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Original Article



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

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## 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].

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

**Author Contributions**
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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 μL of 5× Ion Ampliseq HiFi Master Mix (Thermo Fisher Scientific), 10 μL of 2× Ion AmpliSeq primer pool, 20 ng of genomic DNA per reaction, and 4 μL of nuclease-free water were mixed. The temperature profile for the final 20 μL 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 Therminator 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


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


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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 | *BRCA1* | All *BRCA1* | 11/43 | 25.6 |
| | Menczer et al. [24] | 2003 | Ashkenazi Jewish | *BRCA1/2* | FM | 19/68 | 27.9 |
| | Levine et al. [9] | 2003 | Ashkenazi Jewish | *BRCA1/2* | FM | 9/22 | 40.9 |
| | Alsop et al. [10] | 2012 | Australia | *BRCA1/2* | All *BRCA1/2* | 24/152 | 15.8 |
| | Present study | | Korean | *BRCA1/2* | All *BRCA1/2* | 4/21 | 19.0 |
| Fallopian tube | Aziz et al. [25] | 2001 | Canadian | *BRCA1/2* | All *BRCA1*, FM* | 7/44 | 15.9 |
| | Levine et al. [9] | 2003 | Ashkenazi Jewish | *BRCA1/2* | FM | 5/29 | 17.2 |
| | Vicus et al. [26] | 2010† | Jewish, non-Jewish | *BRCA1/2* | All *BRCA1/2* | 33/108 | 30.6 |
| | Alsop et al. [10] | 2012 | Australia | *BRCA1/2* | All *BRCA1/2* | 8/40 | 20.0 |
| | Present study | | Korean | *BRCA1/2* | All *BRCA1/2* | 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 | *BRCA1* | *BRCA2* | *BRCA1/2* | 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.


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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


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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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## REFERENCES

1. Russo A, Calo V, Bruno L, Rizzo S, Bazan V, Di Fede G. Hereditary ovarian cancer. Crit Rev Oncol Hematol 2009;69:28-44.
PUBMED | CROSSREF
2. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. Science 1994;266:66-71.
PUBMED | CROSSREF
3. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene *BRCA2*. Nature 1995;378:789-92.
PUBMED | CROSSREF
4. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-30.
PUBMED | CROSSREF
5. Schorge JO, Muto MG, Lee SJ, Huang LW, Welch WR, Bell DA, et al. *BRCA1*-related papillary serous carcinoma of the peritoneum has a unique molecular pathogenesis. Cancer Res 2000;60:1361-4.
PUBMED
6. Zweemer RP, van Diest PJ, Verheijen RH, Ryan A, Gille JJ, Sijmons RH, et al. Molecular evidence linking primary cancer of the fallopian tube to *BRCA1* germline mutations. Gynecol Oncol 2000;76:45-50.
PUBMED | CROSSREF
7. Crum CP, Drapkin R, Kindelberger D, Medeiros F, Miron A, Lee Y. Lessons from *BRCA*: the tubal fimbria emerges as an origin for pelvic serous cancer. Clin Med Res 2007;5:35-44.
PUBMED | CROSSREF
8. Kurman RJ, Shih Ie M. The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. Am J Pathol 2016;186:733-47.
PUBMED | CROSSREF
9. Levine DA, Argenta PA, Yee CJ, Marshall DS, Olvera N, Bogomolniy F, et al. Fallopian tube and primary peritoneal carcinomas associated with *BRCA* mutations. J Clin Oncol 2003;21:4222-7.
PUBMED | CROSSREF
10. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30:2654-63.
PUBMED | CROSSREF
11. McLaughlin JR, Rosen B, Moody J, Pal T, Fan I, Shaw PA, et al. Long-term ovarian cancer survival associated with mutation in *BRCA1* or *BRCA2*. J Natl Cancer Inst 2013;105:141-8.
PUBMED | CROSSREF
12. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial. Lancet Oncol 2014;15:852-61.
PUBMED | CROSSREF
13. National Comprehensive Cancer Network (US). NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast and ovarian, version 1. 2018 [Internet]. Fort Washington, PA: National Comprehensive Cancer Network; 2018 [cited 2017 Apr 17]. Available from: https://www.nccn.org.

14. Lancaster JM, Powell CB, Chen LM, Richardson DL. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol 2015;136:3-7.
PUBMED | CROSSREF
15. 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.
PUBMED | CROSSREF
16. den Dunnen JT, Dalgleish R, Maglott DR, Hart RK, Greenblatt MS, McGowan-Jordan J, et al. HGVS recommendations for the description of sequence variants: 2016 update. Hum Mutat 2016;37:564-9.
PUBMED | CROSSREF
17. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
PUBMED | CROSSREF
18. Kim YT, Nam EJ, Yoon BS, Kim SW, Kim SH, Kim JH, et al. Germline mutations of *BRCA1* and *BRCA2* in Korean sporadic ovarian carcinoma. Gynecol Oncol 2005;99:585-90.
PUBMED | CROSSREF
19. 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.
PUBMED | CROSSREF
20. 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.
PUBMED | CROSSREF
21. Eoh KJ, Park HS, Park JS, Lee ST, Han J, Lee JY, et al. Comparison of clinical outcomes of *BRCA1/2* pathologic mutation, variants of unknown significance, or wild type epithelial ovarian cancer patients. Cancer Res Treat 2017;49:408-15.
PUBMED | CROSSREF
22. Heo EJ, Kim B, Choi CH, Lee JW, Lee YY, Kim YM, et al. Prevalence study of germline *BRCA1/2* mutation in Korean patients with high-grade serous and/or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer. J Clin Oncol 2016;34 suppl:e17043.
23. Ramus SJ, Gayther SA. The contribution of *BRCA1* and *BRCA2* to ovarian cancer. Mol Oncol 2009;3:138-50.
PUBMED | CROSSREF
24. Menczer J, Chetrit A, Barda G, Lubin F, Fishler Y, Altaras M, et al. Frequency of *BRCA* mutations in primary peritoneal carcinoma in Israeli Jewish women. Gynecol Oncol 2003;88:58-61.
PUBMED | CROSSREF
25. Aziz S, Kuperstein G, Rosen B, Cole D, Nedelcu R, McLaughlin J, et al. A genetic epidemiological study of carcinoma of the fallopian tube. Gynecol Oncol 2001;80:341-5.
PUBMED | CROSSREF
26. Vicus D, Finch A, Rosen B, Fan I, Bradley L, Cass I, et al. Risk factors for carcinoma of the fallopian tube in women with and without a germline *BRCA* mutation. Gynecol Oncol 2010;118:155-9.
PUBMED | CROSSREF
27. Goodman MT, Shvetsov YB. Incidence of ovarian, peritoneal, and fallopian tube carcinomas in the United States, 1995–2004. Cancer Epidemiol Biomarkers Prev 2009;18:132-9.
PUBMED | CROSSREF
28. Ryu JM, Kang G, Nam SJ, Kim SW, Yu J, Lee SK, et al. Suggestion of *BRCA1* c.5339T>C (p.L1780P) variant confer from 'unknown significance' to 'Likely pathogenic' based on clinical evidence in Korea. Breast 2017;33:109-16.
PUBMED | CROSSREF
29. Choi MC, Jang JH, Jung SG, Park H, Joo WD, Song SH, et al. Unclassified variants of *BRCA1* and *BRCA2* in Korean patients with ovarian cancer. Int J Gynecol Cancer 2018;28:308-15.
PUBMED | CROSSREF
30. Norquist BM, Harrell MI, Brady MF, Walsh T, Lee MK, Gulsuner S, et al. Inherited mutations in women with ovarian carcinoma. JAMA Oncol 2016;2:482-90.
PUBMED | CROSSREF
31. 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.
PUBMED | CROSSREF

32. Ramus SJ, Song H, Dicks E, Tyrer JP, Rosenthal AN, Intermaggio MP, et al. Germline mutations in the *BRIP1*, *BARD1*, *PALB2*, and *NBN* genes in women with ovarian cancer. J Natl Cancer Inst 2015;107:djv214.
PUBMED | CROSSREF
33. Desmond A, Kurian AW, Gabree M, Mills MA, Anderson MJ, Kobayashi Y, et al. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. JAMA Oncol 2015;1:943-51.
PUBMED | CROSSREF