Clinical features of familial ovarian cancer lacking mutations in BRCA1 or BRCA2

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Summary

Purpose of investigation: The purpose of the present study was to identify the clinical and pathologic features of ovarian cancers in patients who have a family history of breast or ovarian cancer but who do not have a mutation in the BRCA1 or BRCA2 gene.

Methods: 303 patients with ovarian cancer were reviewed for clinical features and for cancer family histories. After the exclusion of 51 patients known to carry BRCA1 or BRCA2 mutations, 24 patients with familial cancer were compared with 228 patients with non-familial cancer.

Results: Patients with familial cancer were more likely to have grade 2 tumors, Stage II disease and to present between ages 51 and 60 than were non-familial controls. Ten of 24 patients in the familial group presented between ages 51 and 60 with a grade 2 tumor compared to 3.0 expected (p = 0.001).

Conclusions: Families of women who present with grade 2 ovarian cancer between the ages of 51 and 60 may have an unidentified ovarian cancer susceptibility gene.

Key words: Hereditary ovarian cancer; Epidemiology; *BRCA1*; Poland.

Introduction

Approximately 10% of cases of ovarian cancer are hereditary and are due to inherited mutations in the BRCA1 and BRCA2 genes [1]. In Poland, 14% of unselected cases of ovarian cancer are due to one of three common founder mutations in BRCA1 (185delAG, C61G, 4153delA) [2, 3]. Not all families with multiple cases of ovarian cancer, or with ovarian and breast cancer, are due to BRCA1 and BRCA2 mutations and the identification of additional cancer susceptibility genes is anticipated. To date, genetic linkage studies have not been successful in this regard. One possible reason is the lack of a distinct clinical phenotype associated with the third breast-ovarian cancer susceptibility gene. For example, medullary breast cancers and fallopian tube cancers are over-represented among families with BRCA1 mutations [4], and male breast cancers, fallopian tube cancers and pancreatic cancers are over-represented among families with BRCA2 mutations [5]. In addition, BRCA1-associated breast cancers are more commonly of high grade and estrogen-receptor negative than expected [4]. The goal of the present study was to identify clinical features of ovarian cancers that are familial but not due to mutations in either BRCA1 or BRCA2.

Materials and Methods

The ovarian cancer patients in this study were drawn from a hospital-based series of all ovarian cancers diagnosed at either of two hospitals in Szczecin, Poland between January 1999 and December 2001. Fifty-nine patients were treated at the Clinic of Operative Gynecology and Gynecology for Women and Girls, Pomeranian Medical University and 305 patients were treated at the Chemotherapy Department of the Szczecin Regional Oncology Hospital. This study group included almost all women treated for invasive ovarian cancer and who were residents of the Szczecin region (Poland) between these dates. The medical records were reviewed to determine tumor stage at diagnosis. A paraffin-embedded histology slide was sought for each patient and these were reviewed by the same physician for tumor grade (1-3) and histologic type. Each patient was interviewed and provided details about all breast, ovarian and other cancers in first- and second-degree relatives. Cases were requested to provide a blood sample for testing for BRCA1 founder mutations. A mutation was detected in 49 women. These women were excluded from the present analysis, leaving a study group of 315 cases.

Familial cases were defined as having one or more first- or second-degree relatives with ovarian cancer at any age or breast cancer under the age of 50, or a past history of breast cancer. Of the 315 study subjects there were 26 familial cases. We performed BRCA2 analysis (full sequencing) on the familial cases and identified two mutations. This left a study group of 24 familial cases without a BRCA1 or BRCA2 mutation. These 24 cases represent the familial, non-BRCA1 and non-BRCA2 groups for the present analysis.

Among the 289 non-familial controls a slide was not available for 61 controls. The 228 non-familial controls for whom a slide was available served as the comparison group. BRCA2 testing was not done on controls due to the expense of this test.

Results and Discussion

The characteristics of the 24 familial cases and the 228 non-familial controls are given in Table 1. Although the familial case group was small, it differed from the non-

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Table 1. — *Comparison of the group of familial cancers with non-familial ovarian cancers.*

Feature	Familial Cases	Non-familial controls
Age		
< 40	1 (4.2%)	16 (7.1%)
40-50	7 (29.2%)	63 (27.6%)
51-60	12 (50.0%)	45 (19.7%)
60+	4 (16.6%)	104 (45.6%)
Stage		
I	3 (12.5%)	32 (14.0%)
II	11 (45.8%)	49 (21.5%)
III	8 (33.3%)	114 (50.0%)
IV	2 (8.4%)	33 (14.5%)
Grade		
1	3 (12.5%)	58 (25.4%)
2	17 (70.8%)	105 (45.1%)
3	4 (16.7%)	65 (28.5%)
Histology		
Serous	16 (66.7%)	162 (71.1%)
Mucinous	2 (8.3%)	19 (8.3%)
Endometriod	4 (16.7%)	21 (9.2%)
Other	2 (8.3%)	26 (11.4%)

familial group in several ways. Familial cases were more likely to present between the ages of 51 and 60 (odds ratio 4.1; p = 0.002), were more likely to present at Stage II (odds ratio 3.1; p = 0.01), and were more likely to be of grade 2 (odds ratio 2.8; p = 0.03) than were the non-familial controls. There was no distinct histologic type that appeared to be over-represented among the familial group. There were nine Stage II, grade 2 cancers among the cases in the familial group compared to 4.9 expected (p = 0.07). There were ten cases aged between 51 and 60 years with grade 2 tumors compared to 3.0 expected (p = 0.001). There were six cases aged between 51 and 60 years and with Stage II tumors, compared to 2.6 expected (p = 0.04). There were six cases of grade 2 and Stage II between ages 51 and 60 compared to 1.7 expected (p = 0.01).

Using a hospital-based registry, we have identified certain features of ovarian cancer that may represent a susceptibility phenotype distinct from that of BRCA1 and BRCA2. These include grade 2, Stage II and presentation between ages 51 and 60. This combination is relatively rare and was present in 22 of the 252 (8.7%) ovarian cancer patients in this study. In contrast, the comparable BRCA1-associated ovarian cancer phenotype is high grade, of serous histology and young onset (commonly presenting between the age of 35 and 50) [1, 6, 7]. Very-early onset ovarian cancers do not appear to be featured in families with BRCA1 or BRCA2 mutations [8]. In the present study only one of 24 women diagnosed with ovarian cancer at age 40 or below presented with a positive family history. It is unlikely therefore, that selection of early-onset ovarian cancer cases will help to identify families harboring additional cancer susceptibility genes.

Our study has several strengths. We studied a large group of clinically and histologically-verified patients from two hospitals in a single city. The inhabitants of Szczecin are ethnically homogeneous. Patient participation rates were very high and because of rapid case ascertainment methods no patients were lost to the study because of death or loss of follow-up. There are several weaknesses as well. Although the study was relatively large, many of the subgroups of interest were small. We excluded 20% of potential control subjects because a slide was not available. Also, this is a very well defined ethnic group and it may be that the results of this study are not generalizable to other ethnic groups.

We excluded all known carriers of BRCA1 and BRCA2 mutations from the case and comparison groups. This exclusion was done in order to clarify the features of patients with hereditary cancers due to unknown genes. We were able to perform genetic testing for the common BRCA1 mutations found in Poland for all study subjects, but because the cost of BRCA2 testing was restrictive this analysis was performed on familial cases only. It is possible that we have included some BRCA2-positive patients in the comparison group, but BRCA2 mutations are rare in Poland and we expect these to account for fewer than 4% of the ovarian cancer cases. It is also possible that we have missed some non-founder BRCA1 mutations, but non-founder BRCA1 mutations are rare in Poland [2].

It is important that these observations are confirmed in other large series of unselected cases of ovarian cancer. The features which comprise the susceptibility phenotype are relatively non-specific and it is hoped that additional features will be identified which will help the specificity. It is hoped that selecting cases with these particular features may eventually aid in the identification of families which harbor mutations in a novel breast-ovarian cancer susceptibility gene.

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