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Correspondence to

Min Chul Choi

Department of Obstetrics and Gynecology,
Comprehensive Gynecologic Cancer Center,
CHA Bundang Medical Center, 11 Yatap-ro
65-beon-gil, Bundang-gu, Seongnam 13496,
Korea.

E-mail: oursk79@cha.ac.kr

Sunghoon Lee

Eone-Diagnomics Genome Center (EDGC),
291 Harmony-ro, Yeonsu-gu, Incheon 22014,
Korea.

E-mail: shlee@edgc.com

*Min Chul Choi and Jin-Sik Bae contributed
equally to this study.

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cited.

ORCID iDs

Min Chul Choi

<https://orcid.org/0000-0003-4509-6731>

Jin-Sik Bae

<https://orcid.org/0000-0002-6897-8115>

Sang Geun Jung

<https://orcid.org/0000-0002-0635-6994>

Hyun Park

<https://orcid.org/0000-0002-7825-9165>

<https://ejgo.org>

Prevalence of germline *BRCA* mutations among women with carcinoma of the peritoneum or fallopian tube

Min Chul Choi ^{1,2,*}, Jin-Sik Bae ^{3,*}, Sang Geun Jung ², Hyun Park ²,
Won Duk Joo ², Seung Hun Song², Chan Lee ², Ji-Ho Kim ³, Ki-Chan Lee ³,
Sunghoon Lee ³, Je Ho Lee^{1,2}

¹Hereditary Gynecologic Cancer Clinic, Precision Medicine Center, CHA Bundang Medical Center, CHA University, Seongnam, Korea

²Department of Obstetrics and Gynecology, Comprehensive Gynecologic Cancer Center, CHA Bundang Medical Center, CHA University, Seongnam, Korea

³Eone-Diagnomics Genome Center (EDGC), Incheon, Korea

ABSTRACT

Objective: The aim of the present study was to assess the frequency of germline mutations in patients with peritoneal carcinoma (PC) or the fallopian tube carcinoma (FTC), using a multi-gene panel.

Methods: Twenty-six patients diagnosed with either PC or FTC between January 2013 and December 2016 were recruited consecutively. Germline DNA was sequenced using a 6-gene next generation sequencing (NGS) panel following genetic counseling. Surgico-medical information was obtained from hospital records. Genetic variations were detected using the panel and were cross-validated by Sanger direct sequencing.



Results: Germline *BRCA1/2* mutations were identified in 6 patients (23.1%). Four were detected in patients with PC and 2 were in FTC patients. No mutations were detected in *TP53*, *PTEN*, *CDH1*, or *PALB2*. We identified 11 variant of uncertain significance (VUS) in 9 patients; 2 in *BRCA1*, 3 in *BRCA2*, 2 in *TP53*, and 4 in *CDH1*. We also detected a *CDH1* c.2164+16->A VUS in 3 patients.

Conclusion: The prevalence of germline *BRCA1/2* mutations in patients with PC or FTC is comparable to that of *BRCA1/2* mutations in epithelial ovarian cancer patients.

Keywords: *BRCA1* Gene; *BRCA2* Gene; Mutation; Fallopian Tube Cancer; Peritoneal Neoplasms; Prevalence

INTRODUCTION

Ovarian cancer is known as a solid tumor with a high level of genetic predisposition. It has been reported that approximately 10% to 15% of ovarian cancers have a hereditary background [1]. Two genes in particular, *BRCA1* and *BRCA2*, have been identified to confer a high susceptibility to develop hereditary breast-ovarian cancer [2,3]. Although genes other than *BRCA1* and *BRCA2* are known to cause ovarian cancer, *BRCA1/2* mutations are known to cause the majority of hereditary ovarian carcinoma cases. Women with *BRCA1* mutations have a 39% cumulative lifetime risk of developing ovarian cancer by the age of 70 years and those with *BRCA2* mutations have an 11% risk [4].

Won Duk Joo 
<https://orcid.org/0000-0003-4637-6946>
 Chan Lee 
<https://orcid.org/0000-0003-1654-4398>
 Ji-Ho Kim 
<https://orcid.org/0000-0001-6774-7553>
 Ki-Chan Lee 
<https://orcid.org/0000-0003-3582-9487>
 Sunghoon Lee 
<https://orcid.org/0000-0002-6682-119X>

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: C.M.C.; Data curation: C.M.C., B.J.S., J.S.G., P.H., J.W.D., S.S.H., L.C., L.S., L.J.H.; Formal analysis: C.M.C., B.J.S., K.J.H., L.K.C.; Investigation: C.M.C.; Methodology: C.M.C., B.J.S., P.H., J.W.D., S.S.H., L.C., K.J.H., L.S., L.J.H.; Resources: C.M.C.; Supervision: J.S.G., P.H., J.W.D., S.S.H., L.C., L.S., L.J.H.; Validation: B.J.S., K.J.H., L.K.C.; Writing - original draft: C.M.C., B.J.S.; Writing - review & editing: C.M.C., B.J.S.

The clinico-pathological similarities of fallopian tube carcinoma (FTC), peritoneal carcinoma (PC), and epithelial ovarian cancer (EOC) support the likelihood of a common molecular pathogenesis. There is also molecular evidence that FTC and PC may be causally linked to germline *BRCA* mutations [5,6]. Evidence suggests that women with high-grade ovarian, PC, or FTC should be regarded as having a single disease [7,8]. The prevalence of *BRCA1/2* mutations in PC and FTC is known to be higher than that which occurs in ovarian cancer [9,10].

Interestingly, patients with *BRCA1/2* mutations have shown improved short-term overall survival as compared to those with *BRCA1/2* wild-type [11] and it may identify them as candidates for treatment with poly ADP-ribose polymerase-1 (*PARP1*) inhibitors [12]. Screening of individuals from a family with a known pathogenic *BRCA1/2* mutation may also be beneficial and may allow those detected to carry the mutation to be subjected to tailored risk-reduction strategies, such as surveillance, chemoprevention, and risk-reduction surgery [13]. These clinical applications should be applied not only to patients with ovarian cancer but also to those with PC and FTC. It has already been included in several recommendations [14,15], including the National Comprehensive Cancer Network (NCCN) guidelines, which recommend *BRCA1/2* genetic testing for ovarian cancer patients as well as for patients with PC and FTC [13].

Although there have been reports of *BRCA1/2* mutations in PC and FTC in western countries, there have been no reports of studies in Korean patients. Because the prevalence of *BRCA1/2* mutations is reported to vary according to ethnicity, it is important to investigate the prevalence of *BRCA1/2* mutations in Korean patients with PC and FTC. Therefore, the purpose of the present study was to identify the prevalence of *BRCA1/2* mutations in Korean PC and FTC patients. We then compared our findings with results from previous studies on Korean ovarian cancer patients and with those from studies on PC and FTC in western nations.

MATERIALS AND METHODS

1. Study subjects

A cohort of patients who had been pathologically diagnosed with PC or FTC at the Comprehensive Gynecologic Cancer Center between January 2013 and December 2016 were included in the study.

A total of 35 patients were pathologically confirmed to have PC or FTC. Those patients were invited to provide a detailed family history and a blood sample for genetic testing for mutations in *BRCA1* and *BRCA2* and in 4 other genes (*TP53*, *PTEN*, *CDH1*, and *PALB2*) after receiving genetic counseling and informed consent. Patients were also asked to provide permission for study investigators to review their medical records in order to extract relevant information, including age at time of diagnosis, histological type, family history, and the International Federation of Gynecology and Obstetrics (FIGO) stage. Family history of cancer was recorded and confirmed by direct contact with those patients and their families. A patient was considered to have a family history of cancer if any of the following criteria were met: 1) if there were one or more cases of ovarian, peritoneal, fallopian tubal, breast, pancreas, or prostate cancer among first- or second-degree relatives; or 2) the patient's own primary breast cancer. Written informed consent for genetic testing was obtained from all participants at the time of peripheral blood sampling. Patients who did not provide a blood sample for genetic test were excluded from the study. The Institutional Review Board of CHA Bundang Medical Center approved the present study (approval No. 2016-07-020-011).

2. Next generation sequencing (NGS)

Germline mutation was tested using peripheral blood DNA samples and analyzed by the NGS system (Ion PGM System; Thermo Fisher Scientific, Waltham, MA, USA) with the 6-gene panel (*BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, and *PALB2*). Target gene enrichment was performed with the Ion AmpliSeq DNA panel (Thermo Fisher Scientific). The panel included 3 primer pools (242 amplicons) covering the entire coding region and 10 to 20 bp of the intronic flanking sequences of coding exons. For amplification, 4 μ L of 5 \times Ion AmpliSeq HiFi Master Mix (Thermo Fisher Scientific), 10 μ L of 2 \times Ion AmpliSeq primer pool, 20 ng of genomic DNA per reaction, and 4 μ L of nuclease-free water were mixed. The temperature profile for the final 20 μ L of the polymerase chain reaction (PCR) mixture was as follows: 99°C for 2 minutes, 99°C for 15 seconds, and 60°C for 4 minutes, for a total of 19 cycles, with a final hold at 10°C. The primer sequences were partially digested and adapters and barcodes were ligated to the amplicons according to the Ion AmpliSeq Library 2.0 Kit manual (Thermo Fisher Scientific). A unique adapter was used for each library with the Ion Xpress Barcode Adapters 1 to 16 Kit (Thermo Fisher Scientific). Quantification of the amplified library was performed with the Qubit 3.0 fluorometer (Life Technologies, Gaithersburg, MD, USA) using the Qubit dsDNA HS Assay Kit, diluted to approximately 100 pmol/L. Ion One Touch 2 System and the Ion OnTouch ES Instrument (Thermo Fisher Scientific) was used according to the user guide with the Ion PGM Hi-Q View OT2 Kit (Thermo Fisher Scientific). All barcoded samples were sequenced on the Ion PGM System (Thermo Fisher Scientific) with Ion 316 chips (Thermo Fisher Scientific) using 8 samples on a single chip per sequencing run. Sequencing data were analyzed with the Ion Torrent Suite software ver. 5.2 and contextually with Ion Reporter (Thermo Fisher Scientific). Variant classification (pathogenicity) was manually reviewed, according to the American College of Medical Genetics and Genomics (ACMG) standard and guidelines for the interpretation of sequence variants [16,17]. The values were listed as “pathogenic,” “likely pathogenic,” “variant of uncertain significance (VUS),” “likely benign,” and “benign” in decreasing order of clinical importance.

3. Sanger sequencing confirmation

The pathogenic, likely pathogenic, and uncertain clinical significance variants were confirmed by Sanger sequencing. Sanger sequencing was performed using a BigDye Terminator version 3.1 Cycle Sequencing Kit (Life Technologies) and an ABI 3500 sequencer (Life Technologies). We used Mutation Surveyor software version 5.0.1 (SoftGenetics, State College, PA, USA) for analyzing DNA variants from Sanger sequence traces.

RESULTS

1. Patient characteristics

The clinical characteristics of the 26 patients who were included in the study are presented in **Table 1**. The overall mean age at diagnosis was 54.9 years old (34–84 years). For women with PC, the mean age at diagnosis was 57.1 years (34–84), whereas for FTC patients, it was 45.8 (35–56). Histologically, all tumors were high-grade serous adenocarcinoma. The PC patients were advanced stage (stage III & IV), and the 3 of 5 FTC patients were stage IC. Two patients were diagnosed with breast cancer; 8 patients (30.8%) had a family history of *BRCA1/2*-related cancer in first- or second-degree relatives. Therefore, 10 patients showed “family history” according to the definitions by the present study. The *BRCA1/2* mutation frequency was 50% (5/10) among those ten patients compared 6.3% (1/16) among those without family history. Of the 26 patients with PC or FTC, 6 (23.1%) were found to harbor pathogenic *BRCA1* or

BRCA mutation in peritoneal/fallopian tube cancer

BRCA2 mutations, 4 in *BRCA1* and 2 in *BRCA2* (**Table 2**). The prevalence of mutations was 30% (3/10) for patients diagnosed before age 50, compared with 18.8% (3/16) for patients diagnosed at age 50 and above.

Germline pathogenic mutations and VUS observed in 6 hereditary breast and ovarian cancer (HBOC) genes (*BRCA1/2*, *TP53*, *PTEN*, *CDH1*, and *PALB2*) of the patients are listed in **Table 2**. Of the 6 pathogenic mutations, we detected 4 in PC patients and 2 in FTC patients. We did not detect germline pathogenic mutations in *TP53*, *PTEN*, *CDH1*, and *PALB2*. We identified a total of 11 VUS in 9 patients, including 2 in *BRCA1*, 3 in *BRCA2*, 2 in *TP53*, and 4 in *CDH1*. The *CDH1* c.2164+16->A VUS was detected in 3 patients.

Table 1. Clinical characteristic of patients

Characteristics	Overall (n=26)	PC (n=21)	FTC (n=5)
Age at diagnosis (yr)	54.9 (34–84)	57.1 (34–84)	45.8 (35–56)
Histology			
High grade serous	26	21	5
Others	0	0	0
Stage			
I	3	0	3
II	0	0	0
III	13	11	2
IV	10	10	0
Breast cancer history			
Yes	2	1	1
No	24	20	4
Family history of <i>BRCA</i> -related cancer*			
Yes	8	6	2
No	18	15	3

FTC, fallopian tube carcinoma; PC, peritoneal carcinoma.

*Family history of breast/peritoneal/ovarian/fallopian tubal/pancreas/prostate cancer within second degree relatives.

Table 2. Detected germline mutations and VUS of *BRCA1/2*, *TP53*, *PTEN*, *CDH1*, *PALB2* genes in PC/FTC patients

Cases	Age (yr)	Cancer	Gene	Site	Mutation	Mutation type	Double primary*	Family history†	FH of other cancer
Pathogenic mutations									
CHAPC-001	34	PC	<i>BRCA1</i>	IVS	c.212+1G>T	-	-	Pancreas (father)	Gall bladder (mother)
CHAPC-003	69	PC	<i>BRCA2</i>	Exon 3	c.199_211del13	p.Arg67fs	-	Breast (sister), prostate (father)	
CHAPC-011	60	PC	<i>BRCA2</i>	Exon 11	c.2808_2011delACAA	p.Lys936fs	Breast cancer	-	Cervix (patient), brain (father)
CHAPC-014	38	PC	<i>BRCA1</i>	Exon 11	c.922_924delAGCinsT	p.Ser308Terfs	-	Ovary (grandmother), peritoneal (cousin sister), pancreas (cousin)	Endometrial (cousin sister)
CHATC-003	34	FTC	<i>BRCA1</i>	Exon 21	c.5339T>C	p.Leu1780Pro	-	-	Stomach (father, grandmother)
CHATC-005	56	FTC	<i>BRCA1</i>	Exon 10	c.3895C>T	p.Gln1299Ter	-	Ovary (sister)	
VUS									
CHAPC-002	56	PC	<i>TP53</i>	Exon 5	c.516T>G	p.Val172=			
CHAPC-004	81	PC	<i>BRCA1</i>	Exon 10	c.824G>A	p.Gly275Asp			
CHAPC-005	43	PC	<i>BRCA2</i>	Exon 10	c.964A>C	p.Lys322Gln			
CHAPC-008	80	PC	<i>BRCA2</i>	Exon 14	c.7050C>T	p.Thr2350=			
CHAPC-009	74	PC	<i>CDH1</i>	IVS	c.2164+16->A	-		Breast (daughter)	
CHAPC-010	84	PC	<i>CDH1</i>	IVS	c.2164+16->A	-			
CHAPC-012	50	PC	<i>BRCA1</i>	Exon 10	c.2247T>C	p.Asp749=		Breast (mother)	Thyroid (patient)
CHATC-001	35	FTC	<i>BRCA2</i>	Exon 14	c.7307A>T	p.Asn2436Ile			
CHATC-005	56	FTC	<i>CDH1</i>	Exon 12	c.1888C>G	p.Leu630Val-			
CHATC-005	56	FTC	<i>TP53</i>	Exon 6	c.566C>T	p.Ala189Val		Ovary (sister)	

FH, family history; FTC, fallopian tube carcinoma; PC, peritoneal carcinoma; VUS, variant of uncertain significance.

*Breast cancer history of patient's own; †Family history of *BRCA*-related cancer within second degree relatives.

We also performed confirmatory analysis for the 15 variants (**Table 2**). For the 15 variants, both NGS and Sanger sequencing data showed 100% concordance.

DISCUSSION

As seen in this study, the prevalence of *BRCA1/2* mutations in Korean PC and FTC patients was 23.1% (6/26) for a sample set from a single institution. Among PC patients, the incidence of *BRCA1/2* mutations was 19% (4/21); among FTC patients, the incidence was 40.0% (2/5) (**Table 3**). According to published reports, the prevalence of *BRCA1/2* mutations in Korean EOC patients is 23.8% (142/597, **Table 4**) [18-22]. Therefore, the prevalence of *BRCA1/2* mutations in Korean PC and FTC patients is similar to that in the Korean ovarian cancer. In studies on non-Ashkenazi Jewish, the frequency of *BRCA1/2* mutations ranged from 6% to 15% analyzed in ovarian cancer cases unselected for a family history of the disease [23]. In comparison, the prevalence rate in the Korean EOC patients is not low compared with that in the western countries. In the present study, we included all high-grade serous carcinoma (HGSC) cell types — that is, those that are more likely related to a *BRCA1/2* mutation than non-HGSC cell types. Therefore, it is difficult to directly compare our findings with those of previous studies on Korean HGSC and non-HGSC ovarian cancer patients.

Table 3 summarizes the prevalence of *BRCA1/2* mutations in PC and FTC [5,9,10,24-26]. Although the range of ethnicity and tested *BRCA1/2* genes differs somewhat for each study, the reported prevalence of *BRCA1/2* mutations ranges from 15.8% to 40.9%. Although we cannot compare the results of the present study directly, our data suggest that the prevalence of *BRCA1/2* mutations in Korean PC and FTC patients is not low compared to that in PC and FTC patients in western countries.

The incidence rates for primary ovarian cancer, FTC, and PC are 11.2, 0.37, and 0.68 per 100,000, respectively in the USA [27]. Although the incidence of FTC and PC is much lower

Table 3. Frequency of *BRCA* germline mutations among patients with PC/FTC

Cancer sites	Study	Year	Ethnic group	Genes studied	Region tested	Mutation detected	Mutation frequency (%)
Peritoneum	Schorge et al. [5]	2000	American	<i>BRCA1</i>	All <i>BRCA1</i>	11/43	25.6
	Menczer et al. [24]	2003	Ashkenazi Jewish	<i>BRCA1/2</i>	FM	19/68	27.9
	Levine et al. [9]	2003	Ashkenazi Jewish	<i>BRCA1/2</i>	FM	9/22	40.9
	Alsop et al. [10]	2012	Australia	<i>BRCA1/2</i>	All <i>BRCA1/2</i>	24/152	15.8
	Present study		Korean	<i>BRCA1/2</i>	All <i>BRCA1/2</i>	4/21	19.0
Fallopian tube	Aziz et al. [25]	2001	Canadian	<i>BRCA1/2</i>	All <i>BRCA1</i> , FM*	7/44	15.9
	Levine et al. [9]	2003	Ashkenazi Jewish	<i>BRCA1/2</i>	FM	5/29	17.2
	Vicus et al. [26]	2010 [†]	Jewish, non-Jewish	<i>BRCA1/2</i>	All <i>BRCA1/2</i>	33/108	30.6
	Alsop et al. [10]	2012	Australia	<i>BRCA1/2</i>	All <i>BRCA1/2</i>	8/40	20.0
	Present study		Korean	<i>BRCA1/2</i>	All <i>BRCA1/2</i>	2/5	40.0

FM, founder mutation; FTC, fallopian tube carcinoma; PC, peritoneal carcinoma.

*French-Canadian and Ashkenazi Jewish FMs, all *BRCA1*, exon 10–11 *BRCA2*; [†]This study was expanded form of Aziz et al.'s study [25].

Table 4. Frequency of *BRCA* germline mutations among patients with EOC in Korea

Study	Year	Number	<i>BRCA1</i>	<i>BRCA2</i>	<i>BRCA1/2</i>	Mutation frequency (%)
Kim et al. [18]	2005	37	1	0	1	2.7
Lim et al. [19]	2009	63	13	3	16	25.4
Choi et al. [20]	2015	70	15	3	18	25.7
Eoh et al. [21]	2016	116	30	7	37	31.9
Heo et al. [22]	2017	298			70	23.5
Total		584			142	24.3

EOC, epithelial ovarian cancer.

than that of ovarian cancer, our findings support the proposition that clinicians should still actively perform genetic tests on ovarian cancer patients, as well as patients with FTC and PC. Not only could they then detect more patients with *BRCA1/2* mutations, but they could also find *BRCA1/2* mutation carriers in the patient's family. Those *BRCA* mutation carriers could be offered tailored risk reduction strategies that can dramatically reduce their own ovarian cancer, PC and FTC risks.

A c.5339T>C variation in *BRCA1* (CHATC-003 in **Table 2**) found in an FTC patient had previously been classified as VUS. However, because recent reports have shown pathogenicity for that variation [28,29], it was re-classified as a likely pathogenic mutation according to the ACMG guidelines. The patient's father and grandmother had a family history of gastric cancer, and they were thoroughly counselled and warned about cancer risk management for the patient and their families.

Of the mutations suggested by the previous study as a possible founder mutation in Korean ovarian cancer patients, c.922_924delAGCinsT in *BRCA1* accounts for 10.2% (4/39) [20]. The same mutation was found in 1 PC patient (CHAPC-014). This patient was diagnosed with PC at the young age of 38 years and showed a family history of various carcinomas except breast cancer (**Table 2**).

Numerous new variants in genes associated with the *BRCA1/2*-mediated DNA repair process have been identified. Although most of these genes are at low risk, some, such as *RAD51C*, *RAD51D*, and *BRIP1*, are at moderate risk for ovarian cancer [30-32]. NCCN guidelines recommend consideration of risk-reduction management for women with pathogenic mutations in these genes [13]. With recent advances in NGS test, simultaneous sequencing of multiple cancer susceptibility genes, beyond *BRCA1/2*, has become more cost-effective, technically feasible, and increasingly accessible. Therefore, we analyzed 4 genes in addition to *BRCA1/2* — *TP53*, *PTEN*, *CDH1*, and *PALB2* — but did not find known pathogenic mutations in any of these genes. However, we did identify 2 VUSs in *TP53* and 4 VUSs in *CDH1* (**Table 2**). The same c.2164+16->A *CDH1* VUS was found in 3 patients. It is not exactly known the association between the patient's cancer and that VUS.

The present study was limited by several factors, including the fact that it was based at a single institution and comprised a limited number of patients. Because 9 patients (25.7%, 9/35) declined genetic test, there may have been some selection bias. Large prospective studies will be necessary in the future to confirm the prevalence of *BRCA1/2* mutations in the Korean population. The prevalence of VUS of *BRCA1/2* is 19.2% (5/26) and the prevalence of VUS of other genes is 23.1% (6/26). The sum of prevalence rate is somewhat higher compared with previous reports about Korean ovarian cancer *BRCA* VUS prevalence (21.6%–24.6%) [29], even all mutations and VUS were validated by Sanger sequencing. Recently, various HBOC genes have been evaluated by NGS testing, but in the present study, only several genes were tested. One study showed that 3.8% had positive test results for putative pathogenic mutations in moderate/high-penetrance genes other than *BRCA1/2* [33]. However, in this study, we only found mutations in *BRCA1/2*, which may be due to our small sample size. Subsequent studies should also include *RAD51C* and *MMR* genes in the NGS gene panel and examine them together.

Nevertheless, considering the ethnicity-specific differences in the germline mutations in cancer susceptibility genes, assessing cancer susceptibility genetic variants in all ethnic

groups is necessary. The present study is the first report on *BRCA*-associated genetic testing for PC and FTC patients in Korea. Previous studies have not evaluated the frequency of germline mutations in peritoneal cancer and tubal cancer in Asian populations. Our data in this study provide an initial estimate that the prevalence of *BRCA1/2* mutations in Korean PC and FTC patients is 23.1% (6/26).

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