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Conflict of Interest

No potential conflict of interest relevant to this
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Pathologic findings at risk-reducing salpingo-oophorectomy (RRSO) in germline *BRCA* mutation carriers with breast cancer: significance of bilateral RRSO at the optimal age in germline *BRCA* mutation carriers

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ABSTRACT

Objective: Most *BRCA1/2* carriers do not undergo risk-reducing salpingo-oophorectomy (RRSO) by the recommended age. This study aimed to find the incidence of precursor lesions and cancer after RRSO.

Methods: We retrospectively reviewed breast cancer patients identified as *BRCA* mutation carriers who underwent RRSO at Asan Medical Center, Seoul, Korea, from 2010 to 2014. From 2013, all cases were examined according to the Sectioning and Extensively Examining the Fimbria (SEE/FIM) protocol and underwent immunohistochemically staining. RRSO was performed in 63 patients, 27 in 2010 to 2012 and 36 in 2013 to 2014.

Results: The median age at RRSO was 46.5 years (range, 32 to 73 years). Occult invasive cancer was detected in eight patients, of ovarian origin in five and of tubal origin in three. All occult invasive cancer cases with metastasis were detected in patients older than 40 years. Of the 36 patients from the 2013 to 2014 cohort, seven showed p53 overexpression, one showed Ki-67 overexpression, two showed serous tubal intraepithelial carcinoma, and three showed occult cancer. The detection rate of precursor lesions or cancer was 36.1% (13/36). In the analysis according to age, precursor lesions were more common in *BRCA1* mutation carriers younger than 40 years old (66.7% vs. 20.0%). In *BRCA2* mutation carriers, precursor lesions were only detected in those older than 40 years of age, indicating the possible faster occurrence of precursor lesions in *BRCA1* mutation carriers.

Conclusion: Many patients still tend to delay RRSO until after they are 40 years old. Our findings support the significance of RRSO before the age of 40 in germline *BRCA* mutation carriers.

Keywords: *BRCA*; Risk-Reducing Salpingo-Oophorectomy; Serous Tubal Intraepithelial Carcinoma

INTRODUCTION

High-grade serous ovarian cancer (HGSOC) is the most common histologic subtype of epithelial ovarian cancer, accounting for almost 70% of cases, and >75% of HGSOC patients are diagnosed at an advanced stage. Up to 20% of patients with HGSOC have a *BRCA1* or *2* germline mutation and the prevalence of mutation were more common in patients with a strong family history [1,2]. *BRCA1* and *2* are tumor suppressor genes that play a role in chromosomal damage repair. Mutations in these genes are associated with increased risk of breast and ovarian cancer. *BRCA1* germline mutation carriers have a 40% to 60% risk of developing HGSOC in their lifetime, whereas the risk is 11% to 27% for *BRCA2* germline mutation carriers. These carriers are thus offered risk-reducing salpingo-oophorectomy (RRSO) by age 40 by gynecologic oncologists according to National Comprehensive Cancer Network (NCCN) guidelines. However, most *BRCA1/2* carriers do not undergo RRSO by this age [3].

Since the discovery that tubal intraepithelial carcinomas are the premalignant lesion of HGSOC in women with a *BRCA* mutation, the significance of RRSO until the guideline-recommended age and comprehensive histopathologic examination of the fallopian tubes obtained has increased [4-6]. However, there are limited data on the optimal age for RRSO based on the prevalence of premalignant lesions or occult cancer at RRSO. Here, we analyzed the median age of RRSO in *BRCA* mutation carriers with a history of breast cancer and estimated the prevalence of precursor lesions including serous tubal intraepithelial carcinoma (STIC) and occult invasive cancer in RRSO specimens to help identify the optimal age to undergo RRSO.

MATERIALS AND METHODS

We retrospectively reviewed patients with breast cancer who were identified as *BRCA* mutation carriers and underwent RRSO at Asan Medical Center, Seoul, Korea, from 2010 to 2014. Medical records were reviewed for parity, family history, *BRCA* mutation status, history of tamoxifen use, and age at RRSO. From 2013, both fallopian tubes of all cases were examined according to the Sectioning and Extensively Examining the Fimbria (SEE/FIM) protocol and underwent immunohistochemical staining for p53 and Ki67. Pathology slides from 2010 to 2012 were merely reviewed to identify occult cancer. Thus, we could not review the data on precursor lesions because they were not examined according to the SEE/FIM protocol in the fallopian tube, especially at the fimbriated end. All slides were reviewed by an expert gynecological pathologist. We obtained Institutional Review Board approval for these studies (S2016-0051-0002).

The relationships between variable characteristics and the detection rate of precursor lesions or occult cancer were assessed by univariate analysis using chi-square and Fisher exact tests and by multivariate analysis using logistic regression analysis to identify independent risk factors for precursor lesions or occult cancer. To analyze the relationship between patient age and the detection rate of precursor lesions or occult cancer at RRSO, patient age was dichotomized as ≤ 40 and > 40 years. Descriptive statistics and data analysis were performed using SPSS ver. 20.0 (IBM Co., Armonk, NY, USA).

Table 1. Characteristics of the 63 patients with breast cancer in this study who were identified as *BRCA* mutation carriers and underwent RRSO

Variable	No. of patients (%)
Age at RRSO (yr), median (range)	46.5 (32–73)
<i>BRCA</i> mutation status	
<i>BRCA1</i> mutation	38 (60.3)
<i>BRCA2</i> mutation	25 (39.7)
Nulliparous	1 (1.6)
Tamoxifen use	
Current	14 (22.2)
Former	10 (15.9)
Never	39 (61.9)
Family history	
Ovarian or tubal or peritoneal cancer	
No	50 (79.4)
Yes	13 (20.6)
Breast cancer	
No	30 (47.6)
Yes	33 (52.4)

RRSO, risk-reducing salpingo-oophorectomy.

Table 2. Frequency of precursor lesions and occult cancer in 36 study patients with breast cancer who were identified as *BRCA* mutation carriers and underwent RRSO in 2013 to 2014

Variable	<i>BRCA1</i> (n=23)	<i>BRCA2</i> (n=13)
p53 overexpression	4 (17.4)	3 (23.1)
Ki67 overexpression	1 (4.3)	0
Serous tubal intraepithelial carcinoma.	1 (4.3)	1 (7.7)
Cancer	2 (8.7)	1 (7.7)
Total	8 (34.8)	5 (38.5)

Values are presented as number (%).

RRSO, risk-reducing salpingo-oophorectomy.

RESULTS

From 2010 to 2014, 63 patients with breast cancer who were identified as *BRCA* mutation carriers underwent RRSO at our institution, 27 patients from 2010 to 2012 and 36 patients from 2013 to 2014. The characteristics of the 63 patients are summarized in **Table 1**. Of the 63 patients, 38 were *BRCA1* mutation carriers and 25 were *BRCA2* mutation carriers. The median age at RRSO was 46.5 years (range, 32 to 73 years) and only one patient was nulliparous at the time of RRSO. Regarding tamoxifen use, 14 patients were current users, 10 were former users, and 39 had never used tamoxifen. There was a family history of ovarian or tubal or peritoneal cancer in 13 patients and 33 patients had a family history of breast cancer. In statistical analysis, tamoxifen use ($p=0.736$) and family history ($p=1.000$) were not associated with the detection rate of precursor lesions or occult cancer at RRSO. RRSO was performed before the age of 40 in 13 of the 63 patients (20.6%). The frequency of precursor lesions (p53 overexpression, Ki67 overexpression, STIC) and occult cancer in the 36 patients treated from 2013 to 2014 is indicated in **Table 2**. Of these 36 patients, seven showed p53 overexpression, one showed Ki-67 overexpression, two showed STIC, and three showed occult cancer according to the SEE/FIM protocol. The primary site of all precursor lesions was the distal tube. The detection rate of precursor lesions or cancer was 36.1% (13/36).

The relationship between patient age and the detection rate of precursor lesions or occult cancer at RRSO in 2013 to 2014 is indicated in **Table 3**. There was no statistically significant relationship. However, in the *BRCA1* mutation group, patients who underwent RRSO before 40 years of age were more likely to have precursor lesions. In the *BRCA2* mutation group, precursor lesions were only detected in patients who were older than 40 when they

Pathologic findings in BRCA mutation carriers

Table 3. Relationship between patient age and the detection rate of precursor lesion or occult cancer at risk-reducing salpingo-oophorectomy in 2013 to 2014

Variable	<40 yr (n=6)	>40 yr (n=30)	p-value
Precursor lesion			
<i>BRCA1</i>	2/3 (66.7)	4/20 (20.0)	0.155
<i>BRCA2</i>	0/3	4/10 (40.0)	0.497
<i>BRCA1/2</i>	2/6 (33.3)	8/30 (26.7)	>0.999
Occult cancer			
<i>BRCA1</i>	0/3	2/20 (10.0)	>0.999
<i>BRCA2</i>	0/3	1/10 (10.0)	>0.999
<i>BRCA1/2</i>	0/6	3/30 (10.0)	>0.999
Total			
<i>BRCA1</i>	2/3 (66.7)	6/20 (30.0)	0.269
<i>BRCA2</i>	0/3	5/10 (50.0)	0.231
<i>BRCA1/2</i>	2/6 (33.3)	11/30 (36.7)	>0.999

Values are presented as number (%).

Table 4. Characteristics of the study patients with cancers detected at RRSO

No.	Age at RRSO (yr)	Location	Histologic type	Stage	Cytology	<i>BRCA1/2</i> status	<i>BRCA</i> germline mutation
1	34	Ovary	MAC, WD	IA	Negative	1	5199G>T
2	45	Ovary	EAC, PD	IC2	Negative	1	5312+1G>C
3	67	Ovary	PSC, HG	IIB	Positive	1	1835del A
4	41	FT	PSC, HG	IIIC	Positive	1	509C>A
5	48	FT	PSC, HG	IIB	Negative	1	1418delC
6	52	FT	PSC, HG	IIIC	None [†]	1	2478 del G
7	42	Ovary	PSC, HG	IIB	None	2	1627A>T
8	63	Ovary	PSC, HG	IVB	Positive	2	5820_5821delCA

EAC, endometrioid adenocarcinoma; FT, fallopian tube; HG, high-grade; MAC, mucinous adenocarcinoma; PD, poorly differentiated; PSC, papillary serous carcinoma; RRSO, risk-reducing salpingo-oophorectomy; WD, well differentiated.

[†]Cytology was not performed.

underwent RRSO. In addition, all three patients who were found to have occult cancer were older than 40 when they underwent RRSO.

In the pathology slides from 2010 to 2012, the presence of occult cancer was only assessed because the fallopian tube was not examined according to the SEE/FIM protocol. Occult cancer was detected in five of these 27 patients, four of the 15 *BRCA1* mutation carriers (26.7%), and one of the 12 *BRCA2* mutation carriers (8.3%). Of the five patients with occult cancer, one was younger than 40 at detection (14.3% of the seven patients younger than 40) and four were older than 40 (20.0% of the 20 patients older than 40). Eight occult invasive cancers were identified from 2010 to 2014, five of ovarian origin and three of tubal origin (**Table 4**). The pathologic type of the identified cancer was papillary serous carcinoma in six patients, mucinous adenocarcinoma in one patient, and endometrioid adenocarcinoma in one patient; one of the 13 cancer cases (7.7%) was detected in a patient younger than 40 and seven of the 50 cancer cases (14.0%) were detected in patients older than 40.

DISCUSSION

NCCN guidelines suggest RRSO before the age of 40 in these *BRCA* carriers. However, patients still tend to delay RRSO until after 40 years of age due to worries about the negative hormonal influence of bilateral oophorectomy. The dramatic and rapid decline in estrogen and androgen levels after RRSO may negatively influence quality of life and health [7,8]. Short-term hormone replacement treatment seems to improve quality of life and, moreover, does not seem to have an adverse effect on oncologic outcomes in *BRCA1/2* mutation carriers without breast cancer history [9]. In *BRCA1/2* mutation carriers with breast cancer history,

greater prudence is required regarding the timing of RRSO due to the impossibility of hormone replacement treatment.

In current study, the median age at RRSO was 46.5 years (range, 32 to 73 years), which was higher than the recommended age of the NCCN guidelines. Only 13 patients (20.6%) underwent bilateral RRSO before 40 years of age. This result is similar to that obtained by Garcia et al. [3], who evaluated the adherence to the NCCN guidelines of RRSO by age 35 to 40 and found that only 17% women had undergone RRSO before the age of 40. In comparison between 2010 to 2012 and 2013 to 2014, the median age at RRSO (46 vs. 46.5) was not decreased against steadily increasing mean number of RRSO (9 vs. 18). In Korea, *BRCA* sequencing and number of revealed mutation carrier is steadily increasing by 'Angelina Jolie effect' and insurance policy change of *BRCA* test. RRSO is increasing accordingly, without tendency of delaying RRSO in *BRCA* mutation carriers. In current study, only one woman was nulliparous showing that most women want to undergo RRSO after childbirth, which may be one of the reasons why *BRCA* carriers delay RRSO, given that women tend to conceive at an older age than in previous generations [10]. Statistical analysis of factors such as tamoxifen use and family history revealed no significant relationship with the detection rate of precursor lesions or occult cancer at RRSO in the 2013 to 2014 cohort.

The frequency of precursor lesions and occult cancer in the 36 patients treated from 2013 to 2014 is listed in **Table 2**. The primary site of all precursor cases was distal fallopian tube, supporting the value of the SEE/FIM protocol, which sections the fimbriated end at 2- to 3-mm intervals to expose about a 60% greater surface area [11]. p53 overexpression (p53 signature) is defined as strong nuclear staining in at least six consecutive tubal epithelial cells [6]. Ki-67 is a proliferation marker and its overexpression is defined by Ki-67 staining in more than 50% of nuclei of p53-overexpressing cells. These characteristics are putative precursors to STIC, which is itself a direct precursor of HGSOE. STIC shows significant atypia, p53 overexpression, and Ki-67 overexpression [12]. In our current study, the detection rate of STIC at RRSO was 5.6% (*BRCA1* mutation carriers, 4.3%; *BRCA2* mutation carriers, 7.7%), which is similar to the results of previous studies reporting STIC detection rates of between 5% and 8% [13,14]. The detection rate of occult cancer was 12.7% (*BRCA1* mutation carriers, 15.8%; *BRCA2* mutation carriers, 8.0%) and this is similar to the results of previous studies, which ranged from 4.4% to 17% [15-17]. The detection rate of precursor lesions or cancer at RRSO in the 2013 to 2014 cohort was 36.1% (13/36). There were no significant differences in the distribution of precursor lesions and occult cancer between *BRCA1* and *BRCA2* mutation carriers.

In the analysis according to age, precursor lesions were more common in *BRCA1* mutation carriers younger than 40 years old (66.7% vs. 20.0%). In *BRCA2* mutation carriers, precursor lesions were only detected in those older than 40 years of age, indicating the possible faster occurrence of precursor lesions in *BRCA1* mutation carriers. Occult cancer was detected in three women, all of whom were older than 40 years of age, suggesting that precursor lesions in women younger than 40 years old were progressing and being detected as occult cancer in women older than 40 years of age. However, no statistically significant relationships were found in this analysis due to the small sample size.

In the analysis of pathology slides obtained in 2010 to 2012, occult cancer was detected in five patients, with a higher detection rate in *BRCA1* mutation carriers than in *BRCA2* mutation carriers (26.7% vs. 8.3%). Of the five patients with occult cancer, only one was younger than 40 years. Eight patients were found to have occult cancer from 2010 to 2014, and only one

patient was younger than 40 (12.5%). Occult cancer was more commonly detected in women older than 40 (7.7% vs. 14.0%).

The age at which RRSO provides maximal benefit with minimal adverse hormonal effects is still controversial. The efficacy of RRSO in protecting against ovarian and breast cancer has already been proven [18] and women who undergo RRSO show the same levels of fatigue, fracture incidence, and quality of life as controls [19,20]. However, previous studies showed increased overall and cardiovascular disease mortality in premenopausal women who had undergone bilateral oophorectomy and had not received estrogen replacement therapy [7,21,22]. Moreover, in a study conducted by Michelsen et al. [23], surgical menopause was significantly associated with metabolic syndrome. For this situation, a “two-step prevention strategy” was suggested in which salpingectomy or fimbriectomy with ovarian conservation would be performed in young women, followed by oophorectomy after menopause [24,25]. However, this approach remains to be fully investigated.

Our study had several weaknesses. We were unable to collect data on the history of contraceptive use due to the retrospective nature of our analysis. During the period of 2010 to 2012, pathologic slide reviews considered only for occult cancer because the slides were not assessed according to the SEE/FIM protocol in the fallopian tube. In addition, we were unable to find a statistically significant association between age and the detection of precursor lesions and occult cancer, probably due to the small sample size of the study. However, we analyzed the differences in the detection rate of precursor lesions and occult cancer by 40 years of age according to the NCCN guidelines. Additionally, the current analysis only comprised women with breast cancer who were unable to receive estrogen replacement therapy. The optimal timing of RRSO is more crucial for these patients who are not receiving estrogen support. And our study shows the possible earlier occurrence of precursor lesions in *BRCA1* mutation carriers than *BRCA2* mutation carriers.

The continuous increase in *BRCA* testing is increasing the detection of *BRCA* mutation carriers, with a consequent more widespread use of RRSO. Nonetheless, women still tend to delay RRSO until after they are 40 years of age. However, as shown by our present analysis, occult invasive cancers were more commonly detected in patients older than 40 years. Our findings support the significance of bilateral RRSO by age of 40 in germline *BRCA* mutation carriers, although there was no significant association found between age and the detection rate of precursor lesions and occult cancer due to the small sample size. To resolve this matter, a larger and prospective study is required to determine the optimal timing of RRSO for maximal risk reduction with minimal adverse hormonal effects. A prospective study of the usefulness of the two-step prevention strategy using salpingectomy or fimbriectomy is also necessary.

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