2013 and RRBSO in March 2015, and these announcements helped create global awareness about *BRCA1/2* genetic testing and RRS. We found that RRBSO in *BRCA1/2* mutation carriers increased significantly after Jolie's announcement. Contralateral RRM in affected carriers also increased significantly; however, there was no significant difference in bilateral RRM in unaffected carriers. Many studies have reported the international trends in *BRCA1/2* genetic testing and RRM after Jolie's announcement. For instance, Desai and Jena [10] found that the rate of RRM remained unchanged after news coverage about Jolie's diagnosis, although *BRCA1/2* genetic testing increased significantly. However, several other studies showed an increase

in bilateral RRM in an international database of *BRCA1/2* mutation carriers who had recently undergone genetic testing [3,11]. The uptake of RRM by unaffected carriers varied greatly among countries [3,12]. Metcalfe et al. [3] reported an increase in RRM in 10 countries, with the highest uptake of bilateral RRM being in the United States (49.9%) and the lowest in Poland (4.5%). In Korea, the uptake of RRM was 1.2% in unaffected carriers and 9.9% in affected carriers until August 2018. By August 2018, *BRCA1/2* mutation carriers were more likely to choose RRM than they had been in the preceding decade. The impact of insurance coverage and Angelina Jolie's news resulted in changes in thinking about RRS in Korea.

The increase in numbers of clinicians and hospitals that perform RRS has also affected its uptake, although there are differences in rates of RRS among hospitals in Korea. The lack of significant differences in rates of RRS between secondary and tertiary hospitals may be due to RRS being actively recommended in only a few hospitals, regardless their level of care. The difference in rates among hospitals may be attributed to differences in the clinician's choices, time for genetic testing results, genetic counseling, or multidisciplinary teams between hospitals. It will be necessary to improve the medical environment and clinicians' awareness, so that more clinicians and hospitals may consider the result of *BRCA1/2* genetic testing more carefully, which may further affect decision-making for RRS.

Risk-reducing management of *BRCA1/2* mutation carriers has occurred worldwide [13,14]. In carriers of the *BRCA1/2* mutation, RRM lowers the risk of breast cancer by approximately 90% [15,16]. RRBSO is associated with a 70% reduction in the risk of ovarian cancer in unaffected carriers and an 85% reduction in affected carriers [17]. RRBSO also lowers the risk of breast cancer by 37% in *BRCA1* mutation carriers and by 64% in *BRCA2* mutation carriers [17]. The current National Comprehensive Cancer Network guidelines recommend RRBSO for *BRCA1* mutation carriers who are aged between 35 and 40 years and have completed childbearing [18]. Since the onset of ovarian cancer occurs an average of 8–10 years later in *BRCA2* mutation carriers than in those with the *BRCA1* mutation, RRBSO is recommended until the age of 40–45 years in the former [18]. In unaffected carriers, survival benefits are apparent for RRBSO, but not for RRM. However, Heemskerk-Gerritsen et al. [19] reported that RRM is associated with lower mortality than surveillance for carriers of the *BRCA1* mutation [20,21]. Metcalfe et al. [22] showed that mortality risk was lower in patients with *BRCA1/2* mutation who were treated for stage I or II breast cancer with bilateral mastectomy than those treated with unilateral mastectomy. Although RRS is recommended for carriers of the *BRCA1/2* mutation, the procedure has adverse psychosocial and sexual effects because it removes normal breasts or ovaries. Moreover, sensory changes and skin necrosis may be caused by RRM, and RRBSO may have adverse effects on lipid profiles and may increase the risk of cardiovascular disease and osteoporosis. Because of the benefits and harms of RRS, clinicians should play a major role in the decision-making process of RRM or RRBSO for carriers of the *BRCA1/2* mutation [13,23,24].

The results of *BRCA1/2* genetic testing before surgery may help affected carriers decide whether to undergo contralateral RRM. Traditional Sanger sequencing analysis for *BRCA1/2* mutation has a high cost and long turnaround time (TAT) due to the large size of the genes [25]. Next-generation sequencing (NGS) allows simultaneous sequencing of multiple cancer susceptibility genes, and may be less expensive. NGS can also have a shorter TAT and higher accuracy than conventional methods [25,26], which can allow clinicians and patients to make decisions about RRS. In Korea, insurance coverage of NGS for *BRCA1/2* genetic testing started in September 2017, and both *BRCA1/2* genetic testing and RRS are likely to gradually increase in frequency. Further research is needed on this trend in Korea.

This study demonstrated an increasing incidence of *BRCA1/2* genetic testing and RRS in consecutive years. However, differences in RRS rates depend on the hospital in Korea. We need to provide enough information for patients to understand the results of genetic counseling so that they can make the optimal choice of treatment.

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