Clinicopathological Comparisons of Familial and Sporadic Cases in 219 Consecutive Japanese Epithelial Ovarian Cancer Patients

Tadashi Sagawa, Yoichiro Yamashita, Toshio Fujimoto, Hideto Yamada, Nobuhiko Hoshi, Noriaki Sakuragi and Seiichiro Fujimoto

Department of Obstetrics and Gynecology, Hokkaido University School of Medicine, Sapporo, Japan

Background: It is estimated that approximately 5–10% of epithelial ovarian cancer patients in Western countries are associated with an autosomal dominant inheritance with variable penetrance. There are a few reports of familial ovarian cancer in Japan and considerable uncertainties remain regarding Japanese familial ovarian cancer. The aim of this study was to clarify the clinicopathological features of Japanese familial ovarian cancer.

Methods: We studied clinicopathological findings for 219 consecutive epithelial ovarian cancer patients treated at our institution from April 1987 to September 1997.

Results: Eleven patients in nine families were diagnosed as familial ovarian cancer and the incidence of familial cases was 5.0%. Most women (90.9%) with familial cases were diagnosed as the breast ovarian cancer syndrome, whereas ovarian cancer associated with hereditary nonpolyposis colorectal cancer was relatively rare (9.1%). Serous adenocarcinoma, high histological grade, advanced FIGO stage and breast cancer as multiple primary cancer were significantly more common in familial cases compared with sporadic cases (p < 0.001, p < 0.05, p < 0.005 and p < 0.005, respectively). Earlier age of onset was thought to be a characteristic of familial ovarian cancer in Western countries; however, we did not find any difference in age at diagnosis between familial and sporadic cases (53.4 vs 51.3 years). The prognosis of familial ovarian cancer remains controversial and our data did not show a significant difference (p = 0.45) in prognosis between these two groups.

Conclusion: These findings, except for age at diagnosis, in Japanese familial ovarian cancer are in accordance with the features of familial ovarian cancer in Western countries.

Key words: familial ovarian cancer – breast ovarian cancer syndrome – hereditary nonpolyposis colorectal cancer – epithelial ovarian cancer

INTRODUCTION

It has been estimated that approximately 5–10% of all epithelial ovarian cancer patients are associated with an autosomal dominant inheritance with variable penetrance (1). Two such manifestations of familial ovarian cancer are currently recognized: breast ovarian cancer syndrome and ovarian cancer associated with hereditary nonpolyposis colorectal cancer (HNPCC).

Most women (approximately 85–90%) with familial ovarian cancer belong to the breast ovarian cancer syndrome (2), in which both cancers are seen in excess and in some cases manifest in the same individual. Site-specific ovarian cancer, in which only ovarian cancer patients are seen in excess in the family members, is now considered to be a variant of the breast ovarian cancer syndrome (3). HNPCC, in which ovarian cancer is associated with an excess of colorectal, endometrial, other gastrointestinal and upper urological tract cancer patients, contributes approximately 10–15% of all cases of familial ovarian cancer (4).

The Familial Ovarian Cancer Registry was established in 1981 in the USA (5) and in 1989 in Europe (6) and extraordinary progress has been made in studies of familial ovarian cancer. There are, however, no registry and only a few reports of familial ovarian cancer in Japan (7–9) and considerable uncertainties remain regarding Japanese familial ovarian cancer. The incidence of ovarian cancer is highest in industrialized Western countries, but is low in Japan. A clinicopathological study of Japanese familial ovarian cancer may be helpful in understanding the infrequency of ovarian cancer in Japan.
Figure 1. Breast–ovarian cancer syndrome family pedigrees. Clear circle black upper-left quarter, ovarian cancer; clear circle black lower-left quarter, breast cancer; Co, colorectal cancer; clear circle black lower-right quarter, cancer other site (Bl, bladder cancer; Cu, cutaneous cancer; Pr, prostatic cancer); arrows, proband, numbers below symbols indicate ages at diagnosis and diagonal slash indicates deceased members.

MATERIALS AND METHODS

CLINICOPATHOLOGICAL STUDIES

From April 1987 to September 1997, 219 consecutive patients with epithelial ovarian cancer treated at the Department of Obstetrics and Gynecology of Hokkaido University School of Medicine were enrolled in this study. We reviewed slides of the ovarian tumors for histological review, which was performed by one pathologist. Histological types were decided according to the General Rules for Clinical and Pathological Management of Ovarian Tumours (1990). Histological grade was determined according to the new grading system (10), a universal grading system for ovarian epithelial carcinoma and classified as follows: GB, borderline; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; and GX, undecided. The data on stage according to the 1988 protocol of the FIGO (International Federation of Gynecology and Obstetrics) staging system, multiple primary cancer, survival months and other clinical factors were collected from medical records.

Each patient was interviewed in person by one of the investigators and was asked about a history of cancer among first- and second-degree relatives. We also used a 15 min pretested questionnaire and follow-up telephone interview (11) to obtain reliable information.

We used the following diagnostic criteria of familial ovarian cancer. Breast ovarian cancer syndrome is diagnosed when a patient has (i) two or more ovarian cancer cases, including a patient, among first-degree (mother, sister, daughter) and second-degree (maternal or paternal aunt or grandmother) relatives (5) or (ii) three or more breast and ovarian cancer cases among first- and second-degree relatives (11). HNPCC was diagnosed when a patient, associated with synchronous or metachronous colorectal cancer, has two or more colorectal cancer cases among first-degree relatives. Pathological diagnosis of family members was confirmed by reviewing either slides or, if they were not available, the medical records. Patients except familial ovarian cancer cases were designated as sporadic.

STATISTICAL ANALYSIS

Statistical analysis was performed using Fisher’s exact probability test (histological types, FIGO stage and multiple primary cancer), the chi-squared test (histological grade), the Mann–Whitney U-test (the age at diagnosis) and the unpaired t-test (other clinical factors). Survival curves were calculated according to the method of Kaplan and Meier and the difference in survival tested with the Mantel–Cox (log-rank) test. A p-value <0.05 denoted statistical significance.

RESULTS

Eleven patients in nine families were diagnosed as familial ovarian cancer (Figs 1–5) and the incidence of familial cases was 5.0% (11/219). Most women (90.9%, 10/11) with familial ovarian cancer were diagnosed as the breast ovarian cancer syndrome (Figs 1–4), whereas HNPCC was relatively rare (9.1%, 1/11, Fig. 5).

Table 1 shows the predominant histological type of familial cases to be serous adenocarcinoma (81.8%, 9/11). Serous adenocarcinoma was significantly common in familial cases compared with sporadic cases (29.3%, 61/208) [p < 0.001, odds ratio (OR) 10.8, 95% confidence interval (CI) 3.0–38.9]. The histological grade of familial cases tended more frequently to be G2 and G3 (p < 0.05, OR 0.2, 95% CI 0.1–0.9) (Table 2, top). Stage III cases were most common in familial cases (54.5%, 6/11), in contrast with sporadic cases in which stage I cases were most frequent (56.3%, 117/208) (Table 2, bottom). The stage of familial cases was significantly more advanced than that of sporadic cases (p < 0.005, OR 0.1, 95% CI 0.03–0.4). Breast and colorectal cancer occurred as multiple primary
cancer in three and one patients among familial cases, respectively. The occurrence of breast cancer was significantly higher among familial cases (27.3%, 3/11) than sporadic cases (1.4%, 3/208) \((p < 0.005, \text{OR} 25.6, 95\% \text{CI} 5.6-117.7)\).

The mean age at diagnosis was 53.4 and 51.3 years in familial and sporadic cases, respectively, and no difference was found in age at diagnosis. Comparisons of other clinical features (age at menarche, age at menopause, age at the first marriage, single women, hormonal agent users, gravida, parity, height and weight) were also not significantly different between familial and sporadic cases (Table 3).

Survival curves of the nine stage III and IV familial cases and the 37 stage III and IV sporadic cases, treated in a uniform manner, are shown in Fig. 6. No significant difference in survival was noted between the two groups \((p = 0.45)\). No significant difference was seen in age at diagnosis and the ratio of stage III to IV cases between the two groups.

**DISCUSSION**

The diagnostic criteria for familial ovarian cancer are not clearly established and their definition and nomenclature are still somewhat confusing. Narod et al. (11) described familial ovarian cancer as follows. Families with three or more cases of ovarian cancer in first- or second-degree relatives are considered to be examples of hereditary ovarian cancer. Families
Figure 4. Breast-ovarian cancer syndrome family pedigrees. Clear circle black upper-left quarter, Ov, ovarian cancer; clear circle black lower-left quarter, Br, breast cancer; clear circle black lower-right quarter, cancer other site (St, stomach cancer; La, laryngeal cancer); arrows, proband, numbers below symbols indicate ages at diagnosis and diagonal slash indicates deceased members.

Figure 5. Hereditary nonpolyposis colorectal cancer family pedigree. clear circle black upper-left quarter, Ov, ovarian cancer; clear circle black upper-right quarter, Co, colorectal cancer; clear circle black lower right quarter, cancer other site (St, stomach cancer; Psu, primary site unknown); arrows, proband, numbers below symbols indicate ages at diagnosis and diagonal slash indicates deceased members.

Table 1. Histological types of familial and sporadic ovarian cancers

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Familial (n = 11)</th>
<th>Sporadic (n = 208)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous adenocarcinoma</td>
<td>9</td>
<td>61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>1</td>
<td>71</td>
<td>(serous vs non-serous)</td>
</tr>
<tr>
<td>Clear cell adenocarcinoma</td>
<td>1</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>0</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Mesodermal mixed tumor</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Malignant Brenner tumor</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mixed epithelial tumor</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

with a total of five or more breast or ovarian cancers qualify as having the hereditary breast-ovarian cancer syndrome. Families with three or four breast or ovarian cancers have been designated as familial breast-ovarian cancer syndrome. Piver et al. (5) defined two or more ovarian cancers in first- or second-degree relatives as familial. Greggi et al. (12) defined families with two or more first-degree relatives affected with ovarian cancer as familial ovarian cancer.

The diagnosis of HNPCC in Western countries is currently based on the Amsterdam criteria (13). However, a recognized disadvantage of the Amsterdam criteria is that extracolonic tumors, such as ovarian and endometrial cancer, associated with HNPCC are not included (14). This may lead to a delay or an overlook of the diagnosis of HNPCC in families with such tumors (15). Therefore, a set of clinical criteria for HNPCC were proposed by the Japan Research Society for Colorectal Cancer (JRSCC) (16) and we refer to these Japanese clinical criteria for the diagnosis of HNPCC. Japanese clinical criteria of the breast ovarian cancer syndrome may be needed, considering the socioenvironmental situation in Japan, which includes a low incidence of ovarian cancer and a tendency for women to have fewer children.
Features of familial ovarian cancer

Table 2. Histological grade and FIGO (1988) stage of familial and sporadic ovarian cancers

<table>
<thead>
<tr>
<th></th>
<th>Familial (n = 11)</th>
<th>Sporadic (n = 208)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GB</td>
<td>2</td>
<td>48</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>G1</td>
<td>0</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>6</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>3</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>GX</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>117</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Figure 6. Survival curves of Stage III and IV familial and sporadic ovarian cancers.

The incidence of familial ovarian cancer in this study was 5.0%, which is the lower limit of the incidence reported in Western countries. High frequencies of the breast ovarian cancer syndrome, serous adenocarcinoma, high histological grade, advanced FIGO stage and breast cancer among familial cases are in accordance with the findings previously reported in Western countries (4,11,17,18).

Except for a few reports (12,19), earlier age of onset, a decade earlier than that in the general population, is thought to be a characteristic of familial ovarian cancer in Western countries (4,5,17,18,20,21). However, we did not find any difference in age at diagnosis between familial and sporadic cases. Aida et al. (9) also showed that there was no significant difference in average age at diagnosis between familial and sporadic cases (51.1 vs 52.0 years). Later age of onset may be a characteristic of Japanese familial ovarian cancer.

Unlike the better prognosis of hereditary breast and colon cancer (22,23), the prognosis of familial ovarian cancer has been controversial. Bewtra et al. (4) and Greggi et al. (12) did not show a longer survival of familial ovarian cancer patients when compared with the non-familial control. Rubin et al. (18) and Aida et al. (9) found the survival of familial ovarian cancer to be better than that of sporadic ovarian cancer, while Johannsson et al. (24) reported a trend toward worse survival of familial ovarian cancer after correction for age and stage. Our data on survival did not show a significant difference between familial and sporadic cases. These conflicting results may be associated with a limited number of controls with similar age and time at diagnosis (24) because the onset of familial cases is generally young in Western countries.

Approximately 90% (25) of the breast and ovarian cancer syndrome are linked to germline mutations in BRCA1 and, to a lesser extent, to BRCA2 (26). Somatic mutations of both genes are very rare, especially in BRCA1 (27,28). BRCA1 mutations are generally located throughout the gene except for founder mutations noted in Ashkenazi populations (29,30). BRCA1 mutations are estimated to confer a breast cancer risk of 87% by age 70 and an ovarian cancer risk of 44% by age 70 (31,32). It is suggested, however, that these risk figures were derived from very high-risk families studied for research and may not apply to all BRCA1-mutation carriers (33). Differences in penetrance have been noted among families with identical germline mutations in the BRCA1 gene. It is suggested that environmental and/or other genetic factors play a role in tumorigenesis in these family members (34,35).

It is stressed that genetic variants other than BRCA1 and BRCA2 are likely to exist that confer predisposition with low penetrance, in a Mendelian-recessive fashion or through interactions with other susceptibility loci (2). However, little is known about these types of genes at present. If all the genetic variants that are associated with familial clustering of ovarian cancer were detected in the near future, all the details of familial ovarian cancer would be revealed and more precise diagnostic criteria might be established.
Acknowledgments

We thank the patients and their families for their ongoing cooperation and the clinicians and scientists for assisting in data and sample collection. This work was supported in part by Grants-in-Aid for Scientific Research (Nos 08671854 and 10897013) from the Ministry of Education, Science, Sports and Culture of Japan.

References