pISSN 1598-2998, eISSN 2005-9256
https://doi.org/10.4143/crt.2020.364
Cancer Res Treat. 2021;53(1):207-211

Original Article

Uptake of Family-Specific Mutation Genetic Testing Among Relatives of Patients with Ovarian Cancer with *BRCA1* or *BRCA2* Mutation

Go Woon Jeong[1], **Wonkyo Shin**[1], **Dong Ock Lee**[1], **Sang-Soo Seo**[1], **Sokbom Kang**[1,2,3], **Sang-Yoon Park**[1], **Myong Cheol Lim**[1,3,4,5]

[1]*Center for Gynecologic Cancer,* [2]*Divison of Precision Medicine,* [3]*Graduate School of Cancer Science and Policy,* [4]*Center for Clinical Trials, Hospital,* [5]*Division of Tumor Immunology, Research Institute, National Cancer Center, Goyang, Korea*

Purpose The *BRCA1* or *BRCA2* gene is transmitted in an autosomal dominant fashion, and genetic testing of first-degree relatives of patients with family-specific mutation (FSM) is recommended. This study examined factors affecting the uptake of FSM testing among relatives of patients with peritoneal, ovarian, or fallopian tube (POFT) cancer with confirmed *BRCA1* or *BRCA2* germline mutation.

Materials and Methods Data from medical charts of 392 eligible patients and their relatives who had undergone outpatient genetic counseling/testing were retrospectively reviewed. Clinical factors were compared between family members who had and had not undergone genetic counseling/testing.

Results The uptake of FSM testing was 30.5% (129/423) among first-degree living relatives and 53.5% (69/129) within the overall family unit. The average time from genetic testing of the proband to the first FSM test within a family was 168 days (range, 23 to 681 days). Having a living father (33.8% vs. 13.3%, p=0.007) and daughter (79.4% vs. 60.3%, p=0.019) increased the uptake of FSM testing. FSM testing was more likely among female than among male relatives of cancer patients (40.9% vs. 17.6%, p < 0.001).

Conclusion Approximately one-third of first-degree relatives of patients with a POFT cancer with *BRCA1* or *BRCA2* mutation underwent FSM testing. Having a living father or daughter was a factor affecting the uptake of FSM testing, which was higher among female than among male relatives of the proband. This discrepancy might be due to a misconception that the *BRCA* gene is associated with women rather than with men.

Key words Peritoneal, ovarian, or fallopian tube cancer (POFT), *BRCA*, Family-specific mutation, Pedigree, Genetic test, Genetic counseling

Introduction

Genetic variants related to specific cancer risk have been well established, including in *BRCA1* or *BRCA2*-related ovarian cancer [1]. In the Korean population, germline mutations have been identified in 23.8%-25.7% of peritoneal, ovarian, or fallopian tube (POFT) cancer cases [2,3]. Meanwhile, 16% of patients with epithelial ovarian cancer have a family history of cancer. Among them, 74% of patients undergo genetic testing. Germline *BRCA1* or *BRCA2* mutations have been confirmed in 33% of tested patients [2].

The *BRCA1* or *BRCA2* gene is transmitted in an autosomal dominant fashion [4]. Therefore, familial genetic testing is recommended to first-degree relatives such as children, siblings, and parents of patients with *BRCA1* or *BRCA2* mutation. The National Comprehensive Cancer Network (NCCN) guidelines and Position Statement of Korean Society of Gynecologic Oncology recommend genetic testing to families of patients with *BRCA1* or *BRCA2* mutation [5,6]. However, among patients with ovarian cancer, previous studies have reported that only 20% of eligible individuals had taken advantage of a family-specific variant (FSM) genetic test [7]. Overall, where FSM was identified in a relative, the uptake of risk-reducing salpingo-oophorectomy was approximately 52% [8]. Nevertheless, to-date, the uptake rate of FSM testing among relatives of patients with *BRCA1* or *BRCA2* mutation has not been investigated in Korea. Therefore, the aim of this study was to examine the uptake rate of FSM testing and influencing factors among relatives of patients with a POFT cancer and a *BRCA1* or *BRCA2* germline mutation.

Materials and Methods

We identified a total of 392 patients with POFT cancer who underwent genetic counseling/testing at the National Cancer Center of Korea between April 2016 and February 2019. All of these patients underwent *BRCA1* or *BRCA2* germline

Correspondence: Myong Cheol Lim
Division of Tumor Immunology, Center for Gynecologic Cancer and Center for Clinical Trials, Research Institute and Hospital, Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, Korea
Tel: 82-31-920-1760 Fax: 82-31-920-1238 E-mail: gynlim@gmail.com
Received April 23, 2020 **Accepted** August 8, 2020 **Published Online** August 11, 2020

Table 1. Family-specific mutation genetic test results

Family-specific mutation	No. (%) (n=152)
Positive	77 (50.7)
Negative	75 (49.3)

mutation genetic testing and provided a pedigree.

Outpatient genetic counseling by gynecologic oncologists and nursing staff have been conducted with 392 patients with POFT cancer (April 25, 2016-Febraury 28, 2019). Information about hereditary POFT cancer patterns, penetration of the cancer, cost of genetic tests, advantages and limitations of genetic tests, as well as potential psychosocial impact of genetic testing were explained to the patients. Patients were asked to provide a family pedigree up to three generations. Among 392 women with POFT cancer undergoing genetic counseling/testing, 129 women had a confirmed *BRCA1* or *BRCA2* germline mutation.

Baseline demographic and clinical characteristics, including age, type of cancer, and pedigree information of 129 patients with a *BRCA1* or *BRCA2* germline mutation were collected and analyzed. Relatives of these patients were invited for FSM testing, and their baseline and clinical characteristics were examined. In particular, the characteristics of the 'uptake of FSM group and non-uptake of FSM group were compared.

In statistical analysis, comparisons were made with the Student t test, Wilcoxon test, chi-square test, and Fisher method. Univariate and multivariate Cox regression analysis was performed to identify factors affecting the uptake of FSM testing. A p-value < 0.05 was considered statistically significant.

Results

In this study, among 392 women with POFT cancers undergoing genetic counseling/testing, 129 women had a *BRCA1* or *BRCA2* germline mutation.

The average time from confirmation of a pathogenic variant in a patient with ovarian cancer to the first FSM test of a relative was 168 days (range, 23 to 618 days).

Among 129 patients with *BRCA1* and *BRCA2* mutation, FSM testing was performed within families of 69 patients (53.5%). Overall, the number of families who needed testing

Table 2. Baseline demographic and clinical characteristics: uptake of FSM group vs. non-uptake of FSM group

Characteristic	Uptake of FSM (n=69)	Non-uptake of FSM (n=60)	p-value
Age at the time of genetic test (yr)	54 (31-73)	57 (27-78)	0.171
Age of ovarian cancer diagnosis (yr)	53 (29-73)	55 (37-75)	0.135
Education level attained			
≥ High school	48 (73.8)	39 (67.2)	0.422
< High school	17 (26.2)	19 (32.8)	
Missing	4 (5.7)	2 (3.3)	
FIGO stage			
1	4 (6.1)	5 (10.0)	0.335
2	5 (7.6)	3 (6.0)	
3	44 (66.7)	26 (52.0)	
4	13 (19.7)	16 (32.0)	
Missing	3 (4.3)	10 (16.6)	
Comorbidity			
Yes	30 (43.5)	26 (43.3)	0.987
No	39 (56.5)	34 (56.7)	
Ovarian cancer			
Yes	69 (100)	60 (100)	
No	0	0	
Breast cancer			
Yes	4 (5.8)	4 (6.7)	> 0.99
No	65 (94.2)	56 (93.3)	

Values are presented as median (range) or number (%). FIGO, International Federation of Gynecology and Obstetrics; FSM, family-specific mutation.

Table 3. Comparison of characteristics of relatives: uptake of FSM group vs. 'non-uptake of FSM group

Characteristic	Uptake of FSM (n=69)	Non-uptake of FSM (n=60)	p-value
First-degree living family members	8 (3-15)	8 (4-17)	0.904
Father			
Alive	23 (33.8)	8 (13.3)	0.007
Deceased	45 (66.2)	52 (86.7)	
Missing	1 (1.4)	0	
Mother			
Alive	31 (45.6)	20 (33.3)	0.158
Deceased	37 (54.4)	40 (66.7)	
Missing	1 (1.4)	0	
OC in the first-degree relative	0 (0-2)	0 (0-3)	0.711
BC in the first-degree relative	0 (0-2)	0 (0-1)	0.724
OC in the second-degree relative	0 (0-1)	0 (0-2)	0.869
BC the second-degree relative	0 (0-1)	0 (0-2)	0.668
OC the third-degree relative	0 (0-2)	0 (0-2)	0.483
BC the third-degree relative	0 (0-1)	0 (0-1)	0.170
Children			
Yes	63 (92.6)	53 (91.4)	1.000
No	5 (7.4)	5 (8.6)	
Missing	1 (1.4)	2 (3.3)	
Daughter			
Yes	54 (79.4)	35 (60.3)	0.019
No	14 (20.6)	23 (39.7)	
Missing	1 (1.4)	2 (3.3)	
Son			
Yes	47 (68.1)	46 (76.7)	0.280
No	22 (31.9)	14 (23.3)	
Sister			
Yes	57 (82.6)	51 (85.0)	0.714
No	12 (17.4)	9 (15.0)	
Brother			
Yes	62 (89.9)	52 (86.7)	0.573
No	7 (10.1)	8 (13.3)	
Family history of OC			
Yes	16 (23.5)	13 (22.0)	0.841
No	52 (76.5)	46 (78.0)	
Missing	1 (1.4)	1 (1.6)	
Family history of BC			
Yes	21 (30.4)	17 (29.3)	0.890
No	48 (69.6)	41 (70.7)	
Missing	0	2 (3.3)	

Values are presented as number (range) or number (%). BC, breast cancer; FSM, family-specific mutation; OC, ovarian cancer.

was 423, while the uptake of FSM testing was 129 familial members (30.5%). Half of familial members (50.7%, 77/152) have the FSM (Table 1).

There were no statistically significant differences in characteristics between patients' relatives in the uptake of FSM group and non-uptake FSM group, including in frequency of POFT cancers being diagnosed within the family (Table 2). We compared the between the' uptake of FSM testing' and the 'non-uptake of FSM testing' groups. (Table 3) The median surviving family number did not differ significantly between the two groups (median [range], 8 [3-15] in the uptake of FSM testing group, 8 [4-17] in the non-uptake of

Table 4. Uptake of FSM genetic testing among living relatives of probands according to familial position to the proband

Relationship to proband	Total (n=423)	Uptake of FSM testing (n=129)	Non-uptake of FSM testing (n=294)	p-value
Females	235	96 (40.9)	139 (59.1)	< 0.001
Males	188	33 (17.6)	155 (82.4)	
Mother	31	2 (6.5)	29 (93.5)	0.215
Father	23	0	23 (100)	
Sister	117	35 (29.9)	82 (70.1)	< 0.001
Brother	107	10 (9.3)	97 (90.6)	
Daughter	87	58 (66.7)	29 (33.3)	0.003
Son	58	24 (41.4)	34 (58.6)	

Values are presented as number (%). FSM, family-specific mutation.

FSM testing group). However, the rate of FSM testing was higher within families with living fathers (33.8% vs. 13.3%, p=0.007) or daughters (79.4% vs. 60.3%, p= 0.019) (Table 3).

Comparisons between persons of different sex within a generation, for example, father vs. mother, brother vs. sister, and son vs. daughter, revealed that the uptake of FSM testing was higher among female relatives of cancer patients than among male relatives (40.9% vs. 17.6%, p < 0.001) (Table 4). None of the fathers included in the present study had undergone FSM testing. Sisters were more likely to be tested than were brothers (29.9% vs. 9.3%, p < 0.001). Daughters were more likely to be tested than were sons (67.8% vs. 39.7%, p=0.001).

Discussion

Genetic testing of patients with ovarian cancer is important for appropriate treatment of the patient and for managing cancer risk within the patient's family. Despite this recommendation, not all eligible candidates undergo genetic testing [9]. In the present study, we classified patients with ovarian cancer with *BRCA1* or *BRCA2* mutation into two groups, FSM uptake group vs. FSM non-uptake group and compared their characteristics.

In the present study, the uptake rate of FSM testing was higher among individuals whose fathers were alive. Previous studies have suggested that larger families (which are more likely to include a living father) with close relationships, good communication, and forward-thinking attitudes tend to share health information and treatment plan, when required [10,11]. The larger the number of living relatives, including a living father, the more likely the family is to undergo genetic testing as a result of good communication among family members. It is likely that communication among family members might be facilitated when a father is alive.

Concurrently, the uptake of FSM testing was higher among female relatives of cancer patients than among male relatives (40.9% vs. 17.6%, p < 0.001). The uptake of FSM testing was higher among families with a sister that among families with a brother (29.9% vs. 9.3%, p < 0.001). Among patients' children, the proportion of daughters who received a genetic test was higher than the proportion of sons (67.8% vs. 39.7%, p=0.001).

Meanwhile, although men should undergo FSM testing, they are not commonly tested due to a misconception that they are not vulnerable to these kinds of cancer, such as ovarian or breast cancer, which are considered "female" cancers. Patients need to be informed that the *BRCA* gene is inherited in the autosomal dominant rather than a sex-chromosomal recessive pattern [4,12]. Indeed, *BRCA1* and *BRCA2* mutations are associated with male hereditary cancers, such as male breast cancer, pancreatic cancer, and prostate cancer [13]. Men can be carriers of the mutated gene; therefore, within families at risk, it is as important to test men, as it is to test women [14,15].

To-date, several studies on the importance of genetic testing in various cancer-related fields have been published [16]. Meticulous pre-test counseling is important to improve patients' understanding of disease and increase the number of proband relatives undergoing testing aimed at detecting autosomal dominant cancer syndrome.

The present study has some limitations. This was a single institutional study with a limited number of patients (n=129). This was a retrospective study, resulting in missing information regarding some clinical characteristics of the included patients and their relatives. As a result, we considered only basic rather than comprehensive clinical factors.

Once a diagnosis was reached based on the results of the genetic test, all relatives of patients all relative of patients with a *BRCA1* or *BRCA2* genetic mutation were encouraged

to be tested at our center. However, it was impossible to confirm whether the patient explained the information to all relatives, which could have resulted in selection bias.

There are some strengths to this study. First, this is the first study on family screening among patients with ovarian cancer with *BRCA1* or *BRCA2* mutation in Korea. Second, a single nurse certified in genetic counseling was consistently responsible for all patient interaction, including data collection, which was unlikely to bias the findings.

Further prospective studies are needed to understand factors that increase the uptake rate of FSM testing. Genetic testing might help reduce the rate of cancer within family units and reduce national health care costs [17]. Finally, information and awareness campaigns are required to educate the public about the importance of genetic testing to increase the number of patients' relatives undergoing testing.

Ethical Statement

This retrospective study was approved by Institutional Review Boards and waived the need for informed consent (NCC2018-0259).

Author Contributions

Conceived and designed the analysis: Jeong GW, Lim MC.
Collected the data : Jeong GW.
Contributed data or analysis tools: Jeong GW, Shin W, Lee DO, Seo SS, Kang S, Park SY, Lim MC.
Performed the analysis: Jeong GW, Lim MC.
Wrote the paper: Jeong GW.

Conflicts of Interest

Conflicts of interest relevant to this article was not reported.

Acknowledgments

This work was supported by the National Cancer Center Grant (NCC-1911274).

References

1. Song H, Dicks E, Ramus SJ, Tyrer JP, Intermaggio MP, Hayward J, et al. Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. J Clin Oncol. 2015;33:2901-7.
2. Lim MC, Kang S, Seo SS, Kong SY, Lee BY, Lee SK, et al. BRCA1 and BRCA2 germline mutations in Korean ovarian cancer patients. J Cancer Res Clin Oncol. 2009;135:1593-9.
3. Choi MC, Heo JH, Jang JH, Jung SG, Park H, Joo WD, et al. Germline mutations of BRCA1 and BRCA2 in Korean ovarian cancer patients: finding founder mutations. Int J Gynecol Cancer. 2015;25:1386-91.
4. Yoshida K, Miki Y. Role of BRCA1 and BRCA2 as regulators of DNA repair, transcription, and cell cycle in response to DNA damage. Cancer Sci. 2004;95:866-71.
5. Daly MB, Pilarski R, Berry M, Buys SS, Farmer M, Friedman S, et al. NCCN guidelines insights: genetic/familial high-risk assessment: breast and ovarian, version 2.2017. J Natl Compr Canc Netw. 2017;15:9-20.
6. 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.
7. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National estimates of genetic testing in women with a history of breast or ovarian cancer. J Clin Oncol. 2017;35:3800-6.
8. Hinchcliff EM, Bednar EM, Lu KH, Rauh-Hain JA. Disparities in gynecologic cancer genetics evaluation. Gynecol Oncol. 2019;153:184-91.
9. Hoskins PJ, Gotlieb WH. Missed therapeutic and prevention opportunities in women with BRCA-mutated epithelial ovarian cancer and their families due to low referral rates for genetic counseling and BRCA testing: a review of the literature. CA Cancer J Clin. 2017;67:493-506.
10. McGivern B, Everett J, Yager GG, Baumiller RC, Hafertepen A, Saal HM. Family communication about positive BRCA1 and BRCA2 genetic test results. Genet Med. 2004;6:503-9.
11. Fehniger J, Lin F, Beattie MS, Joseph G, Kaplan C. Family communication of BRCA1/2 results and family uptake of BRCA1/2 testing in a diverse population of BRCA1/2 carriers. J Genet Couns. 2013;22:603-12.
12. Cui J, Antoniou AC, Dite GS, Southey MC, Venter DJ, Easton DF, et al. After BRCA1 and BRCA2-what next? Multifactorial segregation analyses of three-generation, population-based Australian families affected by female breast cancer. Am J Hum Genet. 2001;68:420-31.
13. Marabelli M, Calvello M, Bonanni B. Cancer: more genetic BRCA testing for men. Nature. 2019;573:346.
14. Ibrahim M, Yadav S, Ogunleye F, Zakalik D. Male BRCA mutation carriers: clinical characteristics and cancer spectrum. BMC Cancer. 2018;18:179.
15. Pal T, Vadaparampil S, Kim J, Xu Y, Friedman S, Narod SA, et al. Interest of individuals from BRCA families to participate in research studies focused on male BRCA carriers. Fam Cancer. 2013;12:615-9.
16. Ni J, Cheng X, Zhou R, Xu X, Guo W, Chen X. Olaparib in the therapy of advanced ovarian cancer: first real world experiences in safety and efficacy from China. J Ovarian Res. 2019;12:117.
17. Manchanda R, Gaba F. Population based testing for primary prevention: a systematic review. Cancers (Basel). 2018;10:424.