Borderline Ovarian Tumors in Finland: Epidemiology and Familial Occurrence

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A total of 1,197 borderline ovarian tumors were reported to the Finnish Cancer Registry in 1973–1992. The mean age of the patients was 52 years, while the mean age of the 7,060 patients with an invasive epithelial ovarian carcinoma reported in the same time period was 62 years. The incidence of borderline ovarian tumors did not increase with age after patients became 35 years old and older. The overall age-adjusted incidence of borderline ovarian tumors was 1.8 per 100,000 women-years. Familial cancer occurrence during 1967–1992 was studied among relatives of 144 index patients diagnosed in 1980–1982. No borderline ovarian tumors were detected in the relatives, and only one of the 446 female first-degree relatives had an epithelial ovarian cancer. The expected number (borderline and invasive combined) was 1.9. The mothers of the index patients had an increased risk for pancreatic cancer (standardized incidence ratio 4.9, 95% confidence interval 1.0–14.3) and for cancer of the uterine cervix (standardized incidence ratio 7.8, 95% confidence interval 1.6–22.8). No significant increase in cancer risk was observed for fathers, brothers, or sisters of the patients with borderline ovarian tumors. Am J Epidemiol 1996;144:548–53.

causality; epidemiologic factors; family characteristics; ovarian neoplasms

Epithelial ovarian tumors of low malignant potential, often called borderline ovarian tumors, are a distinct clinical and histologic entity. The division of epithelial ovarian neoplasms into three categories according to the degree of malignancy was first proposed by the Cancer Committee of the International Federation of Gynecology and Obstetrics (FIGO) in 1961 and accepted by the General Assembly of FIGO in 1970. In their classification, borderline ovarian tumors or “cystadenomas with proliferative activity of the epithelial cells and nuclear abnormalities but no infiltrative destructive growth” were recognized as a separate entity from benign cystadenomas and malignant cystadenocarcinomas (1, p. 6). Similar classification was adapted by the World Health Organization in 1973 (2). Lack of invasion of the ovarian stroma by neoplastic cells is the cardinal feature that separates borderline tumors from invasive carcinomas (3). Extraovarian spread, which occurs in approximately 25 percent of the cases (4), plays no role in the definition of borderline tumors.

Despite some of the histologic features suggestive of malignancy, the clinical prognosis of these tumors is excellent compared with that of invasive ovarian carcinoma. The 5-year actuarial survival rate for patients with borderline tumors, all stages combined, has been reported to exceed 90 percent, whereas the respective rate for patients with an invasive carcinoma has been reported to be approximately 40 percent (4). The 15-year corrected survival for patients with borderline tumors is reported to be close to 100 percent in patients with stage I disease, approximately 70 percent in stage II disease, and 60 percent in stage III disease (5).

Knowledge about the epidemiology and risk factors of borderline ovarian tumors is based mainly on hospital series, of which all but one (5) include fewer than 200 patients (6–16). Borderline ovarian tumors are reported to comprise 4–14 percent of all ovarian neoplasms (7, 13, 16) and 12–33 percent of all epithelial ovarian malignancies (5–7, 10, 11, 13, 16, 17). The mean age of the patients with a borderline ovarian tumor in these series has ranged from 40 to 52 years (6–12, 16). Among white women in the United States, the incidence of borderline ovarian tumors during 1973–1983 increased only slightly from 1.3 per 100,000 women-years in the age-group 20–34 years to 4.6 in the age group 65–79 years (17).

Risk factors for borderline ovarian tumor are mostly the same as reported for ovarian cancer. Pregnaness,
lactation, and the use of oral contraceptives have been found to have a protective effect (18–22). Family history of ovarian cancer, which is one of the strongest known risk factors for ovarian cancer (23–25), has not been found to be associated with borderline ovarian tumors (9, 24, 26).

In this study, we describe the epidemiology of borderline ovarian tumors and compare it with the epidemiology of invasive epithelial ovarian cancer in Finland during 1973–1992. We also investigated and here report on the familial risk of borderline ovarian tumor and familial association of borderline ovarian tumors with other malignancies.

PATIENTS AND METHODS

Patients

The population-based and nationwide Finnish Cancer Registry was founded in 1952, and cancer registration started in 1953. Reporting of cancer to the registry was made obligatory in 1961. Physicians, hospitals, and pathology laboratories send reports to the registry independently. On average, five notifications are received per case. The registry files are annually linked to the file of deaths and immigrations issued by the Statistics Finland and Population Register Centre, Finland. Complete follow-up of cancer patients is achieved.

The coding of cancer in the Finnish Cancer Registry includes the primary site, laterality, histologic type, and degree of malignancy among other data. Borderline ovarian tumors, registered as semimalignant ovarian tumors, have been reported to the Cancer Registry since 1968. For this study, all women who had a borderline ovarian tumor or an invasive ovarian cancer diagnosed during 1973–1992 were searched from the Finnish Cancer Registry. Tumors with a nonepithelial histology were excluded. Invasive ovarian tumors with an unknown histology were included inasmuch as 90–95 percent of all ovarian cancers are epithelial (27). The histologic coding system used by the Finnish Cancer Registry specifies mucinous subtypes from other epithelial subtypes but does not differentiate between endometrioid, serous, or clear cell subtypes. In this study, all histologic subtypes of epithelial borderline tumors were combined for the analysis as well as all subtypes of epithelial ovarian carcinoma. Mucinous and nonmucinous tumors were also analyzed separately.

Tracing of relatives

To assess the role of family history of borderline ovarian tumor as a risk factor for ovarian cancer or other malignancies, all patients diagnosed with a borderline ovarian tumor who were younger than 76 years of age during 1980–1982 in Finland were selected as index patients ($n = 165$).

The parishes in which the index patients were born were contacted to obtain the names and dates of birth of the parents and siblings. If the family had moved to another community, tracing was continued through subsequent parish records until one of the parents was deceased or the mother was 50 years of age and additional pregnancies were unlikely. Parents and siblings were followed up through the parish records until death or to the beginning of 1967. Since the beginning of 1967, a unique personal identification number composed of the birth date, a three-numbered code, and a check digit has been given to each person living in Finland. After that, follow-up of the relatives was possible through the computer-based Central Population Register. The data on the children and the husbands of the index patients were obtained from the parishes or from the Central Population Register. The data on relatives were linked with the Central Population Register in February 1994 to obtain the dates of death of the relatives recorded to be alive in 1967.

Tracing of all the family members was successful for 144 of the 165 patients (87 percent). For 16 of the 21 untraced families, information on the patient and her family could not be found from the parish of the reported birth community. For the remaining five families, we were not able to confirm complete tracing of the family. In the 144 traced families, 37 relatives from 25 families (3.6 percent of all relatives) were lost from follow-up, 17 of whom were women.

Statistical methods

The incidence rates were calculated per 100,000 person-years by 5-year age groups and were age adjusted to the World Standard Population (28).

The first-degree relatives were followed up for cancer through the files of the Finnish Cancer Registry. The follow-up was done automatically using the personal identification number as key. The analysis was restricted to the period starting from January 1, 1967. Follow-up for cancer among parents of the index patient started at the date of birth of the index patient or on January 1, 1967, whichever was later, and ended at death or on December 31, 1993, whichever was first. For siblings and children, the follow-up started at the date of their birth or on January 1, 1967, whichever was later.

The numbers of observed cases and person-years at risk in each category of relatives were counted by 5-year age groups separately for three calendar periods (1967–1975, 1976–1984, and 1985–1993). The expected numbers of cancer were calculated by multi-
plying the number of person-years in each age group by the corresponding average cancer incidence in all Finland during the period of observation. Results for sons and daughters are not reported separately due to the small number of cases. The expected number of ovarian cancer during 1980–1982 in women up to 75 years of age was excluded from the expected number of overall cancer and ovarian cancer since no observed cases were possible for this stratum due to the definition of index cases.

To calculate the standardized incidence ratio, the observed number of cases was divided by the expected number (29). The statistical significance was tested by the Mantel-Haenszel chi-square test on the presumption that the number of observed cases followed a Poisson distribution. Ninety-five percent confidence intervals were calculated.

RESULTS

In 1973–1992, a total of 1,197 borderline ovarian tumors and 7,060 invasive epithelial ovarian cancers, including 528 with an unknown histology, were diagnosed in Finland. The mean age at diagnosis of patients with a borderline ovarian tumor was 52 years (standard deviation 18 years) and of patients with an invasive epithelial ovarian cancer, 62 years (standard deviation 13 years). Borderline tumors comprised 14 percent of all epithelial ovarian malignancies. In women younger than 40 years, 44 percent of all epithelial ovarian malignancies were borderline tumors compared with 13 percent in women aged 40 years or older.

Of the 1,197 borderline ovarian tumors, 461 (38 percent) were classified as mucinous, whereas only 13 percent of the invasive cancers were of a mucinous type. There was no difference between the mean ages for mucinous and nonmucinous borderline tumors. Cancer patients with an invasive mucinous cancer were younger than those with a nonmucinous cancer (mean ages at diagnosis 59 and 63 years, respectively).

The age-adjusted incidence rate for invasive ovarian cancer remained stable during the study period, whereas there was a 50 percent increase in the incidence of borderline ovarian tumors in 1973–1977 and in 1988–1992 (table 1). The age-specific incidence for invasive ovarian cancer increased with increasing age (figure 1). The age-specific incidence of borderline ovarian tumors showed an increase up to age 35 years, after which the incidence stabilized at the level of about four per 100,000 women-years.

In the 144 families, there were altogether 1,030 first-degree relatives of whom 835 contributed person-years at risk after January 1, 1967. The overall cancer risk was not increased in the female relatives (table 2).

The male relatives had a significant (*p < 0.05*) 1.4-fold increase in the overall cancer risk. However, no significant increase was detected for male relatives for any of the specific cancer sites analyzed, whereas the female relatives had a significantly increased risk for cancers of the uterine cervix and pancreas (table 3). Only one of the 144 index patients with a borderline ovarian tumor had a first-degree relative diagnosed with an epithelial ovarian cancer, and no relatives with a borderline ovarian tumor were detected. The expected number (borderline and invasive combined) was 1.9.

The mothers had significantly increased risks for cancers of the uterine cervix (observed 3, expected 0.4, standardized incidence ratio 7.8, 95 percent confidence interval 1.6–22.8) and pancreas (observed 3, expected 0.6, standardized incidence ratio 4.9, 95 percent confidence interval 1.0–14.3), but not for any of the other analyzed sites. The fathers, sisters, and brothers did not have significantly increased risk for any of the analyzed cancer sites.

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**TABLE 1. Numbers and incidence rates per 100,000 women-years of borderline and invasive epithelial ovarian tumors in Finland in 1973–1992, by period of diagnosis**

<table>
<thead>
<tr>
<th>Years</th>
<th>Borderline</th>
<th></th>
<th>Invasive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Incidence rate* per 100,000 women-years</td>
<td>No.</td>
<td>Incidence rate* per 100,000 women-years</td>
</tr>
<tr>
<td>1973–1977</td>
<td>220</td>
<td>1.5</td>
<td>1,571</td>
<td>8.3</td>
</tr>
<tr>
<td>1979–1982</td>
<td>288</td>
<td>1.8</td>
<td>1,646</td>
<td>9.0</td>
</tr>
<tr>
<td>1983–1987</td>
<td>291</td>
<td>1.7</td>
<td>1,812</td>
<td>9.3</td>
</tr>
<tr>
<td>1988–1992</td>
<td>398</td>
<td>2.3</td>
<td>2,031</td>
<td>9.8</td>
</tr>
<tr>
<td>1973–1992</td>
<td>1,197</td>
<td>1.8</td>
<td>7,060</td>
<td>9.4</td>
</tr>
</tbody>
</table>

* Age-adjusted to the World Standard Population.
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DISCUSSION

The source of data for this study was a population-based and nationwide cancer registry, which registers over 99 percent of all solid tumors in Finland (30). Thus, the comparison between epidemiologic characteristics of borderline and malignant epithelial ovarian tumors was reliable. The use of a nationwide cancer registry minimized the potential patient referral bias that may occur in the hospital-based studies. This series consisted of nearly 1,200 patients with a borderline ovarian tumor and to our knowledge is the largest series reported so far.

Although the existing criteria for a histologic diagnosis of a borderline ovarian tumor are defined, considerable problems can be encountered in the actual classification process. The presence of invasion of the stroma is difficult to ascertain in some tumors with an inherent pattern of epithelial proliferation. The large variability in the degree of atypia, proliferation, and mitotic activity within an individual tumor necessitates the use of serial sections from each tumor for a correct classification. The classification of mucinous tumors is especially difficult (31, 32). These difficulties are reflected in the large intraobserver and interobserver variation in the classification of borderline ovarian tumors (33-35).

This study was based on the original histologic classification reported to the Finnish Cancer Registry by individual institutions. A reevaluation of the pathologic diagnosis, to define the observer variation, has not been made from this material by us or previously. From these data, we are not able to distinguish whether the increase in the incidence of borderline ovarian tumor observed in the study period is a true biologic phenomenon or whether it represents improvement in the diagnosis and reporting of borderline ovarian tumors to the Finnish Cancer Registry.

The proportion of borderline tumors of all ovarian malignancies in this study was 14 percent. This is in agreement with most of the previous studies based on fewer data (5, 6, 11, 13). The patients with an ovarian tumor of a borderline malignancy were, on the average, 10 years younger than patients with a malignant ovarian tumor. The observed mean age at diagnosis, 52 years, is in agreement with some of the previous studies (6, 7) and also with the data reported in the annual report by FIGO (4).

The pattern of a minor increase in incidence rate of borderline ovarian tumor with increasing age is similar to that reported by Harlow et al. (17). This finding disagrees with the opinion that the incidence of borderline ovarian tumors would be higher in younger women (36). The borderline ovarian tumors occur almost evenly in women between 30 and 70 years of age, whereas invasive ovarian cancer occurs increasingly as women become older.
Family history of ovarian cancer has not been found to be associated with borderline ovarian tumors (9, 24, 26). Our results are consistent with these earlier reports. However, even with more than 400 female relatives and a follow-up of more than 10 years, the statistical power of the present study is still limited. Another limitation of our study is the restriction of cancer case ascertainment to the time period after 1967. We have manually searched the 1953–1966 files of the Cancer Registry for additional cancer diagnoses and have found only one ovarian cancer, which was a 12-year-old sister’s tumor that was classified as a reticulocellular sarcoma of the ovary.

The observed increase in the risk for pancreatic cancer and cancer of the uterine cervix was unexpected. Association between ovarian tumors, either borderline tumors or invasive carcinoma, and cancer of the uterine cervix has not been reported previously. Familial association between pancreatic cancer and invasive ovarian cancer has been reported recently in a Utah population (37), but it has not been confirmed by other authors to date. Given the possible heterogeneity among ovarian tumors, the significance of our finding as it relates to a possible familiality between borderline ovarian tumors and pancreatic and cervical cancers is unclear, especially when no increase was observed in ovarian, uterine, and breast cancer risk, also detected in the Utah study. In males, although the overall cancer risk was significantly increased, only insignificant risk increases were observed for some of the analyzed sites, i.e., stomach, colon, pancreas, and lung. The small numbers of cases restrict us from further conclusions, and the possible association of these tumor types should be tested in larger studies.

The observed difference in the incidence patterns of borderline tumors and invasive ovarian carcinoma suggests that borderline ovarian tumors are a separate entity from invasive ovarian carcinoma. The observation that a family history of a borderline ovarian tumor does not increase the risk for invasive ovarian carcinoma, whereas a family history of ovarian cancer is an established risk factor for an invasive ovarian carcinoma (23–25), indicates that etiologic factors responsible for development of familial ovarian tumors do not predispose to development of borderline ovarian tumors.

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REFERENCES


