Human Reproduction Vol.21, No.5 pp. 1237–1242, 2006 doi:10.1093/humrep/dei462
Advance Access publication January 23, 2006.

Endometriosis and the risk of cancer with special emphasis on ovarian cancer

A.Melin[1,5], P.Sparén[2], I.Persson[2] and A.Bergqvist[3,4]

[1]Department of Obstetrics & Gynaecology, Karolinska University Hospital Huddinge, [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institute and [3]Department of Obstetrics & Gynaecology, Karolinska Institutet, Danderyds Hospital, Stockholm, Sweden

[4]Present address: Pfizer AB, Täby, Sweden

[5]To whom correspondence should be addressed at: Department of Obstetrics and Gynaecology, K57 Karolinska University Hospital, Huddinge, S-14186 Stockholm, Sweden. E-mail: anna-sofia.melin@karolinska.se

BACKGROUND: Several observations of the coexistence of endometriosis and cancer have been published. One study concerning endometriosis patients from 1969 to 1986 showed an overall relative cancer risk of 1.2 and relative risks for breast cancer, ovarian cancer and non-Hodgkin's lymphoma to be 1.3, 1.9 and 1.8, respectively. The aim of this study was to see whether these risk ratios stand in an extended study with longer follow-up. METHODS: Women discharged from a hospital, with a diagnosis of endometriosis from 1969 to 2000, were identified using the National Swedish Inpatient Register. Data were linked to the National Swedish Cancer Register to identify cases of cancer. Data on hysterectomies and oophorectomies were available. Standardized incidence ratios (SIR) were calculated. RESULTS: 64 492 women entered the study. First year of follow-up was excluded, leaving 3349 cases of cancer. There was no increased overall risk of cancer [SIR 1.04, 95% CI 1.00–1.07]. Elevated risks were found for ovarian cancer (SIR 1.43, 95% CI 1.19–1.71), endocrine tumours (SIR 1.36, 95% CI 1.15–1.61), non-Hodgkin's lymphoma (SIR 1.24, 95% CI 1.02–1.49) and brain tumours (SIR 1.22, 95% CI 1.04–1.41). Women with early diagnosed and long-standing endometriosis had a higher risk of ovarian cancer, with SIR of 2.01 and 2.23, respectively. The average age at endometriosis diagnosis was 39.4, indicating that there are the moderate/severe cases that are included in this study. Women who had a hysterectomy before or at the time of the endometriosis diagnosis did not show an increased risk of ovarian cancer. CONCLUSION: Women with endometriosis have an increased risk of some malignancies, particularly ovarian cancer, and the risk increases with early diagnosed or long-standing disease. Hysterectomy may have a preventive effect against ovarian cancer.

Key words: cancer/endometriosis/standardized incidence ratio/Sweden

Introduction

Endometriosis, defined as the presence of endometrial-like tissue outside the uterine cavity, is a chronic disease that causes suffering, pain and infertility in up to 10% of women of fertile age (Eskenazi and Warner, 1997). Endometriotic lesions are most commonly located in the ovaries, the pelvic peritoneum and the uterosacral ligaments but may appear in almost any part of the body (Bergqvist, 1992). Some studies have indicated an association between endometriosis and cancer. The close morphologic relationship between endometriosis and ovarian cancer was described by Sampson (1925). Since then, several case reports have indicated a capacity for malignant development of endometriotic tissue (Ogawa *et al*., 2000; Yoshikawa *et al*., 2000). The ovaries are the most common location for the coexistence of endometriosis and cancer. This has been estimated to occur in 0.7–5.0% of all cases with ovarian endometriosis (Erzen and Kovacic, 1998; Nishida *et al*., 2000; Ogawa *et al*., 2000; Stern *et al*., 2001).

In a study of overall cancer risk after a hospital discharge diagnosis of endometriosis, Brinton *et al*. (1997) used data from the National Swedish Inpatient Register (NSIR) and the National Swedish Cancer Registry (NSCR) to follow-up 20 686 women with a diagnosis of endometriosis. The study showed an overall relative risk for cancer, as well as an increased risk of breast cancer, ovarian cancer and non-Hodgkin's lymphoma in endometriosis patients. For patients with a history of long-standing ovarian endometriosis, the relative risk of ovarian cancer was further increased (standardized incidence ratio, SIR 4.2). The lifetime risk of ovarian cancer for Swedish women is 1.5% (Statistics from Centre of Epidemiology).

In an epidemiological self-report study, 37 434 post-menopausal women with a history of endometriosis were followed-up for 13 years (Olson *et al*., 2002). No overall increased risk of cancer was found in that study, but the risk for non-Hodgkin's lymphoma was increased. In two case–control studies by Ness *et al*.

(2000, 2002), endometriosis turned out as a risk factor for ovarian cancer. Some studies have shown a protective effect of hysterectomy against ovarian cancer (Green *et al*., 1997; Riman *et al*., 1998; Ness *et al*., 2000).

The primary aim of this study was to investigate the relationship between endometriosis and ovarian cancer in a larger cohort of endometriosis patients, including the cohort previously studied by Brinton *et al*. (1997), with a longer follow-up, i.e. three decades. The secondary aim was to study the risk of other malignancies in women with endometriosis.

Materials and methods

Study cohort

All women who had been discharged from a Swedish hospital and coded with a diagnosis of endometriosis for the first time between 1969 and the end of year 2000 were identified using the NSIR. This register, initiated in 1964, covered 60% of the Swedish population in 1969 and 85% in 1983. Since 1987, the register has close to 100% coverage of patients treated through inpatient care in public hospitals in Sweden, statistics from the Centre of Epidemiology, The Inpatient Register 1964–2000, Swedish National Board of Health and Welfare. The time for hospitalization does not always mean the time for diagnosis, which might have been made previously clinically or by laparoscopic day surgery, not covered by the register.

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 of 67 339 cases were identified with a first hospitalization with a diagnosis coded for endometriosis. There was an incomplete personal registration number in 1152 cases, leaving a total of 66 187 women eligible for follow-up. The cohort previously studied by Brinton *et al*. (1997) was included in the present study.

Follow-up

Cases of cancer were identified through the NSCR, from 1958 through 2000, using the ICD 7. Of the 66 187 women, 1691 (2.6%) had a cancer diagnosis before or at the same time as the first hospitalization with a diagnosis coded for endometriosis and therefore were excluded from the statistical calculations. Four cases had to be excluded because of incomplete date of diagnosis, leaving a total of 64 492 women entering the study cohort.

There were 3622 incident cases of cancer recorded (5.6%), and 264 of the women had more than one type of cancer during the follow-up time. To account for cancers prevalent already at the first hospitalization with a diagnosis coded for endometriosis, the start of follow-up was defined as 1 year after that event and continued until the woman died, emigrated or until the end of year 2000. Within the first year of follow-up, 273 of the 3622 cases of cancer (7.5%) were diagnosed, and 14 of these excluded cases were ovarian cancers. Thus, altogether 1968 cases with endometriosis and cancer (37%) were excluded from the statistical calculations.

Data on surgical procedures were collected from the NSIR. When calculating time-at-risk regarding ovarian cancer, cervical cancer and uterine cancer, women were censored at supravaginal or total hysterectomy (uterine cancer), total hysterectomy (cervical cancer) or when both ovaries had been removed (ovarian cancer). In all, 26 334 (40.8%) of the women in the cohort had a hysterectomy before or at the same time as the diagnosis coded for endometriosis, thereby being excluded from the cohort regarding uterine cancer; 22 633 (35.1%) of the women in the cohort had both ovaries removed before or at the same time as the diagnosis coded for endometriosis and were thereby excluded from the cohort regarding ovarian cancer. Women who had one ovary removed before, at the same time or after the diagnosis coded for endometriosis were included in the follow-up. Women who had undergone a total but not a supravaginal hysterectomy were censored from follow-up at that point in time, when calculating the risk for cervical cancer.

To validate the NSIR data regarding the type of surgery performed, randomly selected medical records from 42 of the 326 patients in the cohort treated at Huddinge University Hospital were scrutinized. These records revealed a 100% accuracy regarding the coding of the type of surgery performed in the NSIR.

We also wanted to investigate how many of the patients had their endometriosis diagnosis confirmed with a histological verification. From the same cohort as mentioned above, we randomly selected 47 of 326 patients and were able to retrieve a pathology report describing endometriosis in 38 of these cases (81%). This indicates that a large portion of the patients had their endometriosis diagnosis confirmed histologically. There is no reason to assume that the frequency of histologic verification differs significantly between hospitals in Sweden.

Statistical analysis

SIR 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 to the expected number of cases in the cohort according to the cancer incidence in the female Swedish population by calendar year and 5-year age class (Breslow and Day, 1987).

Results

The total number of person years was 766 556. The average time of follow-up was 12.7 years. The average age at the first hospitalization with a diagnosis coded for endometriosis was 39.4 years (SD ±10.4 years) for the whole study period. Between 1994 and 2000, the average age was 42.1 (SD ±11.7, $P < 0.001$). The average age at cancer diagnosis was 55.1 years (SD ±10.2 years). A total of 3349 cancer cases were included in the cohort (Table I).

There was no significantly increased overall risk of cancer (SIR 1.04, 95% CI 1.00–1.07). However, there was an increased risk of ovarian cancer (SIR 1.43, 95% CI 1.19–1.71) and of non-Hodgkin's lymphoma (SIR 1.24, 95% CI 1.02–1.49). Two other types of cancer were identified with a higher relative risk for endometriosis patients than for the general population, namely brain tumours (SIR 1.22 95% CI 1.04–1.41) and endocrine types of cancer (i.e. cancer of the adrenal glands, thyroid gland, parathyroid glands, pituitary gland, insulinoma of the pancreas and malignant tumours in other endocrine glands, SIR 1.36, 95% CI 1.15–1.61). Women who were hospitalized for the first time with a diagnosis coded for endometriosis between the ages of 50 and 60 had an increased risk of breast cancer (SIR 1.28, 95% CI 1.13–1.45; Table II). There was no increased risk of cancer of the uterus and there was a reduced risk of cervical cancer (SIR 0.64, 95% CI 0.47–0.84) and cancer *in situ* of the cervix (SIR 0.89, 95% CI 0.82–0.97; Table I).

When we divided the women into groups according to the location of the endometriosis, we found that women with a diagnosis coded for ovarian endometriosis (25 430 women, 39.4%) had an increased risk of ovarian cancer (SIR 1.77, 95% CI 1.38–2.24), while women with a diagnosis coded for adenomyosis (i.e. ectopic endometrium within the myometrium) had a non-significantly reduced risk of ovarian cancer (SIR 0.62,

Table I. Number of cases, standardized incidence ratios and 95% confidence intervals for cancer after a diagnosis of endometriosis

Cancer type or site (ICD 7 code)	Number of person years	Observed number	Expected number	Ratio of observed to expected	95% confidence interval
All cancers (140–207)	766 556	3349	3234	1.04	1.00–1.07
Buccal cavity and pharynx (140–148)	766 322	51	45.05	1.13	0.84–1.49
Gastric (151)	766 428	54	59.30	0.91	0.68–1.19
Small intestine (152)	766 460	15	14.28	1.06	0.59–1.74
Large intestine (153)	765 603	188	197.0	0.95	0.82–1.10
Rectal (154)	766 057	118	112.8	1.05	0.87–1.25
Primary liver (1550)	766 516	23	19.00	1.21	0.77–1.82
Pancreatic (157)	766 498	81	67.43	1.20	0.95–1.49
Lung (162)	766 252	181	191.9	0.94	0.81–1.09
Breast (170)	758 433	1288	1244	1.04	0.98–1.09
Cervical (171)	528 441	51	80.18	0.64	0.47–0.84
CIS of the cervix[b]	508 447	523	584.5	0.89	0.82–097
Endometrial (172)	427 114	92	77.37	1.19	0.96–1.46
Uterine not otherwise specified (174)	427 220	11	10.33	1.06	0.53–1.90
Ovarian (1750)	444 931	122	85.09	1.43	1.19–1.71
Fallopian tube (1751, 1758, 1759)	766 498	10	8.32	1.20	0.58–2.21
Other female genital (176)	766 409	25	24.72	1.01	0.65–1.49
Kidney (180)	766 136	85	72.62	1.17	0.93–1.45
Bladder (181)	766 217	64	67.04	0.95	0.74–1.22
Melanoma (190)	765 181	186	160.9	1.16	1.00–1.33
Non-melanoma skin cancer (191)	766 119	75	71.71	1.05	0.82–1.31
Brain (193)	765 567	173	142.3	1.22	1.04–1.41
Thyroid (194)	766 060	55	46.96	1.17	0.88–1.52
Endocrine (195)	765 293	136	99.65	1.36	1.15–1.61
Connective tissue (197)	766 403	28	22.31	1.26	0.83–1.81
All haematopoetic (200–207)	765 628	214	190.0	1.12	0.98–1.28
Hodgkin's disease (201)	766 461	13	11.05	1.18	0.63–2.01
Non-Hodgkin's lymphoma (200, 202)	766 032	113	90.88	1.24	1.02–1.49
Multiple myeloma (203)	766 395	34	31.89	1.07	0.74–1.49
All leukaemia (204–207)	766 407	54	56.42	0.96	0.72–1.25
Secondary and unspecified sites (199)	766 374	113	219.0	0.52	0.43–0.62

[a]Person years of follow-up with censoring for emigration and death only.
[b]Not included in total above.

95% CI 0.31–1.11). Also women with a diagnosis coded for non-ovarian endometriosis showed an increased risk of ovarian cancer (SIR 1.47, 95% CI 1.05–1.99). Women with a longer history of endometriosis in the ovaries (i.e. up to 10–15 years after the time of diagnosis) had an SIR of ovarian cancer of 2.23 (95% CI 1.36–3.44), but the risk was also high 3–4 years after the hospitalization (SIR 2.64, 95% CI 1.20–5.00; Table III). Women who were hospitalized with a diagnosis coded for endometriosis early in life, between the ages of 20 and 30 and between the ages of 30 and 40, had an SIR of ovarian cancer of 2.01 (95% CI 1.26–3.05) and 1.76 (95% CI 1.32–2.31), respectively, while women with their first hospital admittance with a diagnosis coded for endometriosis later in life (i.e. after the age of 40) did not show an increased risk of ovarian cancer (Table III).

Generally, women who had their ovarian cancer diagnosed after the endometriosis diagnosis had their cancer earlier in life than the general population. There was a significantly increased incidence of ovarian cancer at ages 35–49 in the endometriosis group, compared to the general female Swedish population (Figure 1).

Women who had had a hysterectomy before or at the same time as the first admittance with a diagnosis coded for endometriosis had an SIR of 1.05 (95% CI 0.63–1.64) for ovarian cancer as

Table II. Standardized incidence ratios (SIR) for breast cancer by age at time of endometriosis diagnosis

Age	Person years	Observed cases	SIR	95% confidence interval
40–50	27938	610	1.00	0.92–1.08
50–60	74831	250	1.28	1.13–1.45
60–70	7619	28	1.23	0.82–1.78

Table III. Standardized incidence ratios (SIR) for ovarian cancer after the diagnosis of endometriosis (A), by age at time of endometriosis diagnosis (B) and by age at time of endometriosis diagnosis in women with ovarian endometriosis only (C)

(A) Years of follow-up	Person years	Observed cases	SIR	95% confidence interval
1–2	29 786.82	4	1.25	0.34–3.20
3–4	27 350.48	9	2.64	1.20–5.00
5–10	57 202.66	18	1.99	1.18–3.14
10–15	41 182.81	20	2.23	1.36–3.44
15–20	26 774.34	10	1.33	0.64–2.45
20–25	14 909.87	8	1.58	0.68–3.10
(B) Age	Person years	Observed cases	SIR	95% confidence interval
0–20	8582	0	0	0.00–10.26
20–30	143081	22	2.01	1.26–3.05
30–40	167155	52	1.76	1.32–2.31
40–50	108681	37	1.02	0.72–1.40
50–60	15000	9	1.32	0.61–2.52
60–70	1520	2	2.47	0.30–8.94
70+	911	0	0	0.00–7.27
(C)				
20–30	67 622	12	2.02	1.04–3.52
30–40	82 897	37	2.36	1.66–3.25

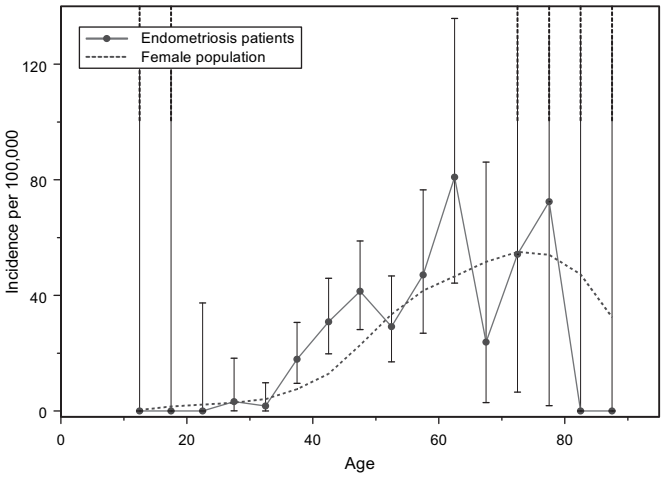

Figure 1. Age specific incidence of ovarian cancer among the endometriosis patients compared to the female Swedish population.

compared with the women who had not had this surgical procedure before or at the same time as the first hospital admittance with a diagnosis coded for endometriosis (SIR 1.54, 95% CI 1.25–1.86).

Discussion

This unique, extensive register study shows a high frequency of malignancies in women with endometriosis (8.0%). The risk was especially significantly increased for ovarian cancer in women with a prior diagnosis of endometriosis, above all when the endometriosis was located to the ovaries. An age/time factor was involved, with the risk being higher when the endometriosis was diagnosed at younger ages and in cases with long-standing endometriosis. Adenomyosis was not related to an increased risk of ovarian cancer, and hysterectomy seemed to have a protective effect.

The strengths of this study, as compared with previous studies, are the large number of women in the cohort, the long follow-up time, the almost complete ascertainment of cases of cancer and the accurate follow-up according to the data on surgical procedures. Confounding factors are the lack of data on parity and the time point for the onset of the endometriosis disease. However, the lack of information about the onset of endometriosis is a general situation, depending on the character of the disease, and a confounding factor in all epidemiological studies on endometriosis. One major factor in this study is the limitation of endometriosis cases to women who have been hospitalized because of endometriosis. The clinical routines have changed through the years, and laparoscopic day surgery has been increasingly common and is nowadays the most common diagnostic technique, leaving more and more of the severe cases for hospitalization. Therefore, it can be assumed that cases included in this study are mainly moderate or severe, although a systematic classification according to Revised American Society for Reproductive Medicine (1997) had not been performed during surgery. There is so far no register available in Sweden that includes cases diagnosed clinically or by invasive techniques like laparoscopic day surgery. The risk of cancer calculated in this study is therefore probably related to the risk in moderate/severe cases. This fact might also explain the high average age at inclusion in the NSIR, which was even higher in the later part of the study period.

A drawback of this material is that a histologic verification has not been secured in all cases. However, many of the cases included in this study cohort had been hospitalized for endometriosis surgery, and a visual diagnosis is normally acceptable when it is obvious (Kennedy *et al*., in press). A specific situation might occur in cases of ovarian endometriomas that are mistaken for luteal cysts and left in place without a biopsy. However, luteal cysts have been shown not to be related to an increased risk of ovarian cancer (Borgfeldt and Andolf, 2004). Thus, again it can be assumed that the cancer risk found in this study is an underestimation.

Another factor that might have an impact on the results is the frequency of hysterectomy. During the early part of the study period, the availability of medical treatment options was very limited. When hormonal treatment alternatives became more extensively used through the decades, the extension of surgical approaches was reduced and hysterectomy became restricted to non-responders and very severe cases. Thus, several factors through the study period might in different ways impact the study results.

The average age at the diagnosis coded for endometriosis in the whole sample was 39.4 years, continuing on the same level from 1969 until 1993 (38.0–38.8 years per 5-year period). However, between 1994 and 2000, the average age had increased to 42.1 years. This change could be due to an increase in the outpatient surgery approach, leaving more severe cases and older patients to inpatient care. There was also a hesitation to perform diagnostic laparoscopies in young women during the first decades. This could be the explanation of why no one in our cohort was diagnosed with endometriosis before the age of 20.

Among patients with an early hysterectomy, 80% had adenomyosis and only 12% had ovarian endometriosis. Thus, the lack of increased risk of ovarian cancer in hysterectomized women could be either due to the fact that patients with adenomyosis do not have an increased risk for ovarian cancer or due to the fact that hysterectomy protects against ovarian cancer.

Other factors with known impact on the risk of ovarian cancer are pregnancy and use of oral contraceptives (OC). Although we did not have data on the patients' fertility in this study, this will certainly be studied further. However, other studies have shown that infertility or decreased fertility is not the only explanation for the increased risk of ovarian cancer in women with endometriosis (Modugno *et al*., 2004). They also showed that although women with endometriosis and ovarian cancer were more likely than controls to use OCs in general, they were no more likely to be long-term users compared to controls. The possibility of hormonal treatment to increase the risk for women with endometriosis to develop ovarian cancer is not known, although an increased risk in women treated with danazol has been proposed, a connection not found for women treated with GnRH agonists (Cottreau *et al*., 2003; Blumenfeld, 2004). Data on hormonal treatment in our study cohort will be carefully explored.

The previous register study (Brinton *et al*., 1997), besides showing an increased risk of breast cancer, also showed an increased risk for endocrine tumours, although only in the group that had a follow-up time of endometriosis for 5–9 years. Although there was no overall increased risk of breast cancer in the present study, women with endometriosis diagnosed later in life did show an increased risk. This raises questions about the hormonal impact in the perimenopause on endometriosis, breast tissue and other endocrine tissues. Interestingly, in the present study, we could not verify an increased risk for breast cancer among patients with adenomyosis.

An interesting finding, like in some other studies (Brinton *et al*., 1997; Olson *et al*., 2002), is the increased risk of non-Hodgkin's lymphoma in patients with endometriosis. This enforces the hypothesis of a defective immune system in women who develop endometriosis and calls for further studies.

Our study also showed an increased risk of brain tumours. This was not shown in the study by Brinton *et al*. (1997). We have for the moment no explanation for this, but a possible impact of pregnancy is now under exploration.

Our study also suggests that women with endometriosis have a decreased risk of cervical cancer. One reason might be more frequent Papanicolauo test in these women with frequent gynaecological exams. However, the risk of Cancer In Situ was also reduced, suggesting that these women in fact have a decreased risk of cervical cancer. When population-based screening for cervical cancer was introduced in Sweden, an increased detection of precancerous stages was observed. This resulted in a decrease of established cases of cervical cancer (Bergström *et al*., 1999). If endometriosis patients have a lower risk of cervical cancer due to more frequent PAP smears, they would be expected to have an increased, rather than decreased risk of CIS/CIN III since the precancerous stages are what the screening method is designed to capture. This finding deserves an explanation.

In the present study, 272 cases of ovarian cancer were diagnosed before or at the same time as the first hospitalization with a diagnosis coded for endometriosis, and 14 ovarian cancer cases were diagnosed within the first year after that occasion. These patients were excluded from follow-up. However, it is important to recognize that endometriosis is an underdiagnosed disease which may result in a delayed diagnosis until surgery for ovarian cancer. The fact that the two diseases were diagnosed at the same time does not exclude the possibility that endometriosis was present before ovarian cancer. Continued research with histological and immunohistochemical studies on material from these patients is underway.

According to the implantation theory, endometriosis is caused by implantation of shed endometrial fragments transported from the uterus through the fallopian tubes. In that respect, the endometrium behaves like tumour cells that can implant into and invade other organs and tissue structures. Ness *et al*. (2000) suggested that the pathogenesis behind ovarian cancer is inflammation. They showed in a case–control study that factors suppressing ovulation and thereby decreasing the need of surface repair of the ovaries (like pregnancy, breastfeeding and the use of OC) decreased the risk of ovarian cancer. Factors increasing the inflammatory response in the ovaries such as the use of talc and having endometriosis increased the risk. Moreover, hysterectomy and tubal ligation decreased the risk. Other studies have also shown a protective effect of hysterectomy and tubal ligation against ovarian cancer, also after adjustment for parity (Green *et al*., 1997; Riman *et al*., 1998). Ness *et al*. (2002) also found an increased risk of ovarian cancer in nulligravidae. These data suggest that retrograde menstruation (in the cases of endometriosis) or other 'irritants' landing on the ovaries cause an inflammatory response that in some cases results in a malignant development. There are indications of a defective local immune response in the pelvic cavity (Koninckx *et al*., 1998; Maeda *et al*., 2002). Other data indicate that the endometrium in women who develop endometriosis differ from normal endometrium in the expression of inflammatory mediators, as well as adhesive and invasive capacity (Bruse *et al*., 1998; Sillem *et al*., 1999; Bergqvist *et al*., 2001; Pizzo *et al*., 2002). Erzen *et al*. (2001) proposed that there is a distinct entity of endometriosis-associated ovarian carcinoma (EAOC) differing from other ovarian carcinomas in several aspects. Patients with EAOC had a lower stage of cancer, a distribution of histological subtypes that differs from the general population (i.e. endometrioid and clear cell cancer being the most common), predominantly lower grade endometriosis lesions, and significantly better overall survival as compared with the group of other ovarian carcinomas. Modesitt *et al*. (2002) found that women with extraovarian cancers arising in endometriosis were more likely to be postmenopausal. The average age at cancer diagnosis for the endometriosis patients was 55.1 years. This is lower than in the general Swedish population, which is 70 years (Centre for Epidemiology, 2000).

In summary, women with endometriosis have an increased risk for some types of malignancies. Women who receive a diagnosis of endometriosis early in life and have endometriosis in their ovaries have the highest risk for ovarian cancer. The increased risk for different forms of malignancies and the lower mean age at diagnosis of the malignancy compared with the general population indicate a basic dysregulation of tumour growth in these women. Further studies are needed to establish the relationship between endometriosis and the development of a malignancy, which will hopefully have an impact on the treatment and follow-up for endometriosis patients at risk in the future.

In conclusion, this study has shown an increased risk of some types of malignancy, above all ovarian cancer, in women with endometriosis. The material indicates that the risk might have been underestimated.

References

Bergqvist A (1992) Extragenital endometriosis. A review. Eur J Surg 158,7–12.

Bergqvist A, Bruse C, Carlberg M and Carlstrom K (2001) Interleukin 1 beta, interleukin-6 and tumor necrosis factor-alpha in endometriotic tissue and in endometrium. Fertil Steril 75,489–495.

Bergström R, Sparén P and Adami H-O (1999) Trends in cancer of the cervix uteri in Sweden following cytological screening. Br J Cancer 81,159–166.

Blumenfeld Z (2004) Hormonal suppressive therapy for endometriosis may not improve patient health. Fertil Steril 81,487–492.

Borgfeldt C and Andolf E (2004) Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis. Acta Obstet Gynecol Scand 83,395–400.

Breslow NE and Day NF (1987) Statistical methods in cancer research. Vol. 2. The design and analysis of cohort studies. International Agency for Research on Cancer, Lyan, France.

Brinton LA, Gridley G, Persson I, Baron J and Bergqvist A (1997) Cancer risk after a hospital discharge diagnosis of endometriosis. Am J Obstet Gynecol 176,572–579.

Bruse C, Bergqvist A, Carlstrom K, Fianu-Jonasson A, Lecander I and Astedt B (1998) Fibrinolytic factors in endometriotic tissue, endometrium, peritoneal fluid, and plasma from women with endometriosis and in endometrium and peritoneal fluid from healthy women. Fertil Steril 70,821–826.

Centre for Epidemiology (2000) *Causes of Death 1997: Official Statistics of Sweden – Health and Disease*, The National Board Health Welfare, Stockholm, Sweden, 3,1–224.

Cottreau CM, Ness RB, Modugno F, Allen GO and Goodman MT (2003) Endometriosis and its treatment with danazol or Lupron in relation to ovarian cancer. Clin Cancer Res 9,5142–5244.

Erzen M and Kovacic J (1998) Relationship between endometriosis and ovarian cancer. Eur J Gynaecol Oncol 19,553–555.

Erzen M, Rakar S, Klancar B and Syrjänen K (2001) Endometriosis-associated ovarian carcinoma (EAOC): an entity distinct from other ovarian carcinomas as suggested by a nested case-control study. Gynecol Oncol 83, 100–108.

Eskenazi B and Warner ML (1997) Epidemiology of endometriosis. Obstet Gynecol Clin North Am 24,235–258.

Green A, Purdie D, Bain C, Siskind V and Russell P (1997) Tubal sterilisation. Hysterectomy and decreased risk of ovarian cancer. Int J Cancer 71, 948–951.

Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R *et al*. ESHRE guidelines for the diagnosis and treatment of endometriosis. Hum Reprod 20, 2698–2704.

Koninckx PR, Kennedy SH and Barlow DH (1998) Endometriotic disease: the role of peritoneal fluid. Hum Reprod Update 4,741–751.

Maeda N, Izumiya C, Oguri H, Kusume T, Yamamoto Y and Fukaya T (2002) Aberrant expression of intercellular adhesion molecule-1 and killer inhibitory receptors induces immune tolerance in women with pelvic endometriosis. Fertil Steril 77,679–683.

Modesitt SC, Tortolero-Luna G, Robinson JB, Gershenson DM and Wolf JK (2002) Ovarian and extraovarian endometriosis-associated cancer. Obstet Gynecol 100,788–795.

Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG and Goodman MT (2004) Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. Am J Obstet Gynecol 191,733–740.

Ness RB, Cramer DW, Goodman MT, Kruger Kjaer S and Mallin K (2002) Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. Am J Epidemiol 155,217–224.

Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M and Schlesselman JJ (2000) Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology 11,111–117.

Nishida M, Watanabe K, Sato N and Ichikawa Y (2000) Malignant transformation of ovarian endometriosis. Gynecol Obstet Invest 50 (Suppl. 1), 18–25.

Ogawa S, Kaku T, Amada S, Kobayashi H, Hirakawa T, Ariyoshi K, Kamura T and Nakano H (2000) Ovarian endometriosis associated with ovarian carcinoma: a clinicopathological and immunohistochemical study. Gynecol Oncol 77,298–304.

Olson JE, Cerhan JR, Janney CA, Anderson KE, Vachon CM and Sellers TA (2002) Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. Cancer 94,1612–1618.

Pizzo A, Salmeri FM, Ardita FV, Sofo V, Tripepi M and Marsico S (2002) Behaviour of cytokine levels in serum and peritoneal fluid of women with endometriosis. Gynecol Obstet Invest 54,82–87.

Revised American Society for Reproductive Medicine Classification of Endometriosis: 1996 (1997) Fertil Steril 67,817–821.

Riman T, Persson I, Nilsson S (1998) Hormonal aspects of epithelial ovarian cancer. Clin Endocrinol (Oxf) 49,695–707.

Sampson J (1925) Endometrial carcinoma of the ovary. Arising in endometrial tissue in that organ. Arch Surg 10,1–72.

Sillem M, Prifti S, Monga B, Arslic T and Runnebaum B (1999) Integrin-mediated adhesion of uterine endometrial cells from endometriosis patients to extracellular matrix proteins is enhanced by tumor necrosis factor alpha (TNF alpha) and interleukin-1 (IL-1). Eur J Obstet Gynecol Reprod Biol 87,123–127.

Statistics from Centre of Epidemiology, The Inpatient Register 1964–2000, Swedish National Board of Health and Welfare.

Stern RC, Dash R, Bentley RC, Snyder MJ, Haney AF and Robboy SJ (2001) Malignancy in endometriosis. Frequency and comparison of ovarian and extraovarian types. Int J Gynecol Pathol 20,133–139.

Yoshikawa H, Jimbo H, Okada S, Matsumoto K, Onda T, Yasugi T and Taketani Y (2000) Prevalence of endometriosis in ovarian cancer. Gynecol Obstet Invest 50 (Suppl. 1),11–17.

Submitted on September 26, 2005; resubmitted on November 17, 2005; accepted on November 25, 2005