The risk of cancer and the role of parity among women with endometriosis

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BACKGROUND: Several epidemiological studies have shown an increased cancer risk among women with endometriosis, especially ovarian cancer. Infertility and nulliparity are also known risk factors for different types of cancer. The aim of this study is to investigate cancer risk among women with endometriosis, stratifying for parity. METHODS: Women discharged from a hospital, with the diagnosis of endometriosis from 1969 to 2002, were identified using the National Swedish Inpatient Register. Data were linked to the National Swedish Cancer Register to identify cases of cancer and to the Swedish Multi-Generation Register to calculate parity and age at first birth. Standardized incidence ratios (SIR) were calculated. RESULTS: A total of 63 630 women entered the study. To exclude cancers already present at the time of endometriosis diagnosis, the first year of follow-up was excluded, leaving a number of 3822 cases of cancer. There was no increased overall risk of cancer (SIR 1.01) among women with endometriosis. Endometriosis was associated with elevated risks for endocrine tumours (SIR 1.38), ovarian cancer (SIR 1.37), renal cancer (SIR 1.36), thyroid cancer (SIR 1.33), brain tumours (SIR 1.27), malignant melanoma (SIR 1.23) and breast cancer (SIR 1.08), as well as a reduced risk for cervical cancer (SIR 0.71). There were no significant differences between nulliparous and parous women with endometriosis regarding cancer risk for any of the cancer types. There was a non-significant decrease in risk of ovarian cancer with increasing parity for women with endometriosis. CONCLUSIONS: Women with endometriosis have an increased risk for several malignancies. The increased risks do not seem to be related to parity.

Keywords: cancer risk; endometriosis; parity

Introduction

Epidemiological studies have recently shown that women with endometriosis have an increased risk of different types of malignancies, especially ovarian cancer and non-Hodgkin’s lymphoma (Brinton et al., 1997; Olson et al., 2002; Melin et al., 2006). In fact, several studies have indicated endometriosis as a risk factor for ovarian cancer (Ness et al., 2000, 2002). A co-existence of endometriosis and cancer has been estimated to occur in 0.7–5.0% of all cases of ovarian endometriosis (Erzen and Kovacic, 1998; Ogawa et al., 2000; Nishida et al., 2000; Stern et al., 2001). Various histological and molecular genetic studies have even indicated that endometriosis may transform into cancer (Ogawa et al., 2000; Yoshikawa et al., 2000; Varma et al., 2004).

Women with endometriosis have a well-documented increased risk for infertility, but endometriosis as a cause of infertility has been a focus of controversy (Kennedy et al., 2005). Infertility and nulliparity per se are known risk factors for cancer, above all in the ovaries (Adami et al., 1994; Brinton et al., 2004a, 2005a). In a cohort study on infertility, increased risks of colon cancer, ovarian cancer, thyroid cancer and malignant melanoma were shown for women with endometriosis when compared with the general population (Brinton et al., 2005a). Whether the increased prevalence of infertility in women with endometriosis may explain the increased risk of cancer is not known. Modugno et al. (2004) found that infertility or decreased fertility is not the single reason for the increased risk of ovarian cancer in women with endometriosis.

The aim of this study is to extend our previous epidemiological studies, which showed an increased risk of certain forms of cancer in women with endometriosis, and investigate the impact of parity on this risk.

Materials and Methods

Study population

Our study population was restricted to women included in the Swedish Multi-Generation Register (MGR) (Multi-Generation Register, 2003). This register comprises all individuals registered in Sweden from
1961, and born since 1932. For these index persons, the register holds information on their parents (also adoptive parents). Via the Swedish National Registration Number (NRN), unique to every individual, familial relationships (father, mother, children and siblings) between individuals in the MGR can be established.

**Study base**

Our study base was created through a linkage between the MGR and the National Swedish Inpatient Register (NSIR), utilizing the NRN (Fig. 1). All women included in the MGR, who had been discharged from a Swedish hospital with the diagnosis of endometriosis for the first time from 1969 through 2002, comprised our study base. The extent of the NSIR has been explained in previous publications (Melin et al., 2006; Statistics from Center of Epidemiology). Patients clinically diagnosed within an open ward system, in private practice or as a day-surgery procedure, are not covered by this register and therefore are not included in this study.

The discharge diagnoses were coded according to the International Classification of Diseases 8, 9 and 10 (ICD 8–10). For ICD 8, the codes 625.30–625.33, 625.38 and 625.39 were used, for ICD 9, the codes 617A–617G and 617X were used and for ICD 10, the codes N80.0–N80.9 were used.

A total number of 65,349 women were identified with a first hospitalization, with a diagnosis coded for endometriosis, and were eligible for follow-up. The Swedish cohorts studied previously (Brinton et al., 1997; Melin et al., 2006) were largely included in the present study. Parity and age at first birth (AAFB) were calculated from the MGR. Women with pregnancies with more than one fetus were counted as a single pregnancy/delivery, since we were interested in the number of births rather than the number of children. Data on miscarriages or spontaneous abortions are not available on an individual basis in Sweden. The MGR only covers live births, which means that stillbirths are not included in this study. The endometriosis patients in our study were equally distributed through the calendar year and year of birth compared with the cohort previously studied.

**Follow-up**

Cases with cancer were identified through the National Swedish Cancer Register (NSCR), from 1958 through 2002, using the ICD 7. Of the 65,349 women in the study cohort, 1,719 (2.7%) had a cancer diagnosis before or at the same time as the first hospitalization with a diagnosis coded for endometriosis and were therefore excluded from follow-up, leaving a total number of 63,630 women entering the study cohort (Fig. 1).

There were a total number of 4,125 incident cases of cancer recorded in the study cohort (6.5%) and 567 of the women had more than one type of cancer during the follow-up period. To exclude cancers already present at the first hospitalization with a diagnosis coded for endometriosis, the follow-up started 1 year after the diagnosis of endometriosis and continued until the woman died, emigrated or until the end of year 2002. Within this first year of follow-up, 303 (7.3%) of the 4125 cases of cancer were diagnosed, leaving 3,822 cancer cases in the study.

Thus, in total 2,022 patients with endometriosis and cancer (34.6% of cancer cases) were excluded from the statistical calculations.

Data on surgical procedures were collected from the NSIR. When calculating time-at-risk regarding ovarian cancer, women were censored when both ovaries had been removed. However, they were still included when calculating time-at-risk for all other types of
cancer. The corresponding censoring procedure was performed regarding cervical cancer and endometrial cancer. Women were censored at supravaginal or total hysterectomy when calculating time-at-risk for endometrial cancer, and at total hysterectomy for cervical cancer.

**Population comparison rates**

To do yearly calculations of age, parity and AAFB and specific cancer incidence rates for the Swedish population, a linkage between the MGR and the NSCR was performed. These rates were used as a comparison with the cancer experience in the cohort of endometriosis patients.

**Statistical analysis**

For each year, attained age, parity and AAFB, specific expected numbers of cancer cases for the endometriosis patients were calculated from the estimated person time-at-risk in the endometriosis patient’s cohort and the calculated parity of the Swedish population and AAFB specific incidence rates. Standardized incidence ratios (SIR), stratified by parity and AAFB, and their 95% confidence intervals were calculated as estimates of relative risk. SIR is the ratio of the observed number of cancer cases in the cohort and the expected number of cases in the cohort according to the population comparison cancer incidence created from the MGR, by calendar year and 5-year age class. P-values for homogeneity in cancer risk between nulliparous and parous women were calculated, assuming the number of cases followed a Poisson distribution. Trend test over parity for parous and parous women were calculated, assuming the number of cases followed a Poisson distribution. Trend test over parity for parous women, whereas this was not the case for nulliparous women.

Analyses of parity-specific risks of ovarian cancer showed that the risks were highest for nulliparous women and women who had given birth to one child. The risk decreased and was no longer significantly increased if the woman had given birth to more than one child, although the trend was not statistically significant (P = 0.12) (Table 2). There was an increased risk of endometrial cancer in women who had given birth to two children only (SIR = 1.60, 95% CI = 1.16–2.16) (data not shown). The highest risk for malignant melanoma was found in nulliparous women (SIR = 1.47, 95% CI 1.13–1.92) (Table 1).

**Parity-specific cancer risk**

The SIRs were statistically independent of whether the women had delivered a child or not, i.e. the SIRs did not differ significantly between parous and nulliparous women (Table 1). However, the SIRs for brain and thyroid cancer were elevated for parous women, whereas this was not the case for nulliparous women.

There was no significantly increased overall risk of cancer [SIR = 1.01, 95% confidence interval (CI) = 0.98–1.05]. However, we found increased risks of ovarian cancer (SIR = 1.37, 95% CI = 1.14–1.62), cancer of the kidney (SIR = 1.36, 95% CI = 1.11–1.64), thyroid cancer (SIR = 1.33, 95% CI = 1.02–1.70), brain tumours (SIR = 1.27, 95% CI = 1.09–1.46), malignant melanoma (SIR = 1.23, 95% CI = 1.07–1.40), breast cancer (SIR = 1.08, 95% CI = 1.02–1.13), and endocrine malignant tumours (i.e. cancer of the adrenal glands, parathyroid glands, pituitary gland, insulinoma of the pancreas and malignant tumours in other endocrine glands) (SIR = 1.38, 95% CI = 1.17–1.62) (Table 1). We could not confirm an increased risk of non-Hodgkin’s lymphoma (SIR = 1.12, 95% CI = 0.92–1.34) or endometrial cancer (SIR = 1.14, 95% CI = 0.93–1.39). A reduced risk of cervical cancer (SIR = 0.71, 95% CI 0.53–0.94) was found.

Women with a diagnosis coded for ovarian endometriosis (24,955 women, 39.2%) had an increased risk of ovarian cancer (SIR = 1.59, 95% CI = 1.26–1.98), contrary to women with a diagnosis coded for adenomyosis (i.e. ectopic endometrium within the myometrium) (SIR = 0.72, 95% CI = 0.37–1.26) (data not shown).

**Results**

**Overall cancer risk**

The total number of person-years in the cohort was 792,013. The average time of follow-up was 13.4 years. The average age at cancer diagnosis in women with endometriosis was 55.9 years (SD 10.4 years) for the whole study period. The average time of follow-up was 13.4 years. The average age at the first hospitalization with a diagnosis coded for endometriosis was 39.5 years (SD 10.5 years) for the whole study period. The average age at cancer diagnosis in women with endometriosis was 55.9 years (SD 10.4 years). A total number of 3822 cancer cases were included in the cohort.

| Table 1: SIR with 95% confidence intervals (CI) of cancer after a diagnosis of endometriosis, for all women, and stratified on non-parous and parous women |
|----------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Type of cancer (ICD-7 code)     | All women     | Non-parous women | Parous women | P-value for homogeneity |
|                                 | Observed no. of cases | SIR (95% CI) | Observed no. of cases | SIR (95% CI) | Observed no. of cases | SIR (95% CI) |     |
| Ovarian (1750)                  | 134           | 1.37 (1.14–1.62) | 48            | 1.48 (1.11–1.96) | 86            | 1.30 (1.05–1.61) | P = 0.49 |
| Breast (170)                    | 1465          | 1.08 (1.02–1.13) | 326           | 1.12 (1.00–1.24) | 1139          | 1.07 (1.01–1.13) | P = 0.48 |
| Endocrine (195)                 | 149           | 1.38 (1.17–1.62) | 26            | 1.29 (0.88–1.90) | 123           | 1.39 (1.17–1.67) | P = 0.72 |
| Thyroid (194)                   | 64            | 1.33 (1.02–1.70) | 9             | 0.85 (0.45–1.65) | 55            | 1.46 (1.11–1.90) | P = 0.12 |
| Brain (193)                     | 186           | 1.27 (1.09–1.46) | 30            | 0.98 (0.68–1.41) | 156           | 1.31 (1.12–1.53) | P = 0.14 |
| Malignant melanoma (190)        | 217           | 1.25 (1.07–1.40) | 55            | 1.47 (1.13–1.92) | 162           | 1.14 (0.98–1.33) | P = 0.11 |
| Kidney (180)                    | 104           | 1.36 (1.11–1.64) | 15            | 1.34 (0.81–2.23) | 89            | 1.34 (1.08–1.65) | P = 0.99 |
| Endometrial (172)               | 97            | 1.14 (0.93–1.39) | 28            | 0.93 (0.64–1.35) | 69            | 1.04 (0.82–1.32) | P = 0.62 |
| Cervical (171)                  | 49            | 0.71 (0.53–0.94) | 13            | 0.70 (0.40–1.21) | 36            | 0.64 (0.46–0.90) | P = 0.80 |
Trends over calendar time

Trend tests for differences in SIRs over calendar time did not show significant trends for any of the cancers investigated here (data not shown).

Discussion

The present study has shown that the increased risk for a number of different types of malignancies in women with endometriosis remained when stratified by parity. The strengths of this study are the large number of women included, the long follow-up time, the ascertainment of cancer diagnosis and the access to data on parity. The study differs from our previous one mainly because of the use of the MGR to access data on parity. Thereby, some endometriosis patients were lost due to lack of information in this register, but these where equally distributed over calendar time and birth year and should therefore not interfere with the results.

One weakness in this study is that the time point for the onset of the disease is not known, as endometriosis may be asymptomatic for a period of time until increasing symptoms lead to a diagnostic procedure. One major reason for this delay is the lack of non-inventional diagnostic tests. A diagnostic delay of median 9 years in different countries has been shown in some studies (Ballweg, 2004). The inpatient register available in Sweden includes only patients hospitalized for the diagnosis of endometriosis. One could thus assume that the cohort includes mainly moderate-to-severe cases of endometriosis. The criteria for hospitalization have changed somewhat during the inclusion period. During the 1970s, laparoscopic diagnosis was performed to a limited extent and the patients were hospitalized. During the 1980s, laparoscopic diagnostic procedures for pain increased substantially and the patients were hospitalized. During the 1990s, day surgery became more common and several patients were managed within the frame of open care, in which case, they were not included in the inpatient register. These changes were of course generalized and the routines differed in parts in different hospitals. In the present cohort, there was no valid way to account for the stage of endometriosis, because staging of the disease has not been a part of the register. Despite this, one might still assume that the cohort includes mainly moderate-to-severe cases of endometriosis. However, some of the women included were hospitalized primarily for a surgical procedure, for instance a hysterectomy and/or an oophorectomy, for other indications, and in these cases, the endometriosis diagnosis may have been an unexpected finding. Given these limitations, the cancer risk found may not be extrapolated to the whole endometriosis population. Whether cancer risk differs in cases with severe endometriosis and cases with mild endometriosis has to be studied further. Since we only can identify those who have been hospitalized for endometriosis, we have fewer observed cases of cancer in our study group than if we had been able to identify and include all women with endometriosis. The unidentified women with endometriosis were classified as unexposed in this study and will therefore have remained in the whole Swedish female population, which was the comparison group. If they increase the cancer rate in this comparison group, then we would have most likely underestimated the true cancer risk of women with endometriosis.

Another limitation of the study is that 34.6% of all cases of cancer had to be excluded from the statistical calculations as it was not possible to show that the endometriosis started 1 year or more before the cancer diagnosis as required according to the inclusion criteria. This may have resulted in an underestimation of the true risk of cancer for women with endometriosis.

A further weakness is the lack of information on unsuccessful pregnancies, including abortions, as there is no Swedish register covering miscarriages in a reliable way and no register at all covering abortions. Stillbirths are also not included since this information is not available from the MGR.

Our study showed that women with endometriosis above all have an increased risk of ovarian cancer, even after controlling for parity. This is a very important finding since a protective effect of parity on the risk of developing epithelial ovarian cancer has consistently been shown previously (Riman et al., 2004). The odds ratios for epithelial ovarian cancer for parous compared with nulliparous women have in several case-control studies ranged from 0.3 to 0.7 (Riman et al., 2004). The impact of ovulation on the risk of ovarian cancer has been extensively debated. Repetitive ovulation trauma to the ovarian surface epithelium, which is also exposed to high levels of estrogen, has been claimed a risk (Fathalla, 1971). Ovulation stimulating drugs for infertility treatment as well as hormonal treatment for endometriosis have been suggested to increase the risk of epithelial ovarian cancer, but the studies are not conclusive (Ness et al., 2002; Cottreau et al., 2003; Blumenfeld, 2004; Brinton et al., 2004b, 2005b; Mahdavi et al., 2006). Whether the women included in this cohort have received ovulation-stimulating drugs or other

<table>
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<th>Parity</th>
<th>Observed number of cases</th>
<th>SIR</th>
<th>95% CI</th>
<th>P-value, homogeneity test for trend</th>
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hormonal treatment is not known. This will, however, be studied further.

Although there was a tendency towards decreased risk of ovarian cancer if the woman had given birth to more than one child, there was no significant trend with increased parity. It is well known that women with severe endometriosis more often have problems with infertility which might lead to an increased risk of ovarian cancer. The importance of aborted pregnancies can only be speculated on. It is reasonable to claim that neither the duration nor hormonal levels of these aborted pregnancies would have a too great an impact on the woman’s risk of cancer. In a study from 2005, the authors could not find any association between incomplete pregnancies and ovarian cancer, either among nulliparous or ever-pregnant women. Among single pregnant women, one full-term pregnancy was more protective against ovarian cancer than an incomplete pregnancy (Gierach et al., 2005).

A higher risk for gliomas in nulliparous compared with parous women was shown in a Swedish case–control study (Lambe et al., 1997). The author’s interpretation of that study was that the reduced androgen level during pregnancy might contribute to the risk, or that the malignant brain tumour itself reduced fertility. The present study showed an increased risk of brain tumours in women with endometriosis. However, the study showed that parity did not have a statistically significant implication on the risk of brain tumours, although the SIR in this case was higher for parous women than for nulliparous women.

Our study also confirmed the increased risk of malignant melanomas shown by Brinton et al. (2005a). An association between endometriosis and dysplastic naevi as well as an increased family history of malignant melanoma among endometriosis patients has also been shown by others (Hornstein et al., 1997).

Further, our study showed an increased risk for breast cancer in women with endometriosis. Previous studies on parity, age at first delivery and risk of breast cancer have shown a decreased risk of breast cancer with increasing parity and an increased risk for breast cancer with increasing AAFB (Lambe et al., 1996; Tamakoshi et al., 2005; Veronesi et al., 2005). The present study showed that these factors did not have any impact on the risk of breast cancer in women with endometriosis. Data on the risk of breast cancer in women with endometriosis have not been consistent (Brinton et al., 1997; Melin et al., 2006), which indicates a more complex multi-factorial relationship.

Our study showed the highest risk for endometrial cancer in women who had given birth to two children when compared with those who had delivered none or one child. Unfortunately, the cohort included too few cases with more than two children to allow a trend analysis. These results should be regarded in the light of other studies on parity and endometrial cancer risk that have shown nulliparity and increased AAFB as risk factors for endometrial cancer (Lambe et al., 1999; Mogren et al., 2001) and multi-parity and childbearing distributed over a long period of time as protective (Lambe et al., 1999; Mogren et al., 2001; Hinkula et al., 2002).

Other factors that might have an impact on the cancer risk are different treatment options of endometriosis. These aspects will be investigated further.

In conclusion, this extensive register study has shown an increased risk for different types of malignancies in women hospitalized with the diagnosis of endometriosis, even when controlled for parity. The study clearly shows that parity, or lack of parity, is not the cause of the increased risk of ovarian cancer in women with endometriosis. Thus, other risk factors are certainly involved and need to be studied further. The limitation of the study group to patients included in the inpatient register, who are more likely to have had moderate–severe endometriosis, might have contributed to an underestimation of the risk.

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