ABSTRACT

Papillary serous carcinoma of the peritoneum (PSCP) is believed to develop de novo from the peritoneal lining of the pelvis and abdomen. Although it is histologically indistinguishable from serous ovarian carcinoma, PSCP exhibits minimal or absent ovarian involvement and may even develop in a woman years after prophylactic oophorectomy. We have shown previously that patients with germ-line BRCA1 mutations who develop PSCP are more likely to have disease originating from multiple peritoneal sites compared with patients with wild-type BRCA1. In this study, we tested the hypothesis that BRCA1-related PSCP has a unique molecular pathogenesis. DNA was extracted from normal tissue and multiple tumor sites in patients with PSCP. BRCA1 and p53 gene mutations were screened for using single-strand conformation polymorphism. Loss of heterozygosity was determined at the BRCA1 and p53 loci. Immunohistochemical analyses of p53, epidermal growth factor receptor, erbB-2, erbB-3, erbB-4, and Bcl-2 expression were performed. We detected germ-line BRCA1 mutations in 11 (26%) of 43 PSCP patients. BRCA1 mutation carriers had a higher overall incidence of p53 mutations (89% versus 47%; P = 0.052), were more likely to exhibit multifocal or null p53 mutations (63% versus 7%; P = 0.014), and were less likely to exhibit erbB-2 overexpression (P = 0.013) than wild-type BRCA1 case subjects. We propose that the unique molecular pathogenesis of BRCA1-related PSCP may affect the ability of current methods to reliably prevent or detect this disease prior to metastasis.

INTRODUCTION

PSCP is believed to develop de novo from the peritoneal lining of the pelvis and abdomen. Although it is histologically indistinguishable from serous ovarian carcinoma, PSCP exhibits minimal or absent ovarian involvement and may even develop in a woman years after prophylactic oophorectomy (1, 2). Gynecological Oncology Group inclusionary criteria for PSCP requires that: (a) both ovaries must be normal in size or enlarged by a benign process; (b) the involvement in the extravarian sites must be greater than the involvement on the surface of either ovary; (c) the ovarian tumor component must be either nonexistent, confined to ovarian surface epithelium without stromal invasion, or involving the cortical stroma with tumor size up to 5 × 5 mm; and (d) serous histology is present (3).

Unlike ovarian carcinoma, which originates from a single site, some cases of PSCP have been shown to originate from multiple peritoneal sites (4, 5). Patients with germ-line BRCA1 mutations who develop PSCP are more likely to have a multifocal disease origin, compared with patients with wild-type BRCA1 (5). Interestingly, BRCA1-related PSCP has been reported to be a common cause of detection failures in a familial ovarian cancer screening program (6). In breast cancer, BRCA1-associated tumors exhibit a higher frequency of p53 expression and gene mutation than sporadic grade-matched tumors (7). BRCA1 and p53 proteins physically associate to coordinately regulate the cell cycle (8, 9). Because LOH is a common event at the BRCA1 and p53 loci in PSCP (10, 11), both may be involved in the development of this disease. In addition, other genetic alterations may be specific to the development and progression of BRCA1-associated PSCP. The purpose of this study was to test the hypothesis that BRCA1-related PSCP has a unique molecular pathogenesis.

MATERIALS AND METHODS

Clinical and Pathological Analyses. We identified 43 patients meeting criteria (3) for the diagnosis of PSCP and having primary treatment at Brigham and Women’s Hospital and Massachusetts General Hospital from 1989 to 1997. The diagnosis was histologically confirmed in each case by a gynecological pathologist (W. R. W. and D. A. B.). All tumors were surgically staged (12). After institutional review board approval, age, stage, histological grade, serum CA125 level, degree of surgical cytoreduction, family history, type of chemotherapy, and clinical follow-up were obtained from medical records, tumor registry data, and correspondence with local care providers. Optimal surgical cytoreduction was defined as residual disease <2 cm at the completion of primary debulking surgery. A strong family history of breast-ovarian cancer was defined as a personal history of primary breast cancer and one first-degree relative with ovarian cancer or at least two first-degree relatives with ovarian cancer.

DNA Extraction. Both formalin-fixed, paraffin-embedded archival material and fresh surgical specimens were collected under a protocol approved by the human subjects committee. In blocks of tissue exhibiting focal tumor involvement, areas with at least 70% tumor cells were microdissected. DNA was extracted from normal control tissue (either uninvolved round ligament, fallopian tube, or bowel serosa) and from one to seven different tumor sites in each patient (5).

SSCP Analysis. SSCP analysis was performed for the BRCA1 gene in 26 patients using 38 oligonucleotide primers (13); 17 of the patients had been screened previously (14). SSCP screening of the p53 gene was performed in all patients using intron-based PCR primers for exons 2–11 (Clontech, Palo Alto, CA). Amplification of the BRCA1 and p53 genes was carried out with 50 ng of genomic DNA using 40 cycles of PCR (each for 1 min at 94°C, 1–2 min at 37–52°C, and 1–3 min at 72°C), after an initial denaturation at 94°C for 10 min. SSCP analysis and direct sequencing of shifted bands was performed as described previously (15), using the Thermo Sequenase cycle sequencing kit (Amersham Life Science, Inc., Cleveland, OH). Null p53 mutations were defined as either missense mutations resulting in transcription to a stop codon or a frameshift insertion/deletion leading to premature protein truncation. “Hot spots” were defined as identical mutations occurring in >10% of the total number of mutations.

LOH. LOH was performed at the BRCA1/11q21 locus using primer set D17S1322 and at the p53/17p13.1 locus using primer set TP53 (both from Research Genetics, Huntsville, AL) as described previously (10). LOH was defined as a visible reduction of 50% or more in the band intensity of one of the tumor sample alleles when compared with the normal tissue control. Cases with a homozygous normal tissue pattern were not informative for LOH analysis.
Table 1 Genetic alterations of BRCA1 and p53 in patients with papillary serous carcinoma of the peritoneum

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>BRCA1 mutations Exon (nucleotide: mutation)</th>
<th>BRCA1 LOH&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p53 mutations Exon (codon: mutation)</th>
<th>p53 LOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wild-type</td>
<td>NL</td>
<td>6 (199: GGA→GAA; Gly→Glu)</td>
<td>n.i.</td>
</tr>
<tr>
<td>2</td>
<td>Wild-type</td>
<td>L</td>
<td>7 (252: in-frame deletion 6 bp)</td>
<td>n.i.</td>
</tr>
<tr>
<td>3</td>
<td>Wild-type</td>
<td>L</td>
<td>10 (337: CGG→TGG; Arg→Trp)</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tumor site 1: 8 (277: TGG→TAT; Cys→Tyr)</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tumor site 2: 6 (218: TGG→ATG; Val→Met)</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tumor site 3: 6 (225: GTT→TTT; Val→Phe)</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 (279: GGG→AGG; Gly→Arg)</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 (282: CGG→CAG; Arg→Gln)</td>
<td>L</td>
</tr>
<tr>
<td>4</td>
<td>Wild-type</td>
<td>n.i.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>11 (2787: G→A; Gly→Arg)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Wild-type</td>
<td>L</td>
<td>8 (261: in-frame deletion 9 bp)</td>
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</tr>
<tr>
<td>7</td>
<td>Wild-type</td>
<td>n.i.</td>
<td>6 (199: GGA→GAA; Gly→Glu)</td>
<td>L</td>
</tr>
<tr>
<td>8</td>
<td>2 (199: G→A; Cys→Tyr)</td>
<td>n.i.</td>
<td>8 (275: insertion T)</td>
<td>L</td>
</tr>
<tr>
<td>9</td>
<td>2 (185: deletion AG)</td>
<td>NL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Wild-type</td>
<td>n.i.</td>
<td></td>
<td></td>
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<td>Wild-type</td>
<td>n.i.</td>
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<td>Wild-type</td>
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<td></td>
<td></td>
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<tr>
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<td>11 (2080: deletion A)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>3 (222: G→A; Val→Ile)</td>
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<td>6 (218: GTG→ATG; Val→Met)</td>
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</tr>
<tr>
<td>16</td>
<td>Wild-type</td>
<td>NL</td>
<td>6 (220: TAT→TCT; Tyr→Ser)</td>
<td>NL</td>
</tr>
<tr>
<td>17</td>
<td>Wild-type</td>
<td>L</td>
<td>6 (218: GTG→ATG; Val→Met)</td>
<td>NL</td>
</tr>
<tr>
<td>18</td>
<td>Wild-type</td>
<td>n.i.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>11 (3830: A→G; Ile→Met)</td>
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<td></td>
<td></td>
</tr>
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<td>Wild-type</td>
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<td></td>
<td></td>
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<td>Wild-type</td>
<td>NL</td>
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<td>Wild-type</td>
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<td>Wild-type</td>
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<td></td>
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<td>Wild-type</td>
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<td></td>
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<td>Wild-type</td>
<td>Wild-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>11 (3719: G→C; Gln→His)</td>
<td>NL</td>
<td>8 (282: CGG→GAG; Arg→Trp)</td>
<td>NL</td>
</tr>
<tr>
<td>28</td>
<td>2 (185: deletion AG)</td>
<td>L</td>
<td>Tumor site 1: intron 6 G→A</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tumor site 2: 6 (199: GGA→GAA; Gly→Glu)</td>
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</tr>
<tr>
<td>29</td>
<td>Wild-type</td>
<td>NL</td>
<td>7 (258: GAA→AAA; Glu→Eys)</td>
<td>NL</td>
</tr>
<tr>
<td>30</td>
<td>Wild-type</td>
<td>NL</td>
<td>7 (252: CTC→CCC; Leu→Pro)</td>
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</tr>
<tr>
<td>31</td>
<td>2 (185: deletion AG)</td>
<td>NL</td>
<td>8 (266: GGA→AGA; Gly→Arg)</td>
<td>NL</td>
</tr>
<tr>
<td>32</td>
<td>Wild-type</td>
<td>NL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Wild-type</td>
<td>L</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Wild-type</td>
<td>L</td>
<td></td>
<td></td>
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<tr>
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<td>Wild-type</td>
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<td>Wild-type</td>
<td>Wild-type</td>
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<td></td>
</tr>
<tr>
<td>37</td>
<td>Wild-type</td>
<td>L</td>
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<td>Wild-type</td>
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<td>Wild-type</td>
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<td></td>
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<tr>
<td>41</td>
<td>11 (3238: G→A; Ser→Asn)</td>
<td>n.i.</td>
<td>10 (342: CGA→TGA; Arg→STOP)</td>
<td>NL</td>
</tr>
<tr>
<td>42</td>
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<td>L</td>
<td>Wild-type</td>
<td>NL</td>
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<td>43</td>
<td>Wild-type</td>
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<td>Wild-type</td>
<td>NL</td>
</tr>
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<td>na</td>
<td>Wild-type</td>
<td>NL</td>
</tr>
<tr>
<td>45</td>
<td>2 (185: deletion AG)</td>
<td>L</td>
<td>Tumor site 1: intron 6 G→T</td>
<td>n.i.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tumor site 2: 6 (199: GGA→GAA; Gly→Glu)</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tumor site 3: 6 (218: TGG→ATG; Val→Met)</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 (322: CCA→CTA; Pro→Leu)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> NL, no loss of heterozygosity; L, loss of heterozygosity; n.i., not informative; na, DNA not available.

**Immunohistochemistry.** Immunohistochemical analysis was performed using 5-μm sections of archival formalin-fixed, paraffin-embedded tissue. For enhancement of antigen detection, slides were incubated in a 10 mM citrate method using the Elite Vectastain ABC kit (Vector Laboratories, Burlingame, CA). Nuclear localization of immunoreactivity was evaluated by two independent observers, and H&E slides were available for all cases. The extent of nuclear reactivity was quantified as the percentage of the total number of cells and was scored in five categories: 0, <5%; 1, 5–25%; 2, 25–50%; 3, 51–75%; and 4, 76–100%. The intensity of staining was noted by a semiquantitative three-point scale: 1, weak; 2, moderate; and 3, intense. A weighted score for purposes of statistical analysis; a score of 5–12 was considered (+). For each tumor specimen was produced by multiplying the percentage score with the intensity score. Patients with a score of 0–4 were considered (−) for purposes of statistical analysis; a score of 5–12 was considered (+).

**Statistical Analysis.** Correlation of clinical and molecular features was performed using Fisher’s exact test; reported Ps resulted from use of two-sided tests. Survival data were calculated by the method of Kaplan and Meier and compared by the log-rank test. Given the exploratory nature of this study, the statistical analysis was not adjusted for multiple comparisons.

**RESULTS**

The 43 patients had a median age of 62 years (range, 35–80). Four had undergone bilateral oophorectomy for benign disease 1–21 years prior to the diagnosis of PSCP; one was diagnosed at the time of prophylactic surgery for a strong family history of ovarian cancer. Thirty-five (81%) women had stage III disease; eight (19%) had stage...
IV. Eleven (26%) patients had histological grade 1 or 2 disease; 32 (74%) had grade 3. Thirty-four (79%) underwent optimal surgical cytoreduction. Twenty-one (49%) patients were initially treated with Taxol/platinum; the remainder received platinum-based chemotherapy usually combined with Cytotoxan. Optimal surgical cytoreduction (P = 0.001) and histological grades 1 and 2 (P = 0.037) were the only clinical factors associated with longer median survival. As of April 1999, the median survival of all patients was 27 months (95% confidence interval, 23–54). The median follow-up time of 16 surviving patients was 49 months (range, 20–92). Ten women are alive with disease; six have no evidence of disease.

As of April 1999, the median survival of all patients was 27 months (95% confidence interval, 23–54). The median follow-up time of 16 surviving patients was 49 months (range, 20–92). Ten women are alive with disease; six have no evidence of disease.

Germ-line BRCA1 mutations were detected in 11 (26%) of 43 patients (Table 1). Twenty-two (56%) of 39 patients had a total of 29 p53 gene mutations. Twenty-three (80%) of 29 p53 mutations were missense, three (10%) were in-frame deletions, and three (10%) were null (case subjects 5, 8, and 41). Fifteen (68%) of 22 patients with p53 mutations had a single mutation, three (14%) had two separate mutations at every tumor site (case subjects 1, 2, and 4), and four (18%) had up to three different multifocal p53 mutations at separate tumor sites (case subjects 3, 5, 28, and 45; Fig. 1). Two p53 “hot spot” mutations were identified in exon 6: codon 199 GGA>GAA (case subjects 1, 5, 7, and 28) and codon 218 GTG>ATG (case subjects 3, 15, 35, and 45).

There were no clinical differences between BRCA1 mutation carriers and wild-type BRCA1 case subjects. Of six patients with a strong family history of breast-ovarian cancer, five had germ-line BRCA1 mutations (P = 0.003). BRCA1-related patients had a higher incidence of p53 mutations (P = 0.052), were more likely to exhibit multifocal and null mutations (P = 0.014), and were less likely to exhibit erbB-2 overexpression (P = 0.013; Table 2). No molecular alterations were significantly associated with survival.

DISCUSSION

Our findings support the hypothesis that BRCA1-related PSCP has a unique molecular pathogenesis. We detected a higher incidence of p53 gene mutations in these patients, as reported previously in BRCA1-related breast cancer (7). The 80% incidence of p53 mutations reported in BRCA1-linked ovarian cancer cases may be higher than sporadic cases, but no comparison studies have been performed (16). Interestingly, neither BRCA1-associated breast or ovarian carcinomas appear to exhibit a generalized increase in susceptibility to the acquisition of other somatic mutations (7, 16). The BRCA1 and p53 proteins physically associate both in vivo and in vitro and function in a common pathway of tumor suppression (8, 9). Wild-type BRCA1 increases p53-dependent transcription, yet truncation mutants of BRCA1 have been shown to act as dominant inhibitors (8). Our findings suggest that p53 has a unique role in the development and progression of BRCA1-related PSCP.

Patients with BRCA1-related PSCP exhibit specific types of p53 mutations. Three of four PSCP cases with multifocal p53 mutations in this study were BRCA1 mutation carriers, supporting the hypothesis that BRCA1-related PSCP frequently develops from separate peritoneal sites (5, 6). The development of multifocal disease also may occur in patients without germ-line BRCA1 mutations, albeit less commonly (5). All three null p53 mutations occurred in BRCA1-related patients. Unique insertion/deletion and null mutations have also been reported in BRCA1-related breast cancer (17). Eight PSCP patients exhibited “hot spot” p53 mutations that have not been characterized previously in breast or ovarian cancer; four of these patients were BRCA1 mutation carriers. These findings support the hypothesis that PSCP has a unique, potentially multifocal pathogenesis and refute the notion that it originates from a microscopic ovarian site with subsequent exfoliation throughout the abdominal cavity. The presence of a germ-line BRCA1 mutation may create a peritoneal field defect, predisposing to multifocality.

BRCA1 mutation carriers in this study had a lower incidence of erbB-2 overexpression. This finding has been reported in BRCA1-associated breast cancer (17) and supports the previously reported lack of erbB-2 expression in cancer-dense families (18). Our data are consistent with other reports finding LOH to be a common, but not required, event in the development of disease in patients with BRCA1 or p53 mutations (17). In addition, we did not perform analyses at all.

<table>
<thead>
<tr>
<th>Molecular feature</th>
<th>Totala (%)</th>
<th>BRCA1 mutation carriers (%)</th>
<th>Wild-type BRCA1 case subjects (%)</th>
<th>Pab</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 LOH</td>
<td>12/24 (50)</td>
<td>2/5 (40)</td>
<td>10/19 (53)</td>
<td>1.000</td>
</tr>
<tr>
<td>p53 multilocus or null mutations</td>
<td>6/22 (27)</td>
<td>3/8 (63)</td>
<td>1/4 (7)</td>
<td>0.014</td>
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<tr>
<td>p52 LOH</td>
<td>10/34 (29)</td>
<td>2/8 (25)</td>
<td>8/26 (31)</td>
<td>1.000</td>
</tr>
<tr>
<td>erbB-2 overexpression</td>
<td>19/34 (56)</td>
<td>6/9 (67)</td>
<td>13/25 (52)</td>
<td>0.679</td>
</tr>
<tr>
<td>erbB-3 overexpression</td>
<td>28/36 (78)</td>
<td>4/9 (44)</td>
<td>24/27 (89)</td>
<td>0.013</td>
</tr>
<tr>
<td>erbB-4 overexpression</td>
<td>22/37 (51)</td>
<td>8/9 (89)</td>
<td>14/28 (50)</td>
<td>0.036</td>
</tr>
<tr>
<td>BRCA1 LOH</td>
<td>15/38 (39)</td>
<td>5/6 (83)</td>
<td>10/32 (31)</td>
<td>0.259</td>
</tr>
<tr>
<td>erbB-2 overexpression</td>
<td>19/37 (51)</td>
<td>3/10 (30)</td>
<td>16/27 (59)</td>
<td>0.151</td>
</tr>
</tbody>
</table>

a DNA was not available in four cases for LOH analysis of p53 mutation screening; 15 cases were not informative at the BRCA1 locus, and five cases were not informative at the p53 locus. Tissue sections were not available for immunohistochemical analysis in all cases. 

b Statistical analysis has not been adjusted for multiple comparisons.

Fig. 1. Multifocal p53 gene mutations in separate tumor sites from patients with papillary serous carcinoma of the peritoneum. Case 3 demonstrates mobility shift patterns at T2 and T3 that represent different exon 6 p53 mutations. Case 28 exhibits different exon 6 p53 mutations at T1 and T5. Case 45 exhibits different exon 6 p53 mutations at T1, T2, T3, and T4. T1–T7, DNA prepared from tumor tissue; NL, DNA prepared from normal control tissue.

Case 3
Case 28
Case 45
tumor sites in every patient, which may have increased the detection of LOH in PSCP (10). The lack of identifiable $Bcl-2$ overexpression may reflect the high frequency of histological grade 3 specimens and advanced disease stage in our study.

We found a high incidence (26%) of germ-line $BRCA1$ mutations in patients with PSCP. Although most of our archival PSCP cases were screened for $BRCA1$ mutations without knowing their family history, the frequency of $BRCA1$ mutation carriers may be skewed in our study by referrals to the Familial Ovarian Cancer Center at Brigham and Women’s Hospital. $BRCA1$ mutation carriers may have a disproportionately high risk of developing peritoneal cancer; however, this requires further study.

Prophylactic oophorectomy has previously been shown to have limitations in patients with a family history of ovarian carcinoma (1, 2). We speculate that most $BRCA1$-associated Müllerian tumors develop from the ovarian surface because of an increased vulnerability to malignant transformation, possibly attributable to repeated ovulation-induced injury, high levels of estrogen exposure, and/or proximity to environmental agents. However, patients with known germ-line $BRCA1$ mutations or a family history of ovarian cancer (if untested) should be counseled about the possibility of developing PSCP, despite prophylactic surgery.

Karlan et al. (6) found seven PSCP cases among 10 cancers arising during a familial ovarian cancer screening program; all three of the screened PSCP cases had germ-line $BRCA1$ mutations. One $BRCA1$ mutation carrier (case subject 14) with a strong family history of BRCA1-related PSCP may affect the ability of curative treatment in gynecological cancer, Vol. 21, pp. 238–239. Stockholm: Panorama Press, 1991.


BRCA1-related Papillary Serous Carcinoma of the Peritoneum Has a Unique Molecular Pathogenesis


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