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].
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.

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 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
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

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

FTC, fallopian tube carcinoma; PC, peritoneal carcinoma.
*Family history of breast/peritoneal/ovarian/fallopian tubal/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

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age (yr)</th>
<th>Cancer</th>
<th>Gene</th>
<th>Site</th>
<th>Mutation</th>
<th>Mutation type</th>
<th>Double primary*</th>
<th>Family history†</th>
<th>FH of other cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic mutations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAPC-001</td>
<td>34</td>
<td>PC</td>
<td>BRCA1</td>
<td>IVS</td>
<td>c.212+1G&gt;T</td>
<td>-</td>
<td>-</td>
<td>Pancreas (father)</td>
<td>Gall bladder (mother)</td>
</tr>
<tr>
<td>CHAPC-003</td>
<td>69</td>
<td>PC</td>
<td>BRCA2</td>
<td>Exon 3</td>
<td>c.199_211del13</td>
<td>p.Arg67fs</td>
<td>-</td>
<td>Breast (sister), prostate (father)</td>
<td></td>
</tr>
<tr>
<td>CHAPC-011</td>
<td>60</td>
<td>PC</td>
<td>BRCA1</td>
<td>Exon 11</td>
<td>c.2808_201delACAA</td>
<td>p.Lys936fs</td>
<td>Breast cancer</td>
<td>-</td>
<td>Cervix (patient), brain (father), Endometrial (cousin sister)</td>
</tr>
<tr>
<td>CHAPC-014</td>
<td>38</td>
<td>PC</td>
<td>BRCA1</td>
<td>Exon 11</td>
<td>c.922_924delAGCinsT</td>
<td>p.Ser308Terfs</td>
<td>-</td>
<td>Ovary (grandmother), peritoneal (cousin sister), pancreas (cousin)</td>
<td></td>
</tr>
<tr>
<td>CHATC-003</td>
<td>34</td>
<td>FTC</td>
<td>BRCA1</td>
<td>Exon 21</td>
<td>c.5339T&gt;C</td>
<td>p.Leu1780Pro</td>
<td>-</td>
<td>-</td>
<td>Stomach (father, grandmother)</td>
</tr>
<tr>
<td>CHATC-005</td>
<td>56</td>
<td>FTC</td>
<td>BRCA1</td>
<td>Exon 10</td>
<td>c.3895C&gt;T</td>
<td>p.Gln1299Ter</td>
<td>-</td>
<td>Ovary (sister)</td>
<td></td>
</tr>
<tr>
<td>VUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAPC-002</td>
<td>56</td>
<td>PC</td>
<td>TP53</td>
<td>Exon 5</td>
<td>c.576T&gt;G</td>
<td>p.Val172=</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAPC-004</td>
<td>81</td>
<td>PC</td>
<td>BRCA1</td>
<td>Exon 10</td>
<td>c.824G&gt;A</td>
<td>p.Gly275Asp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAPC-005</td>
<td>43</td>
<td>PC</td>
<td>BRCA2</td>
<td>Exon 10</td>
<td>c.964A&gt;C</td>
<td>p.Lys322Gln</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAPC-008</td>
<td>80</td>
<td>PC</td>
<td>BRCA2</td>
<td>Exon 14</td>
<td>c.7050C&gt;T</td>
<td>p.Thr2350=</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAPC-009</td>
<td>74</td>
<td>PC</td>
<td>CDH1</td>
<td>IVS</td>
<td>c.2164-16&gt;9A</td>
<td>-</td>
<td></td>
<td>Breast (daughter)</td>
<td></td>
</tr>
<tr>
<td>CHAPC-010</td>
<td>84</td>
<td>PC</td>
<td>CDH1</td>
<td>IVS</td>
<td>c.2164-16&gt;9A</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAPC-012</td>
<td>50</td>
<td>PC</td>
<td>BRCA1</td>
<td>Exon 10</td>
<td>c.2247T&gt;C</td>
<td>p.Asp749=</td>
<td>Breast (mother)</td>
<td>Thyroid (patient)</td>
<td></td>
</tr>
<tr>
<td>CHATC-001</td>
<td>35</td>
<td>FTC</td>
<td>BRCA2</td>
<td>Exon 14</td>
<td>c.7307A&gt;T</td>
<td>p.Asn2436Ile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHATC-005</td>
<td>56</td>
<td>FTC</td>
<td>TP53</td>
<td>Exon 6</td>
<td>c.5866C&gt;T</td>
<td>p.Ala1989Val</td>
<td></td>
<td>Ovary (sister)</td>
<td></td>
</tr>
</tbody>
</table>

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 are much lower in Korea, the incidence of FTC and PC is not low compared with that in PC and FTC patients in western countries.

---

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

<table>
<thead>
<tr>
<th>Cancer sites</th>
<th>Study</th>
<th>Year</th>
<th>Ethnic group</th>
<th>Genes studied</th>
<th>Region tested</th>
<th>Mutation detected</th>
<th>Mutation frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneum</td>
<td>Schorge et al. [5]</td>
<td>2000</td>
<td>American</td>
<td>BRCA1</td>
<td>All BRCA1</td>
<td>11/43</td>
<td>25.6</td>
</tr>
<tr>
<td></td>
<td>Menczer et al. [24]</td>
<td>2003</td>
<td>Ashkenazi Jewish</td>
<td>BRCA1/2</td>
<td>FM</td>
<td>19/68</td>
<td>27.9</td>
</tr>
<tr>
<td></td>
<td>Levine et al. [9]</td>
<td>2003</td>
<td>Ashkenazi Jewish</td>
<td>BRCA1/2</td>
<td>FM</td>
<td>9/22</td>
<td>40.9</td>
</tr>
<tr>
<td></td>
<td>Alsop et al. [10]</td>
<td>2012</td>
<td>Australia</td>
<td>BRCA1/2</td>
<td>All BRCA1/2</td>
<td>24/152</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td>Present study</td>
<td></td>
<td>Korean</td>
<td>BRCA1/2</td>
<td>All BRCA1/2</td>
<td>4/21</td>
<td>19.0</td>
</tr>
</tbody>
</table>

| 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   | 32/108            | 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

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

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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REFERENCES

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