PERGAMON

European Journal of Cancer 40 (2004) 90–95

European Journal of Cancer

www.ejconline.com

Familial clustering of ovarian and endometrial cancers

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Received 6 January 2003; received in revised form 25 April 2003; accepted 27 June 2003

Abstract

Data on the association of ovarian cancer with other cancers in families are limited, and no data are available on the involvement of specific morphological types. The nationwide Swedish Family-Cancer Database on 10.2 million individuals and 19 175 invasive ovarian cancers was used to calculate standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) for familial ovarian cancer in 0–66-year-old daughters when mothers or sisters were affected. The SIR for concordant ovarian cancers was increased. When the mother or sister had breast cancer, the SIRs were 1.21 and 1.48, respectively; when they had endometrial cancer, the SIRs were 1.45 and 2.53. Multiple myeloma in the mother was associated with a risk of ovarian cancer in the daughter. The risk of endometrioid ovarian cancer was 3.40 in the daughter when the mother presented with endometrial cancer. Our data show a strong familial coupling of ovarian and endometrial cancers, which appears to be specific to the endometrioid morphology.

Keywords: Familial risk; Sibling risk; Seropapillary cystadenocarcinoma; Endometrioid tumour

1. Introduction

Invasive ovarian cancer has declined in incidence in Sweden over the past two decades and with an incidence of less than 20/100 000, it ranks sixth among all female cancers [1]. The incidence of endometrial cancer has been increasing and it ranks third among female cancers, although the incidence is not much higher than that of ovarian cancer. Both of these cancers are mechanistically linked to reproductive hormones, and the number of ovulatory cycles is a risk factor for both [2–4]. Most ovarian tumours are adenocarcinomas derived from the surface epithelium [5]. They present in many morphological forms such as cystadenocarcinomas, with serous or mucinous secretions, or endometrioid tumours, with endometrial-like tubular gland structures. Endometrial neoplasms are also adenocarcinomas, which may retain a well-defined glandular structure, referred to as endometrioid carcinoma [5].

Ovarian cancer occurs in families with *BRCA1/2* mutations and in hereditary non-polyposis colorectal cancer patients (HNPCC) [6–9]. In the *BRCA1/2* families, the tumours display small histopathological distinctions, being mainly non-mucinous [7,8,10,11]. Even in HNPCC families, the histopathology resembles that of sporadic tumours, with a small excess of endometrioid tumours [12]. Endometrial cancer is the most common extracolonic manifestation in HNPCC families and mismatch repair defects are also common in sporadic tumours [13–15]. The *PTEN* gene is also commonly affected in sporadic endometrial tumours [15–17]. In addition to the known cancer syndromes, both ovarian and endometrial cancers show familial clustering. The reported familial risk among first-degree relatives has been reported to range between 2.0 and 3.0 [18–29]. Many of these studies have also analysed the association of ovarian and endometrial cancers with other cancers in families [18,21,22,24,26–29]. Some studies have noted an association of these cancers to breast cancer, and a few other sites have emerged in individual studies. An association between ovarian and endometrial cancer has been observed in only three studies, all of which analysed young populations of women [21,26,29]. Most

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doi:10.1016/S0959-8049(03)00627-0

family studies, particularly on ovarian cancer, have been based on interviews of cases and controls about cancer in their relatives. The accuracy of reporting intra-abdominal cancers diagnosed a long time ago may have biased the risk estimates in the interview studies.

We examine here, the association of ovarian cancer with other cancers in family members, using the nationwide Swedish Family-Cancer Database [30], which has been updated in 2000 to include over 10 million individuals and over 1 million registered tumours retrieved from the Swedish Cancer Registry from 1961 to 1998. Data on morphological classification, based on the International Classification of Diseases (ICD)-O-2 coding system, are available since 1993. The Database is unique in its size and its unbiased structure, because the data on family relationships and cancers were obtained from registered sources of practically complete coverage.

2. Patients and methods

The Swedish Family-Cancer Database was initially created in the mid-1990s by linking an administrative family register on all Swedish families to the Swedish Cancer Registry, including data from 1961 to 1998 [30–32]. For each child, there are data on both parents at the time of birth. Each person has been assigned a unique technical identification number (which is different from the national identification number, 'personal number'), allowing, for example, the construction of families through the mother. The Database includes anyone born in Sweden after 1931, as well as their biological parents, totalling over 10.2 million individuals, included in 3.2 million families of parents and offspring.

The completeness of cancer registration in the 1970s has been estimated to be over 95%, and is now considered to be close to 100%. The percentage of cytologically- or histologically-verified cases of ovarian and endometrial cancers is close to 100% [1]. The Family-Cancer Database has an incomplete linkage from deceased offspring to parents, particularly among those offspring born between 1932 and 1940. Of a total of 7.0 million offspring, 216 000 have died by the end of follow-up on 31 December 1998. Parental information was missing from 15 600 dead offspring who had a diagnosis of cancer (9.9% of all offspring cancers); most of these were born in the 1930s. This deficit is unlikely to appreciably affect the familial risk estimates in the present study, but may cause a small error in the estimated risks between sisters.

The Swedish Cancer Registry is based on the compulsory notification of cases [1]. A four-digit diagnostic code according to the seventh revision of the ICD-7 has been used since 1958, together with a code for histological type (World Health Organization/HS/CANC/24.1 Histology Code). These codes describe histology in main subgroups, such as adenocarcinoma and squamous cell carcinoma, and an overwhelming proportion of ovarian cancers were classified as adenocarcinomas. From 1993 onwards, ICD-O-2/ICD with histopathological data according to the Systematized Nomenclature of Medicine (SNOMED, http://snomed.org) was used; we refer to this classification as 'SNOMED or morphology'.

Information on the family history of any cancer in all first-degree relatives (parents, siblings and children) was collected, but only the mother–daughter and sister–sister relationships were reported in the present study; all analyses were carried out in gender-specific groups. In the rare families with multiple affected offspring, each patient was counted independently. All tumour incidence rates were based on data in the Family-Cancer Database. Only the first primary cancer was considered in the analysis, but women with ovarian–endometrial double primaries were also considered. Follow-up was started at birth, immigration or on 1 January 1961, whichever was the latest time. Follow-up was terminated upon the diagnosis of first invasive or borderline cancer, death, emigration, or on the closing date of the study, 31 December 1998. Standardised incidence ratios (SIRs) were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated according to 5-year-age-, gender-, tumour type-, period- (10-year bands), parity- (six groups), age at first birth (five groups), socioeconomic status- (six groups) and residential area- (three groups) specific standard incidence rates for all daughters. The applied indirect standardisation is robust, even though many of the cells for the standard rate lacked cases. SIRs for sisters were calculated by the cohort method as described elsewhere in Ref. [33]. In this method, families with multiple affected individuals are ascertained at multiple times and they are not independent, leading to too narrow confidence intervals (CIs) (approximately by a factor of 1.4 [20]); no correction was done in the present paper. SIRs of morphology-specific ovarian cancer were calculated for daughters, whose mothers presented with any invasive cancer and the risk was compared with the rate of morphology-specific ovarian cancers among all daughters. 95% CI were calculated assuming a Poisson distribution.

3. Results

The Family-Cancer Database included data from 1961 to 1998 from the Swedish Cancer Registry, on 15 040 mothers and 4135 daughters with ovarian cancer, respectively. We first considered all ovarian cancers without histological specification. Familial risks for ovarian cancer in daughters are shown in Table 1 by cancer in mothers, and *vice versa*. The data were adjusted for age, period, parity, age at first birth, socio-economic

Table 1
SIR for invasive ovarian cancer in daughters by mother probands and vice versa

Site in proband	O	SIR in daughter (95% CI)	O	SIR in mother (95% CI)
Stomach	34	0.99 (0.68–1.38)	11	1.73 (0.86–3.11)
Colon	64	0.89 (0.69–1.14)	28	1.02 (0.68–1.48)
Rectum	25	0.75 (0.48–1.11)	18	1.35 (0.80–2.13)
Lung	38	1.12 (0.79–1.53)	25	1.09 (0.70–1.61)
Breast	230	**1.21** (1.06–1.38)	387	**1.43** (1.29–1.58)
Cervix	51	1.25 (0.93–1.65)	54	1.07 (0.81–1.40)
Endometrium	71	**1.45** (1.13–1.83)	46	**1.38** (1.01–1.85)
Ovary	119	**2.68** (2.22–3.21)	119	**2.68** (2.22–3.21)
Kidney	27	0.95 (0.63–1.39)	12	1.14 (0.59–2.00)
Melanoma	19	1.00 (0.60–1.57)	58	1.01 (0.76–1.30)
Nervous system	27	1.02 (0.67–1.49)	44	1.12 (0.82–1.51)
Endocrine glands	16	0.74 (0.42–1.21)	20	0.84 (0.51–1.30)
Non-Hodgkin's lymphoma	26	1.14 (0.74–1.67)	8	0.48 (0.21–0.96)
Myeloma	22	**1.63** (1.02–2.48)	2	0.56 (0.05–2.07)
Leukaemia	26	1.15 (0.75–1.69)	14	1.03 (0.56–1.73)
All sites	943	**1.15** (1.08–1.23)	953	**1.28** (1.20–1.37)

SIR, standardised incidence ratio; O, observed; SEI, socio-economic index; 95% CI, 95% Confidence Interval. Bold type: 95% CI does not include 1.00. Period of follow-up: 1961–1998. SIR adjusted for age, period, parity, age at first birth, SEI, residential region.

index (SEI) and region. Only sites with at least 20 cases in any analysis were considered. When the mother had ovarian cancer, the SIR for the daughter was 2.68 and it was equally high in the reverse comparison. The SIR for ovarian cancer in the daughter was increased when the mother had breast cancer (SIR 1.21), endometrial cancer (1.45) and myeloma (1.63). Among the 71 ovarian cancer patients with a maternal endometrial cancer proband, only 1 had a double primary with endometrial cancer as the second tumour. In addition, any cancer in the mothers increased the risk for daughters (SIR 1.15). The SIR for ovarian cancer in the mothers was increased when daughters presented with breast (1.43) and endometrial cancer (1.38; no mother had a second endometrial cancer), but no increase was observed when the daughters were diagnosed with myeloma. Ovarian cancer was non-significantly increased to 1.73 (0.86–3.11) when daughters were diagnosed with stomach cancer. No increase in ovarian cancer was observed from male (son or father) stomach cancer probands. Thyroid cancer was too rare to be included in Table 1, and the SIRs were at or below 1.00. We also analysed the risk for maternal ovarian cancer by using sons as the probands. However, no significant association was observed (data not shown).

The effect of diagnostic age on the risk of ovarian cancer from probands with endometrial cancer was analysed. The SIR was unchanged when a daughter was diagnosed before age 50 years (1.49, $N = 46$, 1.09–1.99) and when the mother was diagnosed with endometrial cancer at any age. However, the SIR was increased to 2.70 (7, 1.07–5.59) for mothers diagnosed with ovarian cancer before age 50 years, when the daughter was diagnosed with endometrial cancer before the age of 67 years.

The association of cancer between sisters is shown in Table 2, for the same sites as those in Table 1. The risk for concordant ovarian cancer was 2.94, and almost equally high was the risk when a sister was diagnosed with endometrial cancer (SIR 2.53). Breast cancer in a sister was associated with a SIR of 1.48. The risk for ovarian cancer was 1.22 when a sister was diagnosed with any cancer. Using the brother as a proband, none of the sites shown in Table 2 associated with ovarian cancer in a sister (data not shown).

The SNOMED codes have been used systematically since 1993 in the Swedish Cancer Registry. The analysis in Table 3 was based on the morphology of ovarian tumours in daughters by any type of endometrial cancer in mothers or sisters. Because the SNOMED code was brought into use relatively recently, the proportion of non-specified histologies, grouped under 'Others', was over half of all ovarian cancers in daughters. Among the daughters in the database, the distribution of the most common morphological types was seropapillary cystadenocarcinoma (41%), endometrioid carcinoma (22%) and serous cystadenocarcinoma (18%). It was clear from the data that endometrioid morphology was associated with endometrial cancer: the risk was 3.40 (95% CI 1.80–5.83) from mother probands and 4.60 (0.87–13.62) from sister probands. The most common morphologies, serous cystadenocarcinoma and seropapillary cystadenocarcinoma showed no association to endometrial cancer. Unfortunately, the SNOMED

classification used does not distinguish endometrioid endometrial cancers and thus further details on endometrial cancer were not available.

4. Discussion

The present study is the largest on familial ovarian cancer published to date and the number of concordant ovarian cancers in mother–daughter pairs is almost as large as that of four previous cohort studies combined [20,22,24,28]. We have used the same population recently in an analysis of concordant ovarian cancer, and we will refer to detailed data in this source [34]. To summarise for concordant ovarian cancer, the most common morphology, seropapillary cystadenocarcinoma, showed the highest familial risk (4.26) and endometrioid tumours showed the smallest familial risk (3.61). Although several previous studies have also analysed the association of ovarian cancer with other cancers in families, many of them have been small and thus lacked power [18,21,22,24,26–29]. The most consistent finding has been the association of ovarian and breast cancers, which was also noted in the present analysis. It is explained, at least in part, by the *BRCA1/2* mutations and, probably, additionally by a shared response to pregnancy hormones [4,9,35]. Another association noted in the present study was that between ovarian cancer and multiple myeloma. Although this was significant only for daughter's ovarian cancer by mother's myeloma (SIR 1.63), it was also above unity between sisters (SIR 1.86, only 2 cases). The association may not be a chance observation because it has also been reported in a previous study [27]. There are no clues as to the possible genetic mechanism, because the aetiology of multiple myeloma is largely unknown [36–38].

The main finding of the present study was the strong and consistent association between ovarian and endometrial cancers. Although the association has been observed in three previous studies, it has been missed in several other studies, probably because of their low power. Even in the three positive studies on young populations of women, two from earlier analyses of the present Database, and thus not independent studies, the findings have been of borderline significance [21,26,29]. An effect of age was also seen in the present study because the mother–daughter associations were weaker (SIRs 1.45 and 1.38) than the sister–sister association of 2.53. Mothers' age was not limited in the Database, whereas all daughters were younger than 67 years. The SIR was 2.70 for maternal ovarian cancer before age 50 years when a daughter was diagnosed with endometrial cancer. The almost exclusive limitation of the risk to the endometrioid morphology of ovarian cancer was particularly interesting. The risk for endometrioid ovarian cancer rose from 1.45 to 3.40 when the mother was diagnosed with endometrial cancer. Endometrioid morphology is also the most common morphology for endometrial cancer, and it is likely that the identical morphology is the common denominator underlying the high familial aggregation. This finding should prompt

Table 2
SIR for ovarian cancer among sisters

Site in proband	O	SIR (95% CI)
Stomach	3	1.64 (0.30–4.74)
Colon	10	1.45 (0.69–2.68)
Rectum	1	0.27 (0.00–1.53)
Lung	5	0.80 (0.25–1.87)
Breast	87	**1.48** (1.19–1.82)
Cervix	11	0.98 (0.48–1.75)
Endometrium	21	**2.53** (1.57–3.87)
Ovary	30	**2.94** (1.40–5.94)
Kidney	3	1.08 (0.20–3.21)
Melanoma	10	0.88 (0.42–1.63)
Nervous system	8	0.92 (0.40–1.83)
Endocrine glands	4	0.66 (0.17–1.70)
Non-Hodgkin's lymphoma	4	0.92 (0.24–2.38)
Myeloma	2	1.86 (0.17–6.68)
Leukaemia	2	0.66 (0.06–2.44)
All sites	159	**1.22** (1.03–1.43)

Bold type: 95% confidence interval (CI) does not include 1.00. O, observed; SIR, standardised incidence ratio.

Table 3
SIR for ovarian cancer in daughters by family history of endometrial cancer

Morphological type	Mother's history			Sister's history		
	O	SIR (95% CI)	Cases in reference group	O	SIR (95% CI)	Cases in reference group
Adenocarcinoma	4	1.11 (0.29–2.87)	306	2	3.07 (0.29–11.3)	156
Endometrioid carcinoma	13	**3.40** (1.80–5.83)	307	3	4.60 (0.87–13.62)	168
Serous cystadenocarcinoma	3	0.95 (0.18–2.82)	267	0		138
Seropapillary cystadenocarcinoma	8	1.18 (0.51–2.35)	555	3	2.26 (0.43–6.7)	315
Others	43	1.36 (0.98–1.83)	2700	13	**2.53** (1.34–4.34)	1430
All	71	**1.45** (1.13–1.83)	4135	21	**2.53** (1.56–3.87)	2207

Bold type: 95% CI does not include 1.00. Period of follow-up: 1961–1998. SIR adjusted for age, period, parity, age at first birth, SEI, residential region. O, observed; SIR, standardised incidence ratio.

further studies of a possible mechanism, which may (or may not) operate via genetic control of hormonal metabolism. Ovarian cancers of endometrioid histology are commonly diagnosed synchronously with endometrial cancers and a small component of familial predisposition to these double primaries has recently been described in Refs. [39–41]. However, the present findings on familial risks between ovarian and endometrial cancers were not explained by double primaries, because we found only a few such cases among the familial cases.

The known heritable risk factors of ovarian and endometrial cancers do not appear to be plausible explanations of our findings. *BRCA1* mutations increase the risk of endometrial cancer, but to a lesser extent than their effect on the risk of breast cancer [42]; *PTEN* alterations, that are common in endometrial cancer, are not known to predispose to ovarian cancer. *PTEN* mutations should additionally increase the risk for thyroid cancer, and no such increased risk was observed in the present study [15]. HNPCC affects both the ovary and the endometrium, but shows only a modest excess of endometrioid morphology in the ovary [12,43]. However, the complete lack of risk for colorectal cancer argues against the involvement of HNPCC, with the caveat that the carriers of the rare *MSH6* germ-line mutations appear to show a high risk of endometrial cancer, but a low risk of colorectal cancer [14,44]. Ovarian and endometrial cancers are also seen in patients with the Peutz–Jeghers syndrome, but the lack of intestinal cancers in the present families suggests that this syndrome is not involved [45].

In summary, our data show a strong familial coupling of ovarian and endometrial cancers, which appears to be specific to a relatively rare form of ovarian cancer, the endometrioid type. Other familial tumours that associated with ovarian cancer were breast cancer and multiple myeloma.

Acknowledgements

The Family-Cancer Database was created by linking registers maintained at Statistics Sweden and the Swedish Cancer Registry.

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