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Disparities between Uptake of Germline *BRCA1/2* Gene Tests and Implementation of Post-test Management Strategies in Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Patients

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ABSTRACT

Background: To assess the rate of germline *BRCA* gene tests in epithelial ovarian cancer (EOC) patients and uptake of post-test risk management strategies in *BRCA1/2*-mutated patients.
Methods: Institutional databases were searched to identify patients who were diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer (EOC) between 2009 and 2019 in two academic hospitals. Retrospective review on medical records was performed to collect clinico-pathologic variables, including performance of germline *BRCA* gene test and its results, as well as conduct of breast cancer screening tests and cascade testing. If annual mammography +/− breast ultrasonography was performed, it was considered that regular breast cancer surveillance was done.
Results: A total of 840 women with EOC were identified during the study period. Of these, 454 patients (54.0%) received *BRCA* gene testing and 106 patients (106/454, 23.3%) were positive for *BRCA1/2* mutations. The rate of *BRCA* tests has markedly increased from 25.8% in 2009-2012 to 62.7% in 2017-2019. Among the 93 patients with *BRCA1/2* mutation without previous personal breast cancer history, 20 patients (21.5%) received annual mammography with or without breast ultrasonography for regular surveillance. Among the 106 *BRCA1/2*-mutated EOC patients, cascade testing on family members was performed only in 13 patients (12.3%).
Conclusion: Although *BRCA1/2* gene tests have been substantially expanded, the uptake of post-test risk management strategies, including breast cancer screening for *BRCA1/2*-mutated patients and cascade testing for family members, has remained low. Strategies to increase its uptake and education about the importance of post-test risk managements are needed.

Keywords: BRCA1; BRCA2; Epithelial Ovarian Cancer; Breast Cancer Screening; Cascade Test

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim MK, Lee M. Data curation: Hur YM, Mun J. Formal analysis: Kim MK. Funding acquisition: Kim MK. Investigation: Hur YM, Mun J, Kim MK, Lee M. Methodology: Kim MK, Lee M. Software: Kim MK. Validation: Kim YH, Kim SC. Visualization: Hur YM, Mun J, Kim MK. Writing - original draft: Kim MK. Writing - review & editing: Hur YM, Mun J, Lee M, Kim YH, Kim SC.

INTRODUCTION

Germline mutations in *BRCA1* or *BRCA2*, the most commonly detected mutations in hereditary breast and ovarian cancer, are found in up to 15–20% of unselected epithelial ovarian cancer (EOC) patients.[1,2] Based on this relatively high prevalence of *BRCA*-mutated EOC, *BRCA* gene testing is recommended in all patients diagnosed with EOC at any age.[3] Conventionally, knowing the *BRCA* mutation status has been important for EOC patients and their family members in terms of assessing the genetic risk of hereditary cancer. However, the development of poly (ADP-ribose) polymerase inhibitors (PARPi) and their demonstrated clinical benefits in *BRCA*-mutated EOC patients have drawn greater attention to genetic testing for *BRCA1* and *BRCA2* as a companion diagnostic test for the usage of PARPi, and the prescription number of *BRCA* gene testing has markedly increased in the last decade along with the health insurance coverage.[4-6]

The cumulative risk of breast cancer up to age 70–80 years in *BRCA1* and *BRCA2* mutation carriers was reported to be 72% for *BRCA1* and 66.3–69% for *BRCA2* mutation.[7,8] Due to the high risk of breast cancer development especially at an early age in these carriers, current guidelines recommend annual mammography and breast MRI starting at 30 years of age.[3]

However, despite the increased performance of *BRCA* gene testing, the uptake of breast cancer risk reduction strategies for *BRCA* mutation carriers, including breast cancer screening, has been suboptimal with significant differences country by country.[9,10] Although there have been a few studies assessing the frequency of risk-reducing salpingo-oophorectomy among *BRCA* mutation carriers, the state of breast cancer screening uptake and cascade testing among Korean women with *BRCA* mutations has not been evaluated up to date.[11,12] Therefore, this study aimed to assess the rate of germline BRCA gene tests in EOC patients and uptake of post-test risk management strategies, including breast cancer surveillance and cascade testing on family members in *BRCA1/2*-mutated patients.

METHODS

The institutional databases were searched to identify patients who were diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer between January 2009 and December 2019 in two academic hospitals (Ewha Womans University Medical Center [EUMC] and Seoul National University Hospital [SNUH]). Exclusion criteria include non-EOC cases, insufficient data, and patients diagnosed outside the study period. Retrospective review of electronic medical records was performed to collect clinico-pathologic variables, which include age at diagnosis, histologic type, stage, performance of germline *BRCA* gene test and its results, and conduct of breast cancer screening tests. If annual mammography with or without breast ultrasonography was performed among women aged ≥ 40 years, it was considered that regular breast cancer surveillance was done. For women aged < 40 years, annual breast ultrasonography with or without mammography was regarded as regular breast screening test. If breast cancer screening test was performed only one time during the follow-up period, it was not counted as performance of regular breast cancer surveillance.

Recommendation and performance of cascade testing for family members were also investigated.

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Statistical analysis was performed using SPSS for Windows (version 20.0; SPSS Inc., Chicago, IL, USA). In most of the cases, descriptive statistical analysis was performed. Either χ^2 test or Fisher's exact test was used when comparing categorical variables. Two-sided *P* value < 0.05 was considered significant.

Ethics statement

Institutional Review Board (IRB) approval of a waiver of informed consent (IRB No. 2020-08-013 [EUMC] and No. 2008-097-1149 [SNUH]) was obtained.

RESULTS

Between 2009 and 2019, a total of 840 patients who were diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer were identified, of which 233 patients were from EUMC and 607 patients were from SNUH. About two thirds of the patients were diagnosed with stage III/IV disease and the most common histologic type was serous type (69.2%, **Table 1**).

In 454 patients (54.0%), germline *BRCA* gene testing was performed. The rate of *BRCA* tests has markedly increased from 25.8% in 2009–2012 to 54.2% in 2013–2016 and 62.7% in 2017–2019. The *BRCA* gene testing was more frequently performed in stage III/IV disease (62.1%, 352/567) compared to stage I/II disease (37.4%, 102/273; *P* < 0.001). Most of the *BRCA* gene tests were performed during or following the course of adjuvant chemotherapy after histologic diagnosis was confirmed (75.1%, **Table 2**). Among the 454 patients who received *BRCA* gene testing, 106 patients (23.3%) were positive for pathogenic/likely pathogenic *BRCA1/2* variants, of which 80 (17.6%) had *BRCA1* and 26 (5.7%) had *BRCA2* mutations. There was no significant difference in the *BRCA1/2* mutation prevalence between the two institutions (data not shown).

Among the 93 patients with *BRCA1/2* mutation without previous personal breast cancer history, 20 patients (21.5%) received annual mammography with or without breast

Table 1. Patient characteristics

Variables	Values
Age at diagnosis, yr	54.5 (18–91)
Cancer type	
Epithelial ovarian cancer	797 (94.9)
Fallopian tube cancer	19 (2.3)
Primary peritoneal cancer	24 (2.9)
Stage	
I	209 (24.9)
II	64 (7.6)
III	315 (37.5)
IV	252 (30.0)
Histology	
Serous	581 (69.2)
Endometrioid	52 (6.2)
Mucinous	77 (9.2)
Clear cell	103 (12.3)
Others	27 (3.2)
Cancer history	
Breast cancer	45 (5.4)
Other cancer	54 (6.4)

Values are presented as median or number (%).

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Table 2. Timing of *BRCA* testing and *BRCA* test results

Variables	Values
Timing of *BRCA* testing	
During or following adjuvant Tx	341 (75.1)
At the time of first recurrence	72 (15.9)
≥ Second recurrence	40 (8.8)
Unknown	1 (0.2)
BRCA1 mutation	
Not detected	349 (76.9)
Benign/likely benign	12 (2.6)
VUS	11 (2.4)
Pathogenic/likely pathogenic	80 (17.6)
Unknown	2 (0.4)
BRCA2 mutation	
Not detected	409 (90.1)
Benign/likely benign	7 (1.5)
VUS	10 (2.2)
Pathogenic/likely pathogenic	26 (5.7)
Unknown	2 (0.4)
Overall prevalence of *BRCA1/2* mutation	106 (23.3)
Cascade testing (family members)	
No mention	88 (83.0)
Recommended, but refused	5 (4.7)
Recommended, and done	13 (12.3)

Values are presented as number (%).
VUS = variants of unknown significance.

ultrasonography. There were only 2 patients aged < 40 years, and one of these two patients received annual breast cancer surveillance with mammography alone. Breast MRI was performed in five patients, of whom only one patient with *BRCA1* pathogenic variant received regular breast MRI for surveillance. And, one patient treated for stage IC EOC was tested to have *BRCA1* mutation and received risk-reducing bilateral mastectomy.

There were significant differences in the uptake of breast cancer screening by institution. In EUMC, 76.9% of patients with *BRCA1/2* mutation received annual mammography, which was significantly higher than patients without *BRCA* mutation (41.5%, **Table 3**). On the other hand, only 12.5% of *BRCA1/2* mutated patients in SNUH received annual mammography.

Table 3. Breast cancer surveillance among patients without history of breast cancer according to the *BRCA* status

Variables	*BRCA* mutation+	*BRCA* mutation−	*BRCA* unknown
Total population (n = 795)			
Annual mammography	20 (21.5)	49 (15.2)	93 (24.5)
Annual breast USG	16 (17.2)	38 (11.8)	63 (16.6)
Breast MRI	5 (5.4)	2 (0.5)	1 (0.3)
Follow-up period, mean, mon	42.57	34.98	33.86
Post-EOC breast ca	2/93 (2.2)	1/323 (0.3)	2/379 (0.5)
EUMC (n = 228)			
Annual mammography	10 (76.9)	22 (41.5)	50 (30.9)
Annual breast USG	6 (46.2)	16 (30.2)	28 (17.3)
Breast MRI	1 (7.7)	1 (1.9)	1 (0.6)
SNUH (n = 567)			
Annual mammography	10 (12.5)	27 (10.0)	43 (19.8)
Annual breast USG	10 (12.5)	22 (8.1)	35 (16.1)
Breast MRI	4 (5.0)	1 (0.4)	0 (0)

Values are presented as number (%).
USG = ultrasonography, MRI = magnetic resonance imaging, EOC = epithelial ovarian cancer, EUMC = Ewha Womans University Medical Center, SNUH = Seoul National University Hospital.

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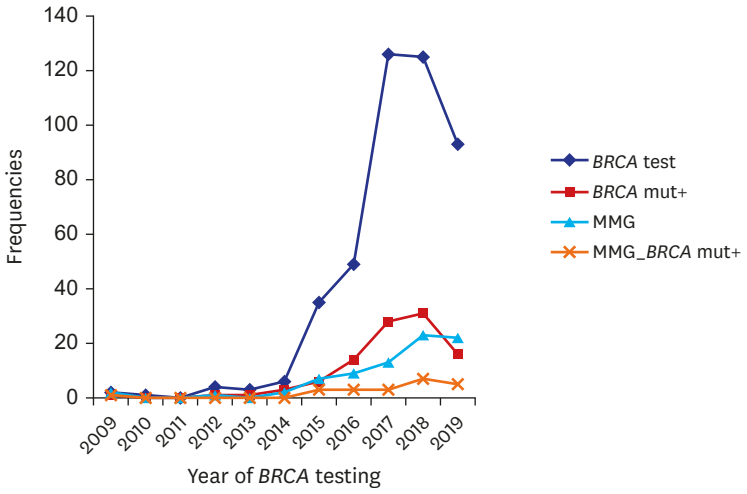

Fig. 1. Annual trend of *BRCA* gene testing prescription (♦), *BRCA1/2* mutation carriers (■), and breast cancer surveillance with mammography in EOC patients as a whole (▲) and EOC patients with *BRCA* mutations (x).
EOC = epithelial ovarian cancer, MMG = mammography.

Among the 106 *BRCA1/2*-mutated EOC patients, cascade testing on family members was performed only in 13 patients (12.3%, **Table 2**). There was no mention or recommendation on family member testing in most of the patients (83.0%). Among the 18 patients who were recommended for the cascade testing, 72.2% received cascade testing. There was also a significant difference in the rate of cascade testing between the two institutions, although the rates in the two institutions were both suboptimal (35.7% in EUMC vs. 8.7% in SNUH; $P = 0.013$).

During the median follow-up period of 42.6 months, two patients, one patient from each institution, were diagnosed with breast cancer before *BRCA* gene testing was done. When counting the prescription number of *BRCA* gene testing in the two institutions by year, there was a marked increase in the number of *BRCA* gene testing, especially after 2016, and the number of *BRCA1/2* mutation carriers has also increased proportionately (**Fig. 1**). However, the rate of performance of breast cancer screening test has not increased accordingly, particularly in patients with *BRCA1/2* mutation.

DISCUSSION

The present study evaluated the rate of germline *BRCA* gene tests among EOC patients and the uptake of breast cancer screening strategies and cascade testing among *BRCA1/2*-mutated patients from two academic institutions in Korea. Although there has been a marked increase in the number of *BRCA* gene testing, the rates of breast cancer surveillance and cascade testing were low at only 21.5% and 12.3%, respectively.

Germline *BRCA* gene test is indicated in every EOC case at any age, and the decision of carrying out the genetic tests is usually made by the attending physicians. Although there was a survey study reporting that pre/post-test counseling and recommendation for risk-reducing surgery were appropriately provided by gynecologic oncologists, the study result was somewhat biased since the survey was done only on members participating in the hereditary gynecologic cancer symposium.[13] Ultimately, the decision on the evaluation of hereditary

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cancer risk and the implementation of the post-test risk management strategies are largely dependent on the individual physician's interest and awareness.

BRCA gene testing has substantially expanded especially after 2016, when Olaparib, one type of PARPi, was first approved in Korea as a maintenance therapy for *BRCA*-mutated, platinum-sensitive recurrent EOC (**Fig. 1**). Although the number of *BRCA1/2* mutation carriers has increased accordingly, the rate of breast cancer screening among EOC patients carrying *BRCA* mutations has remained low. Also, the cascade testing for family members was recommended in only 17% of the patients with *BRCA1/2* mutations. These findings suggest that *BRCA* gene testing itself has gained clinical interest as a companion diagnostic test for the usage of PARPi, but the knowledge of *BRCA* status derived from the test did not lead to appropriate follow-up measures. Also, the observation that *BRCA* gene testing was more frequently performed in advanced stage (62.1% in stage III/IV vs. 37.4% in stage I/II) suggested that the main purpose of the genetic tests might be to find candidates for PARPi, rather than to evaluate the hereditary cancer risk.

Since women with *BRCA1* or *BRCA2* mutation have elevated risks of *BRCA*-related cancer, including breast cancer, the National Comprehensive Cancer Network guidelines recommend beginning breast cancer surveillance with clinical breast exam at age 25 years, annual breast MRI at age 25–29 years, and annual mammography at age 30 years.[3] The sensitivity of MRI has been reported to be consistently higher than that of mammography, and the majority of breast cancers detected by MRI were early-stage cancers.[14] There were also some preliminary studies reporting that MRI screening might offer survival benefit especially in *BRCA2* mutation carriers.[15] Due to the potential risk of radiation exposure and lesser sensitivity of breast cancer detection by mammography, current guidelines prefer screening with MRI over mammography, especially in younger women at a high risk of breast cancer. In Korea, however, breast MRI screening for *BRCA* mutation carriers is not yet covered by national health insurance. In our study, only one patient received annual breast MRI for routine surveillance. To improve the uptake of breast MRI screening in *BRCA* mutation carriers, insurance issues need to be discussed further.

Some researchers reported that the risk of breast cancer following EOC in *BRCA* mutation carriers was low (8.3–8.9%) with the median time of 50 months from diagnosis of EOC to diagnosis of breast cancer, and that the survival was dominated by EOC-related mortality.[16,17] Based on these findings, some argue that breast cancer surveillance in *BRCA*-related EOC patients might not be as important as in unaffected *BRCA* mutation carriers. However, similar mortality rates between *BRCA*-mutated EOC patients with and without breast cancer diagnosis following EOC may be attributed to exceedingly poor survival outcomes of advanced EOC and early detection of early-stage breast cancer. It does not mean that breast cancer surveillance could be overlooked, especially in early-stage EOC patients having good prognosis. In our study, the rate of annual mammography was similarly low in stage I/II EOC (20.0%, 2/10), compared to stage III/IV disease (21.7%, 18/83; $P = 0.092$). Efforts to increase the awareness of importance of breast cancer surveillance in early-stage EOC patients at least are needed.

However, prophylactic mastectomy in *BRCA*-mutated EOC patients needs to be discussed with caution since aforementioned studies demonstrated that survival outcomes of EOC patients with metachronous breast cancer did not differ from those of EOC patients without breast cancer. Risk-reducing mastectomy, which is now covered by national health insurance for *BRCA* mutation carriers, may be considered in a limited number of early-stage EOC patients with *BRCA* mutations, for whom long-term survival can be expected.

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In our study, the cascade testing for family members was performed in only 12.3% of the patients with *BRCA1/2* mutations. Among the patients who were recommended for the cascade testing by their physicians or specialized geneticists, however, 72.2% received cascade testing. And, although the rate was still low, patients treated at EUMC where hereditary cancer clinic has been run by department of laboratory medicine since 2017 more likely received cascade testing (5/14 in EUMC vs. 8/92 in SNUH), and four of the five patients who performed the family member testing received genetic counseling at the hereditary cancer clinic. Based on these findings, it was suggested that performance of cascade testing might be affected by physicians' attitudes and post-test counseling. The knowledge of the *BRCA* mutation status of EOC patients is important for their family members as well in that it can afford opportunities for prevention of *BRCA*-related cancers in unaffected family members with *BRCA* mutations. For patients and their physicians, more education on the importance of post-test counseling, including risk-reducing strategies and cascade testing, is needed. In addition to the education, appropriate allocation of medical charge for genetic counseling is essential. At present, there is no charge for genetic counseling, which makes it difficult to give sufficient genetic counseling to the patients who received hereditary cancer-related genetic tests.

There are several limitations to our study. First, our study may not represent the nationwide uptake of breast cancer screening in the population of *BRCA*-mutated EOC patients since only EOC patients from two hospitals were included in the study population. In addition, the possibility of patients receiving breast cancer surveillance at other institutions was not investigated since the conduct of breast cancer screening was retrospectively reviewed based on medical records. However, higher rates of breast cancer surveillance and cascade testing in the institution where hereditary cancer clinic is settled are remarkable. To develop more comprehensive insight on the trend in the uptake of breast cancer surveillance and cascade testing among EOC patients with *BRCA* mutations, nationwide survey using national health insurance data is needed in the future.

Overall, the uptake of breast cancer screening among Korean EOC patients with *BRCA1/2* mutations is still not optimal (21.5% on annual mammography), and the recommendation of cascade testing for family members is inadequately done (17%). Strategies to increase its uptake and more efforts on educating physicians and patients about the importance of risk-reducing strategies and cascade testing after positive *BRCA* gene testing results as well as applying for appropriate coverage of national health insurance on risk-reducing strategies are needed.

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