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THE RISK OF MALIGNANCY IN WOMEN WITH ENDOMETRIOSIS

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To Calle and our children

Nog finns det mål och mening i vår färd -
men det är vägen, som är mödan värd.

Karin Boye 1927

ABSTRACT

The aim of this thesis was to investigate the association between endometriosis and malignancies also after controlling for parity, to investigate the impact of endometriosis on survival after a malignancy diagnosis and to investigate the association between treatment of endometriosis and ovarian cancer risk.

In a population based cohort study on the association between endometriosis and malignancy, 64 492 women with a first time discharge diagnosis of endometriosis between 1969 and 2000, were included and 3 349 incident cases of a malignancy recorded. The total Swedish female population was used as control group and SIRs were used as estimates of relative risk (paper I). There were statistically significant increased risks for ovarian cancer (SIR 1.43), endocrine tumors (SIR 1.36), non-Hodgkin's lymphoma (SIR 1.24) and brain tumors (SIR 1.22). Endometriosis in the ovaries, younger age at endometriosis diagnosis and long-standing endometriosis were all factors contributing to an even higher risk for ovarian cancer. Women with endometriosis developed ovarian cancer earlier in life than other women and hysterectomy seemed to have a protective effect against ovarian cancer.

The second population based cohort study included 63 630 women with a first time discharge diagnosis of endometriosis between 1969 and 2002 and who also had information on parity and age at first birth from the Multi Generation Register. The aim was to investigate the association between endometriosis and malignancy and control for parity. There were 3 822 incident cases of a malignancy recorded during follow up (paper II). The study showed a statistically significant increased risk of endocrine tumors (SIR 1.38), ovarian cancer (SIR 1.37), kidney cancer (SIR 1.36), thyroid cancer (SIR 1.33), brain tumors (SIR 1.27), malignant melanoma (SIR 1.23) and breast cancer (SIR 1.08). There were no statistical differences in SIRs between nulliparous and parous women in any of the malignancies studied.

The third study was a cohort study on the impact of endometriosis on survival after a malignancy diagnosis. The study included 4 278 women with endometriosis and a malignancy diagnosis (exposed women) and 41 831 women with a malignancy diagnosis only (unexposed women). The results showed a statistically significant improved survival for women with endometriosis for all malignancies combined (HR 0.92), as well as for breast cancer (HR 0.86) and for women diagnosed with ovarian cancer after the age of 54 (HR 0.62). However, there was a worse prognosis after a diagnosis of malignant melanoma for women with endometriosis compared to other women (HR 1.52).

To study the impact of treatment of endometriosis and future ovarian cancer risk, medical records from 220 women with endometriosis and ovarian cancer (cases) and 416 controls were scrutinized (paper IV). The study showed strong reductions in risk for ovarian cancer after one-sided oophorectomy in both the univariate and multivariate analyses (OR 0.42 and OR 0.19, respectively) and when all visible endometriosis had been removed (OR 0.37 and OR 0.30, respectively). The only association between hormonal treatment and ovarian cancer was a borderline significance for months of danocrine use and ovarian cancer risk in the univariate analysis (OR 1.06).

This thesis shows that women with endometriosis have an increased risk of several types of malignancies, above all ovarian cancer. This increased risk is not related to parity. It is indicated that women with endometriosis have a better survival after a malignancy diagnosis than other women, especially for breast and ovarian cancer. However, the prognosis for malignant melanoma is worse for women with endometriosis. One-sided oophorectomy and removal of all visible endometriotic lesions strongly reduce the risk of ovarian cancer and the use of danocrine might be associated with an increased risk of ovarian cancer.

LIST OF PUBLICATIONS

This thesis is based on the following papers:

I. Melin A, Sparén P, Persson I and Bergqvist A.
Endometriosis and the risk of cancer with special emphasis on ovarian cancer.
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II. Melin A, Sparén P and Bergqvist A.
The risk of cancer and the role of parity among women with endometriosis.
Hum Reprod. 2007 22(11):3021-6.

III. Melin A, Lundholm C, Malki N, Sparen P, Swahn M-L and Bergqvist A.
Endometriosis as a prognostic factor for cancer survival.
Submitted

IV. Melin A, Lundholm C, Malki N, Sparen P, Swahn M-L and Bergqvist A.
Hormonal and surgical treatments for endometriosis and risk of ovarian cancer.

CONTENTS

LIST OF ABBREVIATIONS

AAFB	Age at first birth
ASRM	American Society for Reproductive Medicine
BMI	Body Mass Index
CI	Confidence interval
COC	Combined oral contraceptives
EAOC	Endometriosis Associated Ovarian Cancer
ERα	Estrogen Receptor alfa
ERβ	Estrogen Receptor beta
FIGO	International Federation of Gynecology and Obstetrics
GnRH	Gonadotropin Releasing Hormone
HIV	Human immunodeficiency virus
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
ICD	International Classification of Diseases
IL	Interleukin
MGR	Multi Generation Register
MRI	Magnetic Resonance Imaging
NHL	non-Hodgkin lymphomas
no	number
NRN	Swedish National Registration Number
NSAID	Non-steroid anti-inflammatory drugs
NSCR	National Swedish Cancer Register
NSPR	National Swedish Patient Register
Obs.	Observed
OR	Odds ratio
PAP test	Papanicolaou test
RR	Relative risk
SIR	Standardized Incidence Ratio
TENS	Transcutaneous electrical nerve stimulation
TNF	Tumor Necrosis Factor
TNM	Tumor Nodes Metastasis - classification

1 INTRODUCTION

Endometriosis is a chronic, inflammatory, estrogen dependent disease that affects up to 10 % of all women of fertile ages [1]. Its main symptoms are painful menstruations (dysmenorrea), pain during intercourse (dyspareunia) and more or less chronic pain in the lower abdomen and pelvic region. It is also a common cause of infertility.

Endometriosis was first connected with malignancies by Sampson in the 1920's. He described the coexistence of endometriosis and malignant tumors in the same location [2]. Since then many studies have implicated a close relationship between endometriosis and different types of malignancies. The most common location for this coexistence is the ovaries and it has been estimated to occur in 0.7-5.0 % of all cases of ovarian endometriosis [3-6].

Epidemiological studies have indicated endometriosis as a risk factor for malignancies, especially ovarian cancer [7-13].

Endometriosis is present in 25-40 % of infertile women [14]. Nulliparity is a risk factor for malignancies like ovarian cancer, breast cancer and uterine cancer. The connection between endometriosis, parity and cancer risk has not been clarified.

Some limited studies have indicated that endometriosis might be a favorable prognostic factor for ovarian cancer [15-17]. Whether or not this is true also for other types of malignancies is not known.

Women with endometriosis are usually treated with some type of hormonal and surgical treatment during their life time. Combined oral contraceptives have been shown to have a protective effect against ovarian cancer but whether this is true also for women with endometriosis is somewhat unclear since the number of women with endometriosis included in these studies has been quite small [12, 18]. Danocrine, a testosterone derivative used for treatment of endometriosis, has been appointed to potentially increase the risk of ovarian cancer [19]. Little is known about the impact of surgical treatment on later development of ovarian cancer but one study has shown a protective effect when an ovarian cyst was followed by surgery [20].

Since up to 10% of all women in fertile ages have endometriosis, an increased knowledge concerning cancer risk, prognostic factors after a cancer diagnosis and the relationship between treatment of endometriosis and a future risk of malignancy is of great importance, not only to the affected women but also to clinicians treating these women on a daily basis and potentially also for treatment guidelines.

2 BACKGROUND

2.1 ENDOMETRIOSIS

2.1.1 Definition and epidemiology

Endometriosis is defined as a chronic, estrogen dependent, inflammatory disease that affects 5-15 % of all women of fertile ages and is identified in 25-40 % of infertile women [1, 14]. Two to four percent of women with endometriosis are postmenopausal and these cases are usually connected to the use of Hormone Replacement Therapy (HRT) [21] . The incidence of endometriosis has been suggested to be higher in Asian women than in Caucasian women and lowest in African women. However, these studies are not always including factors like socioeconomic status and the availability of healthcare facilities which makes the results uncertain [22, 23]. Studies have shown a 7 times increased risk of endometriosis when a first degree relative has this disease, indicating that genetic factors are important [24].

The disease is defined as the presence of endometrial glands and stroma outside of the uterine cavity, also known as endometriosis externa. Endometrial cells within the muscle wall of the uterus are called adenomyosis or endometriosis interna. Endometriosis can also cause cysts in the ovaries, so called endometriotic cysts or "chocolate cysts".

2.1.2 Pathogenesis

The pathogenesis of endometriosis is not fully understood, but different theories have been presented:

1. The most widely accepted explanation is that the endometrial cells are disseminated into the abdominal cavity by retrograde transport of shed endometrial cells together with blood through the fallopian tubes at time of menstruation. The cells implant on organs and peritoneal structures in the pelvic region. This theory is supported by the fact that endometriosis is extremely unusual in amenorrhoic women. Obstruction of the cervix, leading to increased retrograde menstrual flow increases the risk and tubal ligation decreases the risk [21, 25]. One argument against this theory is the fact that up to 90% of all women have retrograde menstruation but only about 10% develop endometriosis. Obviously some other factor needs to be present as well [21, 26, 27]. Other supports of the implantation theory are the findings of endometriosis in the lungs, pleura and kidneys as well as in other distant places. The theory behind this is that endometriotic cells can spread through lymph and blood vessels and implant distantly [28].
   Iatrogen dissemination of endometrial cells by surgical procedures, i.e. uterotomia and antefixation can lead to endometriosis in surgical scars, a finding also supporting the implantation theory.
2. The other important theory claims that endometriosis develops through the metaplastic transformation of cells lining the pelvic peritoneum, so called coelomic metaplasia. This theory is supported by the fact that both endometrial and peritoneal cells derive from the same embryonal structure (coelomic-wall epithelium) [21]. A closely related theory derives the pathogenesis from the

activation of rests from the Mullerian system. Specifically endometriosis of the recto-vaginal septum has been suggested to have this background [29]. Both these theories can also explain the presence of endometriosis in men. This is however a rare condition and involves only men that have been treated with high doses of estrogen [21].

The pathogenesis of endometriosis is complex and still not completely clear. There are probably several interacting factors needed for the development. A defect immune system has been shown in women with endometriosis, allowing the endometrial fragments to implant on other surfaces. The implantation causes an inflammatory response. Studies have shown that pelvic endometriosis is associated with an activation of macrophages, increased secretion of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-18 and TNF-α), active angiogenesis and impaired function of cell-mediated natural immunity. The natural killer cells in women with endometriosis express for instance a lower cytotoxic activity, which could contribute to a lower ability to identify and destroy displaced endometrial fragments [30-33].

The most common locations are the ovaries, the sacro-uterine ligaments, the fossa Douglasi or the fossa Vesico-uterine, but the cells can also implant on the bladder and the intestines. These implants respond to steroid hormones in a similar way as the uterine endometrial cells and thus bleedings might appear in the lesions monthly at time of menstruation. This also triggers an inflammatory reaction leading to pain and in the long perspective also to adhesions and fibrosis. Endometriosis can expand on the surface as well as more deep into the tissues, for instance in to the recto-vaginal septum. In rare cases endometriosis can grow through the wall of the bladder or bowel, causing haematuria or melena at time of menstruation. Endometriosis can also on rare occasions cause obstruction of the ureter because of infiltrative and extensive growth and/or fibrosis.

2.1.3 Symptoms and diagnostic tools

The main symptoms of endometriosis are dysmenorrea, pain at ovulation, dyspareunia and also an acute or chronic more diffuse pelvic pain. The symptoms may start in adolescence but average age at diagnosis is between 25-29 years [21]. Studies have shown that diagnosis often is delayed on average 7 years from onset of symptoms [34, 35]. Endometriosis can expand more deeply, infiltrating the retroperitoneum and rectovaginal septum. It can also infiltrate the bladder, the bowels or the vaginal wall. This can give rise to blood in the urine and stool at time of menstruation and also visible endometriotic lesions in the vaginal wall.
The diagnosis is made either clinically by the typical history of pain associated with ovulation and menstrual bleedings, deep pain at intercourse or at the gynecological examination revealing painful thickenings of the sacro-uterine ligaments and sometimes visible lesions in the vaginal wall. Vaginal ultrasound examination can reveal endometriotic cysts in the ovaries and adenomyosis in the uterine wall. MRI can be useful in diagnosing deep infiltrating endometriosis as well as adenomyosis. However, the most frequently used diagnostic method for endometriosis is laparoscopy.

This allows treatment at the same time by removing all visible lesions of endometriosis and/or resecting endometriotic cysts from the ovaries.

2.1.4 Treatment

Treatment often starts with **pain killers** like paracetamol and/or NSAID. Sometimes more powerful medications like opioids are needed. Other pain treatments include physiotherapy, acupuncture and TENS.

The aim of **hormonal treatment** is to minimize the estrogen stimulation of the endometriotic lesions and thereby causing atrophy. The treatment induces amenorrhea and can make the woman pain free. Hormonal treatment is often first choice but can also be used in combination with surgical treatment when all of the endometriotic lesions could not be removed and/or to prevent recurrence of the disease after surgery. Four different types of hormonal treatment for endometriosis have been used since the 1960's.

1. *Gestagens* were introduced during the 1960's and are still extensively used. This treatment includes tablets, uterine devices, injections and implants. Gestagens inhibit ovulation and down-regulate the endometrium/endometriotic tissue.

2. *Combined oral contraceptives* (COC) have been used since the 1960's. COCs are often used to treat dysmenorrea in young women whether or not diagnosed with endometriosis. This treatment causes anovulation and down regulation of the endometrium/endometriotic tissue and reduces menstrual bleeding.

3. *Danocrine* (a testosterone derivative) which decreases the levels of gonadtropins and induces a reversible menopausal-like condition, was very popular during the 1980´s and 1990's but the use in Sweden almost disappeared in the late 1990's.

4. *GnRH-agonists* down regulate the ovaries and induce a reversible menopausal-like condition. They were introduced in the late 1980's and increasingly used for a decade until the popularity decreased. However, this treatment remains the drug of choice in severe cases and also in cases where the woman cannot be treated with COC because of elevated risk of thrombosis or gestagens because of severe side-effects. As the hypoestrogenic side-effects can be severe, a low dose of HRT can be added.

The **surgical treatment** for endometriosis has changed over the last decades towards more laparoscopic surgery also in more severe cases. In the 1970's a diagnostic laparoscopy could be performed to confirm the diagnosis of endometriosis but if intervention was needed, for instance a cyst needed to be extirpated; the procedure was often converted into a laparotomy. Since the 1980's more and more of the surgical procedures have been performed laparoscopically and to an increasing degree also performed as day surgery. This has led to shorter stays in hospitals, shorter sick leave and less discomfort [36]. Nowadays severe cases with endometriosis in for instance the rectovaginal septum can be treated with laparoscopically.

The goal for surgical treatment is to relieve pain and improve fertility. Endometriotic lesions are often removed which lowers the inflammatory response in the pelvic region and thereby decreases the patient's discomfort [37-39]. Adhesions, fibrotic tissues and endometriotic cysts can be removed to reduce pain and also improve fertility [6].

Different surgical approaches have been used, for instance punction of endometriotic cysts and aspiration of the content, punction and coagulation of the inside of the cyst wall or complete extirpation of the cyst capsule. Cyst punction and aspiration has no long standing effect. A more persistent effect has been shown after complete extirpation of the cyst compared to after coagulation/vaporization of the cyst wall and this also improves fertility [36, 40]. In severe cases total hysterectomy and/or bilateral oophorectomy is performed to induce amenorrhea and thereby reduce inflammation and relieve pain.

2.1.5 Prognosis and effectiveness of treatment

Endometriosis is considered to be a chronic disease that reoccurs with different intervals in different individuals. Women with endometriosis often go through several types of treatments during their lifetime. The treatment offered may vary greatly depending on health care system, access to private gynaecologists and surgical traditions. The effectiveness of the treatment also have large individually differences. Twenty to 50 % of all women with endometriosis will have new lesions within 5 years after surgery if no prophylactic treatment is given and as many as 50 % will have recurrence 12- 24 months after a 6-month period of hormonal treatment [41].

2.1.6 Endometriosis and infertility

Endometriosis is a common cause of infertility. It is found in 25-40% of infertile women [14, 42]. Several causal factors have been proposed; adhesions, ovulatory dysfunction, defect fertilization or implantation, embryotoxicity and fagocytosis of the sperm cells [43, 44].
Studies have indicated that fertility can be improved after surgical intervention of minimal to mild endometriosis and also after removing endometriotic cysts larger than 4 cm [36, 40, 45, 46].

2.2 ENDOMETRIOSIS AND MALIGNANCY

Sampson was the first to publish data on the coexistence of endometriosis and cancer t in the same ovary [2]. He stipulated three criteria in order to identify a cancer arising within an endometriotic lesion; 1) The coexistence of carcinoma and endometriosis in the same ovary; 2) The presence of tissue resembling endometrial stroma surrounding characteristic epithelial glands; and 3) The exclusion of a second malignant tumor metastatic to the ovary. In the 1950's, Scott added the criteria that there should be possible to demonstrate benign endometriosis being continuous with the malignant tissue [47]. Since then several case reports, as well as clinical, histological and epidemiological studies have shown an association between different types of malignancies and endometriosis [1, 3, 4, 6-11, 13, 21, 25, 48-53]. The ovaries are the most common location for the coexistence of endometriosis and cancer and this has been estimated to occur in 0.7-5.0 % of all cases with ovarian endometriosis [3-6].

2.2.1 Epidemiology

Numerous studies have been published showing an increased risk for several types of malignancies in women with endometriosis (table 1). The RR for ovarian cancer ranges between 1.2 and 8.95 in different studies [7, 8, 10-13].

A population based cohort study from Sweden, including 20 686 women with endometriosis, showed an elevated risk of 1.9 for ovarian cancer and the risk increased to 4.2 if the endometriosis had been diagnosed for ten or more years [7]. A study including 1 392 postmenopausal women with self-reported endometriosis, could not verify an increased risk of ovarian cancer [48]. A case control study of 28 163 endometriotic women, showed an elevated risk of 1.34 for ovarian cancer [11]. A Japanese study where women with endometriotic cysts diagnosed with ultrasound were followed for an average of 12.8 years showed an increased risk for ovarian cancer of 8.95 and even higher if the endometriotic cyst was diagnosed after the age of 50 [13].

There has also been suggested that women with endometriosis are diagnosed with a different type of ovarian cancer than other women. This is called Endometriosis-associated ovarian carcinoma (EAOC) and was explored in a case control study including 58 women with EAOC and 232 controls with ovarian cancer but no endometriosis. The women with EAOC had lower stage of the tumor, less residual tumor after surgery, different distribution of histological subtypes (more endometrioid and clear-cell carcinomas) and better survival [15].

Other types of malignancies shown to be associated with endometriosis are colon cancer, malignant melanoma, breast cancer, thyroid cancer and non-Hodgkin's lymphoma [9, 48, 52, 53]. A case-cohort study from Denmark showed an increased risk of breast cancer in women who were diagnosed with endometriosis after the age of 50, but a lower risk of breast cancer if the woman was young at the time of endometriosis diagnosis [52]. Malignant melanoma has been shown to be associated with endometriosis. One study showed an increased prevalence of dysplastic naevi in endometriotic women as well as an increased risk of having relatives with malignant melanoma[53]. An association, however not statistically significant, between malignant melanoma and endometriosis has been shown in a group of infertile women [9].

Table 1. Studies on risk of malignancy in women with endometriosis.

Author	Study design	Number of women included with endometriosis	Mean (or median*) follow up (years)	Number of cancer cases	SIR/OR
Brinton et al 1997	Cohort	20 686	11.4	738 (29 ovarian cancer)	Overall cancer risk : 1.2 Breast cancer: 1.3 Ovarian cancer: 1.9 Long-standing history of endometriosis ovarian cancer risk: 4.2 Non-Hodgkin's lymphoma: 1.8
Ness et al 2000	Case control	151		66	Ovarian cancer: 1.7
Ness et al 2002	Pooled case control	90		51	Ovarian cancer : 1.73 in women with infertility
Olsen et al 2002	Cohort	1 392		15 NHL 3 ovarian cancer	Non-Hodgkin's lymphoma : 1.7
Borgfeldt et al 2004	Nested case control	28 163		81	Ovarian cancer: 1.34
Brinton et al 2004	Cohort	1 919	18.8 *	13	Ovarian cancer : 2.48 and 4.19 in women with primary infertility
Modugno et al 2004	Case control			177	Ovarian cancer : 1.3
Kobayashi et al 2007	Cohort	6 398	12.8	46	Ovarian cancer: 8.95
Bertelsen et al 2007	Case cohort	1 978	17.8	236	Breast cancer: 2.21 in women diagnosed with endometriosis ≥50 years of age

2.2.2 Histopathological and molecular indications of a connection between endometriosis and malignancies

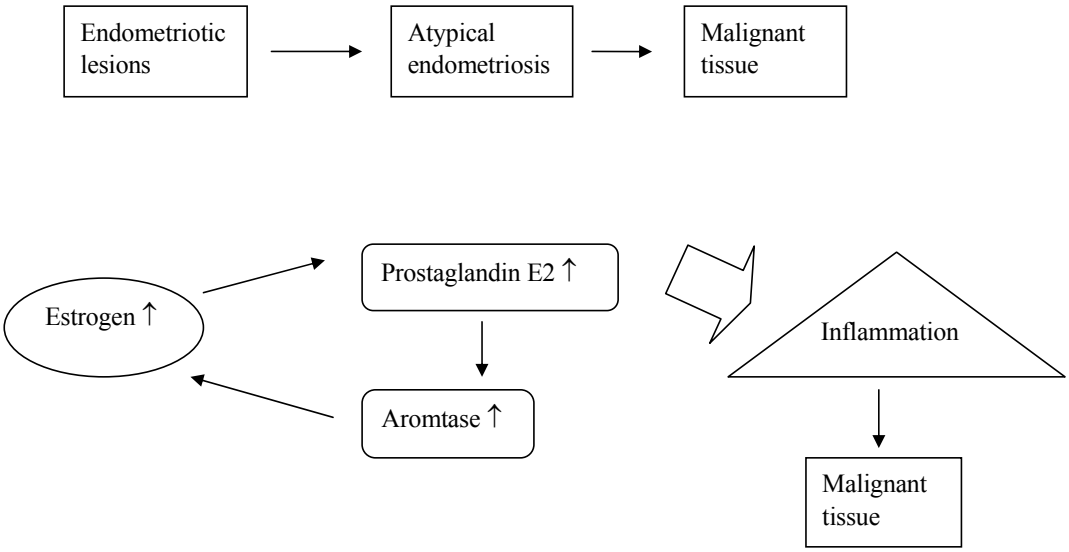
Endometriosis is not considered a malignant disease but it shares many similarities with a malignancy, i.e. atypia, adherence, invasion and metastases [54]. Atypical endometriosis has been observed in 12-35 % of ovarian endometriosis and atypical endometriosis has been shown to occur in 60-80% of endometriosis-associated ovarian cancer [4, 54]. Around 60 % of the ovarian cancers associated with endometriosis occur with the cancer adjacent to or directly in the endometriotic tissue [3, 55]. It has been estimated that malignant transformation of ovarian endometriosis occurs in 0.7-5.0 % [3-6].

Inflammation has been proposed as a cause of malignant development in women with endometriosis. Inflammation causes cell damage and increased levels of cytokines and prostaglandins. Hysterectomy and tubal ligation has been proven to decrease the risk of ovarian cancer, probably by preventing inflammatory agents to be transported through the tubes and into the abdomen, i.e. retrograde menstruation [56]. Ovulation causes a disruption of the ovarian epithelium and results in an inflammatory activity and a need for wound repair. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer was evaluated in a population based case-control study [10]. This study showed that factors that suppress ovulation (and thereby decreases inflammation), for instance the use of COC, pregnancies and breast feeding also reduce the risk of ovarian cancer. These factors, especially long time use of COC, have also been shown to be associated with a decreased ovarian cancer risk also in women with endometriosis [12].

Inflammatory mediators (e.g. IL-1, IL-8, IL-6, TNF-α and TNF-β) are involved in endometriosis as well as ovarian cancer development. There are elevated levels of estradiol in endometriotic lesions, caused by the over expression of P450-aromatase and further increasing the level of prostaglandin E2, a known factor to increase inflammation as well as being involved in ovarian cancer development. Resistance to apoptosis, a pathological angiogenesis and the ability to invade through the basement membranes are all factors shared by endometriosis and malignancies. All this and the up-regulation or dysregulation of growth factors (e.g. IGF-1) associated with increased levels of estrogen, are all promoting the microenvironment around ovarian endometriosis to possibly transform into a malignancy [25, 44, 54].

In summary, there are at least two possible ways for endometriosis to be directly connected to malignancies, either through a transformation from benign endometriotic lesions, to more atypical cells and then malignant cells, or by endometriosis causing an inflammatory environment by increased levels of estrogen, cytokines, growth factors and prostaglandin E2 that works together to induce tumor growth (figure 1).

Figure 1. Two alternative ways for endometriosis to influence malignant development.



2.2.3 Malignancies related to reproductive factors

2.2.3.1 Ovarian cancer

Endometriosis and ovarian cancer both share risk factors like early menarche and late menopause. Endometriosis is a well known cause for infertility and nulliparity is a risk factor for ovarian cancer. Hyperestrogenism, for instance by obesity or by taking unopposed estrogen, has also been shown to be a risk factor for cancer in women with endometriosis [57-60]. Protective factors like COC, tubal ligation, hysterectomy and pregnancy are also shared by these two diseases [25, 58, 59]. One study have implicated an increased risk of ovarian cancer after the use of danocrine, a testosterone derivative used as treatment of endometriosis [19].

2.2.3.2 Breast cancer

Reproductive risk factors for developing breast cancer include for instance early menarche, late menopause, nulliparity and age at first birth. Hormone replacement therapy (HRT) and obesity has also been shown to increase breast cancer risk [61-63] . The use of COC has been indicated to increase the risk of breast cancer but the results are not conclusive [64-67]. There is evidence to support the theory that it is the estrogen produced within breast adipose tissue in postmenopausal women that makes malignant transformation possible. Aromatase catalyzes the estrogen formation and inflammatory agents like prostaglandin E2 stimulate the expression of aromatase [63]. This is the same way for malignant development as that proposed for endometriosis and ovarian cancer and could therefore offer an explanation for the increased risk of breast cancer in endometriotic women.

2.2.3.3 Malignant melanoma

Reproductive hormones seem to be involved in the development of malignant melanoma [9, 68]. A higher incidence of melanoma in premenopausal women compared to men, the rare occurrence of melanoma before puberty and pigment changes during pregnancy are examples of indications that reproductive hormones might be a contributing factor to the development of malignant melanoma. One study showed an association between endometriosis and dysplastic naevi as well as an increased family history of malignant melanoma among endometriosis patients [53]. In a self-reporting case-control study on reproductive risk factors for malignant melanoma the results showed an increased risk for melanoma with increasing number of births (OR 3.3 for ≥3 births) but no increased risk if COC or HRT had been used [68]. A larger case-control study showed the opposite with lower risk in parous women compared to nulliparous women. The risk reduction was 8% for each additional birth. The age at first birth was an important factor with lower risk in cases with a first birth at younger age [69].

2.2.3.4 Role of estrogen

Estrogen has been linked to several types of malignancies for example ovarian cancer, breast cancer and malignant melanoma [70]. The effect of estrogen is mediated by two types of estrogen receptors, ERα and ERβ. A decreased expression of ERβ in malignant tissue versus normal tissue in for instance breast cancer, ovarian cancer and malignant melanoma has been shown, indicating a protective effect on tumor growth by ERβ that inhibit an ERα induced hyperproliferation [70-79]. These studies indicate that loss of ERβ is a marker for more invasive tumor growth and poorer prognosis. An increased level of ERβ and a decreased level of ERα in ovarian endometriotic tissue as compared to normal uterine endometrium has been shown [80, 81]. Whether endometriotic tissue in ovaries that develop cancer has an unfavourable balance between ERα and ERβ is not known, but the findings are interesting.

2.2.4 Hereditary factors

There is a well known genetic connection between breast and ovarian cancer by the identified genes BRCA-1 and BRCA-2. Whether or not these genes are connected to endometriosis is not known. Women with endometriosis have an increased risk to have first degree relatives with endometriosis as well as breast cancer, ovarian cancer, colon cancer and malignant melanoma [24, 53, 82, 83]. This could be an indirect indication of a shared genetic predisposition for endometriosis and cancer.

2.3 ENDOMETRIOSIS AND SURVIVAL AFTER A DIAGNOSIS OF A MALIGNANCY

Endometriosis might have an impact on the prognosis of ovarian cancer, at least in cases of clear cell carcinoma [15-17] (Table 2). The studies published include only a small number of endometriotic women and whether or not endometriosis has an impact on the survival in other types of malignancies is not known.

Table 2. Studies on endometriosis as a prognostic factor for ovarian cancer survival.

Author	Study design	Number of women with endometriosis/total number of women	Number of events	Results
Komiyama et al 1993	Case series	20/53	?	Better 5-year survival in women with endometriosis and stage 1 tumor
Erzen et al 2001	Nested case control	58/290	11	OR 2.89 for better survival in women with endometriosis
Orezzoli et al 2008	Cohort	41/84	14	Better median survival in women with endometriosis

2.3.1 Prognostic factors in malignancy survival

2.3.1.1 Ovarian cancer

A case control study on women with endometriosis and ovarian cancer showed a more favorable prognosis in women with endometriosis compared to the controls. The women with endometriosis had a lower stage of the tumor, lower tumor grade and a different distribution of histological subtypes which could have contributed to the better prognosis. They were also on average younger at time of ovarian cancer diagnosis which could be a positive prognostic factor [15].

Reproductive and hormonal factors like parity, use of COC, and tubal ligation or hysterectomy have not been shown as significant factors for better survival of ovarian cancer. However, breastfeeding has a significant protective effect according to a population-based cohort study of 676 Australian women, diagnosed with invasive epithelial ovarian cancer [84]. Number of lifetime ovulations and age at menarche have been shown to be associated with ovarian cancer survival in the way that the more lifetime ovulations, the poorer the prognosis [85, 86]. The use of HRT prior to diagnosis of serous ovarian carcinoma has been associated with significantly higher survival [85, 87].

2.3.1.2 Malignant melanoma

Studies have shown women to have an advantage in survival in malignant melanoma over men. However, no clear relationship between exogenous or endogenous hormones or parity and risk for melanoma have been clearly demonstrated [88]. Estrogens inhibit

invasion of malignant melanoma but, interestingly, dehydroepiandrosterone (DHEA) seems to enhance invasion [89]. However, whether or not the usage of danocrine as a treatment for endometriosis enhances invasion of malignant melanoma and thereby influences the prognosis of survival is not known.

2.4 TREATMENT OF ENDOMETRIOSIS AND OVARIAN CANCER RISK

2.4.1 Hormonal treatments

Hormonal treatment of endometriosis is common. The purpose is to minimize the estrogen stimulation of the endometriotic lesions. The treatment makes the woman amenorrhoic and reduces the endometriotic tissue and thereby the symptoms can be relieved. Gestagens, COC, danocrine (a testosterone derivative) and GnRH-agonists are the four cornerstones of hormonal treatment for endometriosis; however danocrine has not been used in Sweden for the last decade.

So far no studies have indicated that gestagens promote the development of ovarian cancer. Several studies have shown that birth control pills protect against ovarian cancer, however these studies have only included a small number of women with endometriosis [12, 18]. One study suggests that danocrine might increase the risk of ovarian cancer, but no elevated risk was associated with the use of GnRH-agonists [19].

HRT is not a treatment for endometriosis but is used by many women independent of a history of endometriosis and is a risk factor for ovarian cancer [90-92]. Hyperestrogenism, either in the role of unopposed estrogen treatment or as obesity, has also been shown to be a risk factor for cancer development in women with endometriosis [90].

2.4.2 Surgical treatments

Surgical treatment of endometriosis is common. The purpose is to reduce the pain and discomfort as well as improving fertility by removing the endometriotic lesions. Little is known about the impact of different surgical methods on later cancer development.

Studies have shown that hysterectomy and tubal ligation have a protective effect against ovarian cancer [10, 91, 93, 94]. One study has shown a protective effect against ovarian cancer if a diagnosis of an ovarian cyst was followed by surgical treatment [20].

2.5 CANCER EPIDEMIOLOGY IN SWEDEN

The incidence of malignancies has increased slowly since the 1970's and about 23 000 women are diagnosed with a malignancy each year in Sweden. This correlates to an incidence of 510 /100 000 women. The five most common types of malignancies in Swedish women are breast cancer, colon cancer, lung cancer, endometrial cancer and skin cancer (not including malignant melanoma). Malignant melanoma, rectal cancer and ovarian cancer follow as the most common cancers. About 30% of all cases of malignancies in Swedish women are breast cancer and this fact is shared by many countries in the industrialized part of the world [95].

2.5.1 Ovarian cancer

2.5.1.1 Epidemiology and risk factors

Ovarian cancer is the eighth most common cancer in Swedish women. Sweden has one of the highest incidences of ovarian cancer in the world. However, in the last 20 years the incidence has declined. Each year, about 800 women are diagnosed with this disease with the highest incidence in women 65-70 years of age. The life time risk of

ovarian cancer in Swedish women is 1.5 % [95]. Due to lack of reliable screening methods and because the tumour grows silently in the beginning, most women are diagnosed in a later stage of the disease and consequently five year survival is only 44 % [95].
Risk factors for ovarian cancer include hereditary factors, nulliparity and increased number of ovulations. Protective factors include giving birth and the usage of COC.

2.5.1.2 Pathogenesis and classification

Ovarian cancer can be divided into three groups; epithelial tumors, non epithelial tumors and metastases from other malignancies. Eighty to 90 % of all ovarian cancers are epithelial tumors. These tumors develop from the surface epithelium. This epithelium shares the same origin as the endometrial and peritoneal cells and is derived from the coelomic-wall epithelium.
The epithelial tumors are classified into benign, borderline and malignant tumors and also into 6 histological subtypes according to the FIGO-classification of gynaecological cancers. The histological subtypes are: serous, mucinous, endometrioid, clear-cell, mixed and unclassified tumors.
The non epithelial tumors are germcells tumors (i.e. dysgerminoma, choriocarcinoma and teratoma), stromacells tumors (i.e. granulosacells tumors, tekoma and androbalstoma) and so called lipid cells tumors (i.e. luteoma and Leydig cells tumors).

2.5.2 Other types of malignancies

2.5.2.1 Breast cancer

Breast cancer is the most common type of malignancy in Swedish women. About 6 900 women are diagnosed with this disease each year. The incidence has increased since the 1970's. One theory behind this increase is the screening program introduced in the 1980's that detects more cases at an earlier stage. The 5-year survival is 86% [95].
Reproductive hormones play an important role in breast cancer. Risk factors for breast cancer include hereditary factors, early menarche and late menopause [96]. Use of HRT and obesity are also risk factors for breast cancer [61, 62]. Earlier age at first birth and increasing parity are factors that are protective against breast cancer [96].

2.5.2.2 Malignant melanoma

The incidence of malignant melanoma has increased drastically since the 1970's. One reason for this is more exposure to ultraviolet radiation through increased travelling to warmer countries and the use of tanning beds.
About 900 women are diagnosed with this disease each year and the 5-year survival is 91% [95]. Indications to support the theory that this disease is steroid hormone dependent include worse prognosis in men compared to premenopausal women, no cases of malignant melanoma before puberty and pigment changes during pregnancy [9, 68]. However, the more exact relationship between exogenous or endogenous hormones or parity and risk for melanoma is not clear [88].

2.5.2.3 Non-Hodgkin's lymphoma

About 650 women are diagnosed with non-Hodgkin's lymphoma (NHL) each year. The incidence increased during the 1970's until the 1990's but has then stabilized. The

increase in incidence was more pronounced in men than in women. The 5-year survival is 54 % [95]. NHL is more common in Europe and North America and is rare in Asia and West Africa. Risk factors for NHL are mostly unknown. Immunosuppressive conditions, like HIV-infection or chemotherapy treatments increase the risk of NHL. Whether or not reproductive factors influence the risk of NHL is not known [95].

3 AIMS

The overall objective of this thesis was to investigate the association between endometriosis and malignancy, to study cancer-survival in women with endometriosis and the impact of medical and surgical treatment of endometriosis on ovarian cancer development.

The specific aims were

1. To investigate whether women with endometriosis have an increased risk of malignancy as compared to the general Swedish female population. (Paper I)

2. To investigate whether parity influences the risk of malignancy in women with endometriosis. (Paper II)

3. To investigate whether a previously diagnosed endometriosis has an impact on the woman's survival after a diagnosis of a malignancy. (Paper III)

4. To investigate whether hormonal or surgical treatment of endometriosis influence the later risk of ovarian cancer. (Paper IV)

4 SUBJECTS AND METHODS

All four papers in this thesis are epidemiological studies, using the large Swedish population based registers. Linkages between the registers are possible by the 10-digit National Registration Number (NRN) that is unique to each citizen living in Sweden. Regarding women with endometriosis are only those who have been registered for inpatient care with an overnight stay in a public hospital included in the studies.

4.1 POPULATION BASED REGISTERS USED IN PAPER I-IV

4.1.1 The National Swedish Patient Register (NSPR)

This register was initiated in 1964 and initially included data on patients registered for inpatient care in public hospitals. In 1969 the register covered 60% of the Swedish population and in 1983 85%. Since 1987, the register has close to 100% coverage of inpatient care. In 1997 visits to day surgery clinics began to be included in the NSPR and since 2001 out patients' visits are registered, both in public and private practice. Primary care is not included in the NSPR.

Data from this register, including for instance discharge diagnoses, date of discharge, information on surgical procedures and in which hospital the patient was treated, are available for research purposes from the Swedish National Board of Health and Welfare.

The discharge diagnoses in NSPR are coded according to the International Classification of Diseases 8, 9 and 10 (ICD 8–10).
The discharge diagnoses for endometriosis used in all four studies are for ICD 8 the codes 625.30-625.33, 625.38 and 625.39, for ICD 9 the codes 617A-617G and 617X, and for ICD 10 the codes N80.0-N80.9.

4.1.2 The National Swedish Cancer Register (NSCR)

The NSCR was founded in 1958. The purpose was to create a national, population based register of malignancies to enable clinical and epidemiological research as well as to keep track of changes in prevalence and incidence of malignancies over time. This register is kept at the Swedish National Board of Health and Welfare, which also initially managed all the registration. However, since the 1980's six regional oncologic centres take care of coding and registration from the hospitals and once a year send their information to the Swedish National Board of Health and Welfare to be included in the NSCR. The register contains for instance information on sex, age at diagnosis, type of malignancy, date of diagnosis and which hospital and clinic that made the diagnosis, tumor location and TNM classification. The codes used for malignant diseases are according to the International Classification of Diseases 7-10 (ICD7-10). All codes are translated into ICD 7 in the NSCR to enable comparisons over time and ICD 7 is the code used for malignancy diagnoses in all four studies in this thesis.

Histological subtypes and stage are included in the NSCR since 2005, also for gynaecological cancers. This information could earlier be retrieved only from some of the regional oncologic centres and for a limited time period.

4.1.3 The Multi Generation Register (MGR)

The MGR comprises all individuals registered in Sweden from 1961, and born since 1932. For each person, the register includes information on parents (also adoptive parents). The register was initiated in 2000 and is part of the Register of the Total Population at Statitics Sweden. The MGR has almost complete coverage of the population since 1968 and is updated each year.
By use of the NRN, familial relationships (father, mother, children and siblings) between individuals in the MGR can be established and information on parity and age at first birth calculated.

4.1.4 The Causes of Death Register (CDR)

The CDR was initiated in its present form in 1961. The register covers 100% of all death events since 1997 and missing information on cause of death is estimated to be around 0.5%. By use of a specific death certificate issued by a physician when a Swedish citizen dies in Sweden or abroad, information on time of death, main cause of death as well as underlying causes, sex and age is collected and registered. Causes of death are coded according to ICD 7-10. The register is updated each year and kept at The National Board of Health and Welfare.

4.1.5 Medical records

Medical records are kept at local archives in hospitals and also in regional archives in each county. The records are stored according to the NRN. After permission from the Regional Ethics Committee, medical records can be retrieved from these archives for research purposes. If the information needed is sensitive to the individual, the Regional Ethics Committee may decide on written consent from the study participants before the records can be handed out.

4.2 PAPER I

4.2.1 Study population and design

By use of the NSPR, we identified 67 339 women with a first time hospitalization with a diagnosis of endometriosis between 1969 and 2000. Women with endometriosis and a malignancy were identified by linkage to the NSCR. A total of 2 847 women were excluded because of incomplete registration in the NSPR, a malignancy diagnosis before or at the same time as the endometriosis diagnosis or because of an incomplete date of diagnosis, thus leaving 64 492 women with endometriosis eligible for follow up. The Swedish cohort studied previously by Brinton et al was largely included in this present study [7].

To account for malignancies prevalent already at the first hospitalization with an endometriosis diagnosis, 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. 3 349 cases with endometriosis and malignancy were included in the analyses.

Since data on surgical procedures were available from the NSPR, we could censor follow up regarding ovarian cancer, cervical cancer and uterine cancer when a woman had a subtotal or total hysterectomy (uterine cancer), total hysterectomy (cervical cancer) or when both ovaries had been extirpated (ovarian cancer).

4.2.2 Statistical methods

Standardized Incidence Ratios (SIR) and their 95% confidence intervals (CI) were calculated as estimates of relative risk. SIR is defined as the ratio of the observed number of malignancies in the cohort to the expected number of cases in the cohort according to the incidence of malignancy in the female Swedish population by calendar year and 5-year age class.

4.3 PAPER II

4.3.1 Study population and design

This study population included all women in the MGR to enable us to get information on parity and age at first birth.
The study base was created through a linkage between the MGR and the NSPR by use of the NRN. All women included in the MGR, who had been discharged from a Swedish hospital with the diagnosis of endometriosis for the first time during 1969 through 2002 were included and 65 439 women were eligible for follow up.
By linkage to the NSCR we were able to obtain information on malignancy diagnosis for all women included in the study base. Of the 65 349 women in the study base, 1719 were excluded because they had a diagnosis of a malignancy before or at the same time as the first time discharge diagnosis for endometriosis leaving a total number of 63 630 women to enter the study cohort.
The follow-up started one year after the diagnosis of endometriosis and continued until the woman died, emigrated or until the end of year 2002. During follow up were 3 822 incident cases of malignancies registered.

Information on parity and age at first birth were obtained from the MGR. Only live births are included in this register. Twin births were counted as one birth since we were more interested in number of succesful pregnancies than actual number of children. Information on miscarriges are not included in the MGR and information on legal abortions are not available on individual basis in Sweden and was therefore not included in this study.

Information on surgical procedures were collected from the NSPR and censoring women at time of hysterectomy and/or oophorectomy for different types of malignancies was done in the same way as in paper I.

4.3.2 Statistical methods

To create population comparison, yearly specific cancer incidence rates were calculated by age, parity and age at first birth for the Swedish population, by linkage between the MGR and the NSCR. SIR, stratified by parity and AAFB, and their 95% confidence intervals were calculated as estimates of relative risk. P-values for homogeneity between nulliparous and parous women were calculated, assuming a Poisson distribution of number of cases. For ovarian cancer a trend test over parity

was performed utilizing a Poisson regression model, as well as for trends over calendar time, controlling for time of follow-up.

4.4 PAPER III

4.4.1 Study population and design

This study population constituted all Swedish women with a malignancy diagnosis between 1969 and 2005.To create the study cohort, cancer cases from the NSCR were linked with data from the NSPR identifying those women who had been discharged from a hospital with a first time diagnosis of endometriosis between 1969 and 2005 and later had a first diagnosis of one out of 18 different types of malignancies, in total 4 309 women. Only women who had their malignancy diagnosed 30 days or more after their endometriosis diagnosis were included. For each of these 4 309 women, we randomly selected up to a maximum of 10 other women from our study population that did not have a hospital discharge diagnosis of endometriosis in the NSPR. The unexposed women were matched for year of birth (± 2 years) and living in the same county as the corresponding exposed woman at the time of her hospital discharge diagnosis of endometriosis. They had to have been diagnosed with the same type of malignancy with the date of the diagnosis of the malignancy at least 30 days after the corresponding exposed woman's date of endometriosis diagnosis.

Twenty exposed women were excluded because no matching unexposed women could be found. Another 105 women, 94 unexposed and 11 exposed, were excluded because date of the diagnosis of a malignancy and date of death were the same.
In the end, 4 278 exposed women and 41 831 unexposed women constituted our study cohort, with 1-10 unexposed women matched to each exposed woman.

Data on parity were collected from the MGR and data on cause and time of death were collected from the CDR.
Each woman was followed from the date of the diagnosis of the malignancy until she died, emigrated or until the end of year 2005.

We were able to retrieve information on stage and histological subtype from three regional oncologic centres for a subgroup of 218 women with ovarian cancer, 64 exposed and 154 unexposed. Stage and histological subtypes were classified according to the FIGO-classification of gynaecological cancers [97].

4.4.2 Statistical methods

Cox regression models were used for all analyses to obtain crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI). Cause specific mortality rates were used in the analyses only counting events where the person died from the same type of malignancy that was diagnosed at the inclusion of the study.
The analyses were adjusted for age at diagnosis of the malignancy, parity and calendar time at malignancy diagnosis and stratified on matching strata to account for the study design. For malignant melanoma we performed the analyses adjusted for location and for ovarian cancer we made separate analyses for stage at cancer diagnosis and histological subtype for the subgroup of women where we had obtained this information.

In order to study if there was a potential effect modification of the association between endometriosis and cancer survival, we tested whether or not there was an interaction between the exposure variable and age at malignancy diagnosis, calendar time at malignancy diagnosis and parity.
For the exposed women only, we also investigated the impact of age at endometriosis diagnosis on survival after a diagnosis of a malignancy as well as the impact of time lapse between endometriosis diagnosis and the malignancy diagnosis on survival.

4.5 PAPER IV

4.5.1 Study population and design

In this nested case control study , we initially identified all women with a discharge diagnosis of endometriosis and at least on year later a diagnosis of ovarian cancer during the period 1969 to 2007 using the NSPR and the NSCR. For each case two randomly selected and age-matched controls were identified with a discharge diagnosis of endometriosis but no diagnosis of ovarian cancer. Medical records for all women were collected from hospitals all over Sweden. In all 220 cases and 416 controls entered the study. Medical records were scrutinized for information on age at endometriosis diagnosis, menopausal status at endometriosis diagnosis, type of surgery performed, whether or not the surgery was radical in respect of removing all visible endometriosis and months use of each hormonal treatment. In order to verify the data collected, medical records from 50 cases and 50 controls were also reviewed by a second person and a kappa-measure was calculated.

Hormonal treatments included were COC, gestagens (including levonorgestrel containing intrauterine devices), danocrine and GnRH-agonists. We also included data on use of HRT since it is an estrogen treatment commonly used also by this group of women. Surgical treatments recorded were hysterectomy, unilateral oophorectomy or salpingo-oophorectomy and sterilization by tubal ligation or bilateral salpingectomy. Location of endometriosis was classified into three groups; ovarian endometriosis, peritoneal endometriosis or adenomyosis. If a woman had ovarian endometriosis and peritoneal endometriosis and/or adenomyosis she was referred to the group ovarian endometriosis only.

We designed a “severity score” in order to evaluate grade of severity of endometriosis and relate this to future cancer risk. This score (maximum 37 points) was obtained by summarizing the points for age at endometriosis diagnosis, symptom severity at diagnosis, number of endometriosis related doctors visits, number of endometriosis related surgical procedures, stage of endometriosis and blood tests indicating inflammatory activity (Appendix 1) [98, 99].

4.5.2 Statistical methods

Conditional logistic regression was used to calculate both crude and adjusted odds ratios and 95 % confidence interval.
Hormonal treatment was considered both as a continuous variable; months of use, and as a categorical variable, categorized as never user, user for 1-6 months and > 6 months of use for danocrine, GnRH-agonists and HRT, and as never user, user for 1-12 months and > 12 months of use for COC and gestagens. Surgical procedures as well as

complete extirpation of the endometriotic tissue were categorized as yes or no. Age at endometriosis diagnosis was treated as continuous variables. A kappa-measure was performed to analyse the agreement between the two investigators that red the medical records.

4.6 ETHICAL CONSIDERATIONS

All four studies included in this thesis have been approved by the Regional Ethics Committee of Karolinska Institutet. In paper IV, all women participating as cases and still alive gave written informed consent before medical records were obtained. According to approval by the Regional Ethics Committee no such consent needed to be obtained from the controls.

5 RESULTS

5.1 WOMEN WITH ENDOMETRIOSIS HAVE AN INCREASED RISK OF SEVERAL TYPES OF MALIGNANCIES (PAPER I)

Our cohort consisted of 64 492 Swedish women who had been hospitalized for the first time with a diagnosis of endometriosis between years 1969 and 2000. After excluding the first year of follow up 3 349 cases of a malignancy were identified within the cohort.
The study showed no increased overall risk of cancer (SIR 1.04, 95 % CI 1.00–1.07) but there were elevated risks for ovarian cancer (SIR 1.43, 95 % CI 1.19–1.71), endocrine tumors (SIR 1.36, 95 % CI 1.15–1.61), non-Hodgkin's lymphoma (SIR 1.24, 95 % CI 1.02–1.49) and brain tumors (SIR 1.22, 95 % CI 1.04–1.41).

5.1.1 Ovarian cancer

The risk of ovarian cancer was 1.43 (95% CI 1.19-1.71). Women with ovarian endometriosis or peritoneal endometriosis had an elevated risk for ovarian cancer (SIR 1.77, 95 % CI 1.38–2.24 and SIR 1.47, 95 % CI 1.05–1.99, respectively), while women with adenomyosis did not show an increased risk of ovarian cancer (SIR 0.62, 95 % CI 0.31-1.11). Sub analysis on age at endometriosis diagnosis showed an even higher risk for women who were diagnosed early in life, i.e. between the ages 20-30 (SIR 2.01 95 % CI 1.26-3.05) and the ages 30-40 (SIR 1.76 95 % CI 1.32-2.31) and also an increased risk for ovarian cancer after long-standing endometriosis, especially if the endometriosis was located in the ovaries (Table 3).

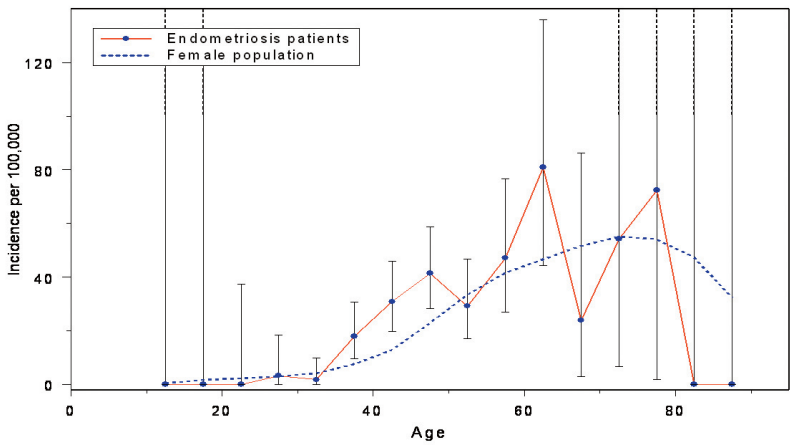
Table 3. SIR for ovarian cancer after the diagnosis of endometriosis (**A**), by age at time of endometriosis diagnosis (**B**) and by age at time of endometriosis diagnosis in women with ovarian endometriosis only (**C**).

A.Years of follow-up	Person years	Observed cases	SIR	95 % CI
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 % CI
0-20	8,582	0	0	0.00-10.26
20-30	143,081	22	2.01	1.26-3.05
30-40	167,155	52	1.76	1.32-2.31
40-50	108,681	37	1.02	0.72-1.40
50-60	15,000	9	1.32	0.61-2.52

60-70	1,520	2	2.47	0.30-8.94
70 +	911	0	0	0.00-7.27
C. Age	Person years	Observed cases	SIR	95 % CI
20-30	67,622	12	2.02	1.04-3.52
30-40	82,897	37	2.36	1.66-3.25

The study also showed that women with endometriosis were diagnosed with ovarian cancer earlier in life than other women. There was a statistically significant higher incidence of ovarian cancer diagnosed between the ages 35-50 in women with endometriosis compared to the general female population (figure 2).

Figure 2 Age specific incidence of ovarian cancer in the endometriosis patients compared to the Swedish female population.



The study showed no statistically significant increased risk for ovarian cancer in women who had had a hysterectomy before or at the same time as the first discharge diagnosis of endometriosis (SIR 1.05, 95 % CI 0.63–1.64), compared to women who had not (SIR 1.54, 95 % CI 1.25–1.86). However, among the patients with an early hysterectomy, 80% were diagnosed with adenomyosis and only 12% with ovarian endometriosis.

5.1.2 Breast cancer

There was also a statistically significant increased risk of breast cancer in women who were diagnosed with endometriosis later in life, that is after the age of 50, SIR= 1.28 (95 %, CI 1.13-1.45) (Table 4).

Table 4. Standardised incidence ratios for breast cancer by age at time of endometriosis diagnosis.

Age at endo-metriosis-diagnosis	Person years	Observed cases	SIR	95% CI
40-50	279 138	610	1.00	0.92-1.08
50-60	74 831	250	1.28	1.13-1.45
60-70	7 619	28	1.23	0.82-1.78

5.1.3 Cervical cancer

The study showed a statistically significant reduced risk for cervical cancer (SIR 0.64, 95% CI 0.47–0.84) in women with endometriosis. There was also a statistically significant reduced risk for cancer *in situ* of the cervix (SIR 0.89, 95% CI 0.82–0.97).

5.2 WOMEN WITH ENDOMETRIOSIS HAVE AN INCREASED RISK OF SEVERAL TYPES OF MALIGNANCIES INDEPENDENT OF PARITY (PAPER II)

This large and extended cohort study including 63 630 women hospitalized with a first time diagnosis of endometriosis between years 1969 and 2002 showed an increased risk of several types of malignancies. 3 822 incident cases of malignancies were identified and the results showed a statistically significant increased risk of endocrine tumors (SIR1.38, 95 % CI 1.17-1.62), ovarian cancer (SIR 1.37, 95 % CI 1.14-1.62), renal cancer (SIR 1.36, 95 % CI 1.11-1.64), thyroid cancer (SIR 1.33, 95 % CI 1.02-1.70), brain tumors (SIR 1.27, 95 % CI 1.09-1.46), malignant melanoma (SIR 1.23, 95 % CI 1.07-1.40) and breast cancer (SIR 1.08, 95 % CI 1.02-1.13). The study also showed a reduced risk for cervical cancer (SIR 0.71, 95 % CI 0.53-0.94). Women with ovarian endometriosis had an even higher risk of ovarian cancer (SIR 1.59, 95 % CI 1.26-1.98) and women with adenomyosis had no increased risk of ovarian cancer (SIR 0.72, 95 % CI 0.37-1.26).

5.2.1 Parity

There was no statistically significant difference in SIRs between nulliparous and parous women (Table 5). The SIRs for brain and thyroid cancer were elevated for parous women but not for nulliparous women. However, the differences were not statistically significant (p= 0.14 and 0.12, respectively). There was a trend with number of births for ovarian cancer; the highest risk expressed for nulliparous women (SIR 1.48, 95% CI 1.11-1.96) and the risk decreased and was no longer significantly increased if the woman had given birth to more than one child. However, this trend was not statistically significant (p= 0.12). For malignant melanoma, the highest risk was found in nulliparous women (SIR 1.47, 95% CI 1.13-1.92).

Table 5. Standardized Incidence Ratios (SIR) with 95% confidence intervals (CI) of malignancy after a diagnosis of endometriosis, for all women, and stratified on nulli-parous and parous women.

Type of cancer (ICD-7 code)	**All women**		**Non-parous women**		**Parous women**		**P-value for homo-geneity**
	Obs. no. of cases	**SIR (95% CI)**	**Obs. no. of cases**	**SIR (95% CI)**	**Obs. 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)	1,465	1.08 (1.02-1.13)	326	1.12 (1.00-1.24)	1,139	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 mealnoma (190)	217	1.23 (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**

5.3 WOMEN WITH ENDOMETRIOSIS HAVE A BETTER PROGNOSIS AFTER A DIAGNOSIS OF A MALIGNANCY (PAPER III)

This large population based cohort study on survival after a malignancy diagnosis included 4 278 women with endometriosis and a malignancy and 41 831 women with a malignancy diagnosis but no endometriosis diagnosis. There was a statistically significant better survival for women with endometriosis for all malignancies combined (HR 0.92, 95 % CI 0.86-0.98), as well as for breast cancer separately (HR 0.86, 95 % CI 0.75-0.97) and for women diagnosed with ovarian cancer after the age of 54 (HR 0.62, 95 % CI 0.44-0.88). Women with endometriosis showed a worse prognosis after a diagnosis of malignant melanoma (HR 1.52, 95 % CI 1.02-2.27).

5.3.1 Age at malignancy diagnosis

There was a statistically significant interaction between endometriosis diagnosis and age at malignancy diagnosis with better survival when the woman was diagnosed with a malignancy after the age of 54. This was shown for all malignancies combined ($p= 0.04$), for pancreatic cancer ($p=0.04$, data not shown) and ovarian cancer ($p=0.03$). It was also a tendency for breast cancer, however not statistically significant ($p=0.06$) (Table 6).

5.3.2 Parity

Women with endometriosis had fewer births compared to other women ($p<0.001$). However, the analyses for all malignancies combined as well as for each type of malignancy, only showed a statistically significant interaction between breast cancer and parity with improved survival for exposed nulliparous women than for women who had given birth ($p=0.03$) (Table 6).

5.3.3 Calendar time for malignancy diagnosis

No statistically significant interactions were found between diagnosis of endometriosis and calendar time for malignancy diagnosis, for any of the malignancies included in this study. However, for malignant melanoma inferior prognosis was found for women with endometriosis diagnosed with malignant melanoma during the 1990's (HR 2.40, 95 % CI 1.33-4.34)(Table 6). However, this interaction was not statistically significant ($p=0.11$).

5.3.4 Stage and histological subtype in cases with ovarian cancer

When stratifying for stage and histological subtype of ovarian cancer, no statistically significant differences in prognosis was found between women with and without endometriosis. However, these analyses were based on a small subgroup of women (Table 7).

Table 6. HR and 95 % confidence intervals (CI) for all malignancies combined, breast cancer, ovarian cancer and malignant melanoma, stratified by age at malignancy diagnosis, parity and calendar time for malignancy diagnosis. In the analyses concerning malignant melanoma we also adjusted for location. #= p-value for the interaction between endometriosis and age at malignancy diagnosis. ## = p-value for the interaction between endometriosis and parity. ### = p-value for the interaction between endometriosis and calendar time for malignant diagnosis.

	Age at malignancy diagnosis. HR and 95 % CI			**Parity HR and 95 % CI**				**Calender time for malignant diagnosis. HR and 95 % CI**			
Type of malignancy	Age 0-54	Age >54	**p-value** #	0 children	1-2 children	3 or more children	**p-value** ##	1969-1989	1990-1999	2000-2005	**p-value ###**
All malignancies	**1.03** 0.92-1.16	**0.87** 0.79-0.96	0.04	**0.88** 0.70-1.12	**0.93** 0.84-1.03	**0.83** 0.70-0.98	0.73	**0.96** 0.81-1.14	**0.91** 0.81-1.02	**0.89** 0.78-1.02	0.86
Breast cancer	**0.99** 0.83-1.18	**0.77** 0.63-0.94	0.06	**0.71** 0.48-1.05	**0.93** 0.77-1.11	**0.87** 0.63-1.20	0.03	**1.02** 0.81-1.30	**0.73** 0.60-0.89	**0.87** 0.60-1.26	0.09
Ovarian cancer	**1.04** 0.77-1.41	**0.62** 0.44-0.88	0.03	**1.05** 0.59-1.87	**0.84** 0.61-1.15	**0.66** 0.37-1.19	0.80	**0.60** 0.33-1.11	**0.86** 0.63-1.18	**0.71** 0.42-1.20	0.76
Malignant melanoma	**1.47** 0.85-2.54	**1.59** 0.86-2.94	0.82	**2.06** 0.85-5.00	**0.95** 0.47-1.89	**1.41** 0.42-4.71	0.38	**0.78** 0.32-1.92	**2.40** 1.33-4.34	**1.04** 0.36-2.97	0.11

Table 7. Stratified analyses on stage and histological subtypes for a subgroup of women with ovarian cancer.
*= too few cases to allow statistical analysis

	Women with endometriosis N=64		**Women without endometriosis N=154**		**HR and 95 % CI**
	Number of women	Number of events	Number of women	Number of events	
Stage at diagnosis (according to FIGO)					
1A-C	32	5	65	5	1.92 (0.55-6.76)
2A-C	7	2	12	6	0.81 (0.16-4.10)
3A-C and 4	25	16	77	51	0.98 (0.56-1.72)
Histological subtypes (according to FIGO)					
Serous	26	12	72	39	0.85 (0.44-1.62)
Mucinous	5	0	13	1	0 *
Endometrioid	18	5	46	16	0.76 (0.28-2.09)
Clear-cell	15	6	18	4	2.48 (0.70-8.82)
Other epithelial ovarian cancer	0	0	5	2	0 *

5.4 ONE-SIDED OOPHORECTOMY AND EXTIRPATION OF ALL VISIBLE ENDOMETRIOSIS REDUCES FUTURE RISK OF OVARIAN CANCER (PAPER IV)

5.4.1 Main findings and surgical treatment

The main findings in this nested case control study on the impact of endometriosis treatment on future ovarian cancer risk were the strong risk reduction for ovarian cancer after one-sided oophorectomy in both the univariate and multivariate analyses (OR 0.42, 95 % CI 0.28-0.62 and OR 0.19, 95 % CI 0.08-0.46, respectively) and when all visible endometriosis had been removed (OR 0.37, 95 % CI 0.25-0.55 and OR 0.30, 95 % CI 0.12-0.74, respectively) (Table 8).

5.4.2 Hormonal treatment

No statistically significant differences were found regarding type of hormonal treatment and risk of ovarian cancer, but a borderline significance for months of danocrine use and ovarian cancer risk in the univariate analysis(OR 1.06, 95 % CI 1.00-1.12) (Table 8).

5.4.3 Severity score

An association was shown in the univariate analysis with an increased risk of ovarian cancer with increasing severity score (OR=1.06, 95 % CI 1.02-1.11). This could however not be verified in the multivariate analysis (Table 8).

Table 8. OR and 95 % CI for univariate and multivariate analyses. Severity is treated as a continuous variable and hormonal treatments are analyzed both as categorical and continuous variables in separate analyses. All analyses are controlled for age at endometriosis diagnosis, menopausal status at endometriosis diagnosis, location of endometriosis and parity.

Variable	**Univariate analysis OR and 95% CI**	**Multivariate analysis OR and 95% CI Hormonal treatments included as *categorical variables.***	**Multivariate analysis OR and 95% CI Hormonal treatments included as *continuous variables***
Severity score	1.06 (1.02-1.11)	1.00 (0.91-1.10)	1.02 (0.93-1.11)
Months of combined oral contraceptive use	1.00 (0.99-1.00)		1.00 (0.99-1.00)
Combined oral contraceptive use			
Never user	1	1	
User for 1-12 months	0.89 (0.56-1.41)	0.81 (0.41-1.63)	
User for > 12 months	1.22 (0.76-1.98)	0.96 (0.44-2.06)	
Months of gestagen use	1.00 (0.98-1.01)		0.99 (0.97-1.02)
Gestagen use			
Never user	1	1	
User for 1-12 months	0.99 (0.69-1.43)	0.89 (0.48-1.66)	
User for > 12 months	1.22 (0.68-2.15)	1.75 (0.67-4.54)	
Months of danocrine use	1.06 (1.00-1.12)		1.04 (0.94-1.14)
Danocrine use			
Never user	1	1	
User for 1-6 months	1.18 (0.72-1.93)	1.02 (0.44-2.34)	
User for > 6 months	1.84 (0.92-3.68)	1.32 (0.42-4.13)	
Months of GnRH use	1.02 (0.96-1.09)		0.85 (0.66-1.09)
GnRH use			
Never user	1	1	
User for 1-6 months	0.43 (0.14-1.29)	0.26 (0.05-1.26)	
User for >6 months	3.21 (0.29-36.0)	1.64 (0.05-52.0)	
Months of HRT use	1.00 (0.99-1.00)		1.00 (0.99-1.01)
Months of HRT use			
Never user	1	1	
User for 1-6 months	0.56 (0.27-1.15)	0.65 (0.22-1.86)	
User for >6 months	1.07 (0.66-1.73)	2.06 (0.93-4.57)	
Hysterectomy			
No	1	1	1
Yes	1.00 (0.71-1.43)	2.04 (0.92-4.52)	2.00 (0.92-4.31)
One sided oophorectomy	1	1	1
No	0.42 (0.28-0.62)	0.19 (0.08-0.46)	0.29 (0.13-0.62)
Yes			
Sterilization			
No	1	1	1
Yes	0.68 (0.41-1.10)	0.76 (0.30-1.93)	0.81 (0.33-2.01)
Radical surgery performed			
No	1	1	1
Yes	0.37 (0.25-0.55)	0.30 (0.12-0.74)	0.33 (0.14-0.77)

The kappa-measure regarding agreement between the two investigators that red through the medical records showed a good agreement for type of surgery performed (kappa = 0.58-0.94) and for hormonal treatment (kappa= 0.84-1.00) and a lower agreement for radical surgery (kappa=0.29) (table 9).

Table 9. Kappa-measure performed for variables in paper IV.

Variable	**Kappa-value**	**Kappa-value for hormonal treatments included as categorical variables**
Location of endometriosis	0.76	
Months of COC use		0.88
Months of gestagen use		0.84
Months of danocrine use		1.00
Months of GnRH use		1.00
Hysterectomy performed Yes or no	0.94	
One-sided oophorectomy performed Yes or no	0.80	
Sterilazation performed Yes or no	0.64	
Removal of all visible endometriosis Yes or no	0.29	

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6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study design

The two most common study designs used in epidemiological research are cohort studies and case control studies.

For a cohort study a group of individuals is selected in which exposed and unexposed subjects are identified. These individuals are followed over time and the occurrence of disease, the outcome, is registered. The unexposed individuals are the comparison group and they can be part of the cohort, be a group outside of the cohort or a whole population. All individuals in a cohort must be at risk of developing the outcome, meaning that all individuals have to be alive at the beginning of the follow up and not already have obtained the outcome studied. A cohort study can be prospective in the sense that the cohort is defined and then followed forward in time and the outcome is then recorded. It can also be retrospective where the outcome already has occurred and data on exposure and outcome is collected from records or registers. In cohort studies both absolute and relative risks can be calculated.

Advantages with cohort studies are the possibilities to study many outcomes. It is a good way to study rare exposures and you have a time axis where the exposure occurs before the outcome. Disadvantages are the economic and time-consuming costs of a prospective cohort study and the ineffectiveness to study rare outcomes. Loss to follow up can influence the validity of the study.

In a case control study a group of individuals who have the outcome (cases) is identified as well as a group without the outcome (controls). The difference in exposure between the two groups is studied. The controls must come from the same population that has generated the cases and must be eligible to become cases. In a case control study the cases and the controls can be matched on important factors to improve the efficiency of the study. However, then the effect of the matching variables cannot be measured in the analyses.

Advantages with a case control study are usually lower costs and a design convenient for studying many exposures as well as rare outcomes. Disadvantages are the limitation to one outcome and it is not suitable to study very rare exposures.

Paper I, II and III are retrospective cohort studies with prospectively collected data where the exposed individuals are identified from the NSPR with a first time discharge diagnosis of endometriosis from 1969 and onward. The cohorts are open, i.e. women are included over time as they are diagnosed with endometriosis and each individual contribute with a specific amount of person time during the follow up.
The comparison group in paper I and II constitutes all female residents in Sweden during the same time-period. In paper III does the comparison group include women with a malignancy but no endometriosis diagnosis. The outcome in paper I and II, i.e. a first time diagnosis of a malignancy, is obtained from the NSCR. In paper III is the

outcome death by the same malignancy diagnosed at inclusion and information on this was obtained from the CDR.
In the exposed group in paper I and II only individuals with a malignancy diagnosis one year or later after the endometriosis diagnosis were included. This ensures a causative perspective where the exposure (endometriosis) precedes the outcome (a malignancy diagnosis). In paper III we used a limit of minimum 30 days between endometriosis diagnosis and malignancy diagnosis to be able to exclude cases of malignancy that had been accidently diagnosed at the same time as the endometriosis diagnosis, since this could have influenced the prognosis because of the malignancy being diagnosed in an earlier stage.

One great concern in epidemiologic endometriosis studies is the onset of exposure. We identified the start of follow up as the first time of discharge from a hospital with a diagnosis of endometriosis. However, this time point is usually not identical with the debut of the disease. Studies have shown that there is on average a delay of seven years from onset of symptoms until time of endometriosis diagnosis [34, 35]. Therefore we might have under estimate the true (usually unknown) time of exposure.

One challenge in survival analysis is so called 'competing risks', i.e. when another event prevents the studied event to occur. For example the fact that people may die from other causes than the one studied. We used cause specific mortality rates in paper III and registered only deaths from the same malignancy as diagnosed at inclusion as an event. This opens up the door to competing risks. To deal with this we analysed the difference in mortality from other causes than a malignancy and found no statistically significant differences between the exposed and unexposed individuals and the HR's was close to one. This shows that we did not have a problem with competing risks in this study.

In case control studies is there always a crucial process of selecting the controls. In paper IV we were able to ensure that the cases and the controls came from the same source population as we used a well identified cohort. We could also certify that the controls were eligible as cases as they were all alive, living in Sweden and had at least one ovary left at time of the case's cancer diagnosis, according to the register data. We matched only on year of birth and not on for instance year of endometriosis diagnosis. This was important since the treatment of endometriosis has changed partially over the decades and treatment was the exposure that we wanted to study. A match for this variable would have disabled such analyses.

6.1.2 Internal validity

There are two major types of errors that affect epidemiological studies; random errors and systematic errors. Random errors are the variability in the data that remains after controlling for systematic errors. Another word for systematic errors is bias and this can be divided into selection bias, information bias and confounding.
Random errors can be decreased with increased sample size while this is not the case with systematic errors.

6.1.2.1 Selection bias

Selection bias is a systematic error that has to do with selecting the subjects included in the study and study participation. If the association between the exposure and the outcome differs between the participants and the non-participants in the study, selection bias might have been introduced. The association between exposure and outcome in the non-participating group is often unknown and cannot be observed. Therefore selection bias must always be considered and evaluated when a study is conducted. In general case-control studies are more vulnerable to selection bias than cohort studies. To minimize the risk of selection bias, data should be collected prospectively.

In paper I, II and III which all are cohort studies, the study design is retrospective since the outcome already has occurred. However the information on exposure and outcome are prospectively collected and therefore selection bias is not very likely. Although we only include women who have been hospitalized with a diagnosis of endometriosis in our cohort and this might have the effect that it is the more moderate to severe cases that we are studying, this should not be a problem of selection bias but more of external validity and generalizability of the study.

In paper IV where the effect of medical and surgical treatments of endometriosis and future risk of ovarian cancer was studied, a selection bias could have been introduced if for instance the cases all came from university hospitals and the controls from county hospitals, since treatment regimes and resources could vary greatly between these two levels of health care.

6.1.2.2 Information bias

Information bias or misclassification is present if an error occurs when a variable is measured and places the subject in the wrong category. Misclassification can occur for both exposure and outcome and it can be differential or non-differential. A misclassification of exposure is differential if it is different for those with and without the outcome and non-differential if it is nonrelated to the outcome. The same goes for misclassification of the outcome.
Differential misclassification can either overestimate or underestimate an effect. Non-differential misclassification leads to an estimate of the effect that is diluted or moves towards the null-value.

In paper I-III all information on exposure and outcome is retrieved from population based registers and there is no reason to believe that misclassification occurring in these registers should be related either to exposure or outcome, i.e. it is therefore likely to be non-differential. In the first two papers, the women exposed in the cohorts are also part of the respective control group, the general female Swedish population; however this could only lead to an underestimation of the true relative risks between exposed and unexposed subjects.

In paper IV we have categorized the exposure variable for hormonal treatments, for instance as never user, user for 1-12 months and > 12 months of use of COC. Here it is inevitable to introduce misclassification since the true exposure time for COC might be unclear due to incomplete information in the medical records. Some women may have

been prescribed COC from a general practitioner, a midwife or a gynecologist in private practice and these data might not appear in the medical record. For other women a prescription of COC is documented in the medical records but the woman never used them. All cases like these might contribute to a misclassification of the women as ever or never user. However, it will be a non-differential misclassification since there is no difference between cases and controls in this respect.

6.1.2.3 Confounding

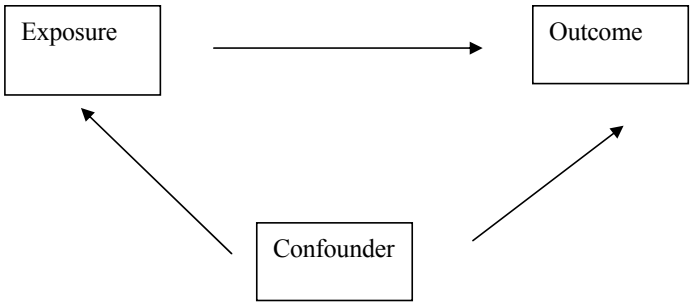
Confounding is a disturbance factor that is associated with both the exposure and the outcome but is not an effect of the exposure (figure 3). It can cause either an overestimation or an underestimation of the effect. Confounding must always be considered in a study. Randomization and restriction are two ways of preventing confounding. Randomization has the advantage that it can control for unknown confounders while restriction cannot. A third way to prevent confounding is to stratify the data so that the confounder is held constant within each stratum. Matching, which gives identical distribution of a factor between the two groups is also a way of preventing confounding. Matching works well in cohort studies as well as in case control studies. Yet another way to deal with confounding is the use of regression analyses where several potential (and measured) confounders can be taken into account simultaneously and adjusted for.

In paper I where we wanted to investigate the association between endometriosis and the risk of malignancies, we controlled for age at and calendar year of malignancy diagnosis in the statistical analyses to avoid confounding. We also stratified on age at endometriosis diagnosis as well as for how long the disease had been diagnosed. However in this study we did not have access to data on parity which could be a serious confounder. In paper II we were able to control for parity by stratifying the women into nulli parous or parous women.

In paper III we studied the effect of endometriosis on survival after a malignancy diagnosis and were able to control for confounders in the Cox regression analyses. We identified the following possible confounders: age at malignancy diagnosis, calendar year of malignancy diagnosis and parity. Information on these variables could be retrieved from the national population based registers. The exposed and unexposed subjects were also matched on year of birth and county of residence, also to avoid confounding. Calendar year of malignancy diagnosis can influence the prognosis both by different diagnostic tools and different treatment routines. The same goes for county of residence since treatment routines might differ slightly in different counties.

In the case control study in paper IV we matched cases and controls on year of birth and used conditional logistic regression for analyses, where we also controlled for other possible confounders. We did not match for county of residence in this study, since the effect of different treatments that might have different use in different counties was one of the variables that we wanted to investigate.

Figure 3 Theoretical model of a confounder acting on both exposure and outcome.



6.1.2.4 Effect modification

Effect modification is when the association between an exposure and the outcome differs in relation to a third factor. In a combined analysis where effect modification is not considered, a true effect can therefore be hidden. Stratification is one way of making effect modification visible and regression analyses with interaction variables are used to test the effect statistically.

In paper III where we analyzed the impact of endometriosis on survival after a malignancy diagnosis, we found two types of effect modification. Endometriosis had its largest effect on survival when the malignancy was diagnosed after the age of 54, meaning that endometriosis (the exposure) had different effects on the outcome in relation to age at malignancy diagnosis (third factor). For breast cancer and parity (third factor) an effect modification was shown with lower HR in nulliparous exposed women compared to parous exposed women.

6.1.3 External validity

External validity has to do with the generalizability of the results, that is whether or not the results can be applicable to the general population and non studied individuals. If a study has low internal validity it also has low external validity.

In paper I-IV only women who have been discharged with a first time diagnosis of endometriosis in a public hospital after an overnight stay were included. Since the diagnostic tools have changed over the years and for the last twenty years gone towards more laparoscopic procedures in day-surgery clinics one might suspect that only women with moderate to severe endometriosis that has required hospitalization, and not women with minimal to mild endometriosis, have been included. This might influence the generalizability of the study results to only be applicable to the moderate to severe cases of endometriosis.

6.2 FINDINGS AND INTERPRETATIONS

6.2.1 Women with endometriosis have an increased risk of several types of malignancies (Paper I and II).

The occurrence of malignant tumors growing at the same location as endometriotic lesions has been known since the 1920's [2]. The ovaries have been the most common organ were this coexistence has taken place, but epidemiological studies have also shown an increased risk for other types of malignancies, for instance breast cancer, non-Hodgkin's lymphoma, thyroid cancer and colon cancer [3-6, 9, 48, 52].

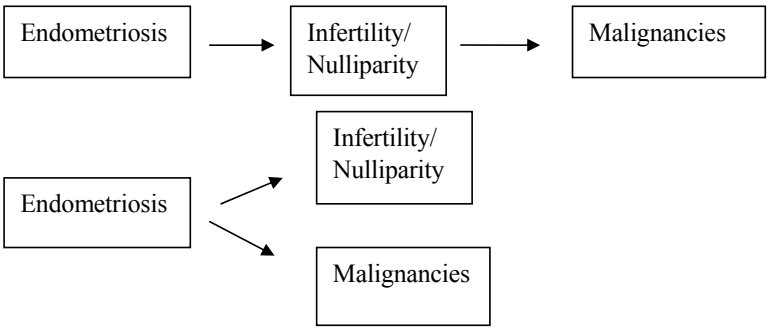
Findings: in paper I we found an increased risk for ovarian cancer, endocrine tumors, brain tumors and non-Hodgkin's lymphoma in women with endometriosis compared to other women. We also found that endometriosis in the ovaries, endometriosis diagnosis in young age and endometriosis for many years were factors that increased the risk of ovarian cancer even more. Women with endometriosis were also diagnosed with ovarian cancer earlier in life than other women. Hysterectomy seemed to have a protective effect against ovarian cancer. There was also a decreased risk for cervical cancer in women with endometriosis.
Paper II showed an increased risk for endocrine tumors, ovarian cancer, kidney cancer, thyroid cancer, brain tumors, malignant melanoma and breast cancer in women with endometriosis compared to other women and the study showed that the increased risks for several types of malignancies remained even after adjustment for parity. There was a trend for ovarian cancer with lowered risks if the woman had given birth to more than one child; however this trend was not statistically significant.

Interpretation: the findings in paper I and II are consistent with other epidemiological studies [7, 13, 48, 52]. The strengths with paper I and II compared to other studies are the large number of women included, the long follow up time, the accuracy of the diagnoses and also the ability to censor the follow up time for different types of malignancies when different kinds of surgical procedures had been performed.
One weakness is the fact that only women who have been treated over night in a public hospital are included and since more and more laparoscopic surgeries are performed in day surgery clinics one might suspect that the women who stay overnight have a more complicated disease and perhaps are older. This affects the generalizability of the results to only be applicable for women with moderate to severe endometriosis.
Another weakness is the fact that we don't really know the exact starting point of the endometriosis disease. The known delay of several years between onset of symptoms and the diagnosis limits the interpretation of the importance of age at diagnosis. However to ensure a causal relationship with endometriosis diagnosis and a malignancy introduced later, we only included women were the endometriosis diagnosis proceeded the malignancy diagnosis with at least one year [34, 35].

One weakness in paper I was the fact that we did not have information on parity. Nulliparity and infertility are well known risk factors for several types of malignancies [9]. Since endometriosis is a common cause for infertility we needed to study this relationship more closely. In paper II we had only information on parity and not about any infertility problems. We used parity as an approximation for infertility, well aware

of the fact that not having children can be an active choice and not always be connected to infertility. There are at least two ways where endometriosis, parity and cancer risk could be associated: 1) Endometriosis causes infertility and this causes a malignancy or 2) Endometriosis is the cause of infertility and malignancy separately (figure 4).

Figure 4. Two ways for endometriosis to be connected to malignancies



The results of the study showed an increased risk for several types of malignancies after controlling for parity and should be interpreted in the way that women with endometriosis have an increased risk for malignancies and this risk increase is not related to parity. Therefore, the first of the pathways described in Figure 4 do not seem to be supported by our data.

Both papers I and II showed a decreased risk for cervical cancer as well as cancer in situ of the cervix for women with endometriosis compared to other women. This indicates that the reason for this reduced risk is not that women with endometriosis go more often to a gynecologist and take more Pap smears than other women, but actually have a decreased risk of this disease. The screening program is designed to detect cancer *in situ* of the cervix and if women with endometriosis would have Pap smears more often than other women, the risk of cancer *in situ* should be found to be at least as high as in the general population or higher [100].

The results in paper I showed an increased risk of breast cancer in women with endometriosis diagnosed at age 50 or older. This finding is consistent with the results from another epidemiological study that in addition could show a decreased risk of breast cancer if endometriosis was diagnosed at young age [52]. Women with endometriosis often receive medical treatment with anti-estrogenic effect and this could be an explanation for the reduced risk of breast cancer in endometriosis women diagnosed in young age. The findings of post-menopausal endometriosis is often connected to elevated levels of estrogen, either by the use of HRT or because of obesity [21]. HRT and obesity are well known risk factors for breast cancer [61-63]. It is therefore possible that the increased risk of breast cancer in women with endometriosis diagnosed after menopause, is connected to elevated levels of estrogen, either endogenously or exogenously.

Study I showed a decreased risk of ovarian cancer if the woman had had a hysterectomy before or at the same time as the endometriosis diagnosis. As many as

80 % of these women had adenomyosis and only 12 % had ovarian endometriosis. This result could therefore be interpreted in either of two ways; 1) Patients with adenomyosis do not have an increased risk for ovarian cancer; 2) Hysterectomy protects against ovarian cancer and since many women with adenomyosis are hysterectomized they are protected against ovarian cancer.

6.2.2 Endometriosis have an impact on survival in a malignancy (Paper III)

A few, small studies have indicated that endometriosis might have a positive effect on survival after a diagnosis of ovarian cancer, whether or not this is the case for other types of malignancies is not known [15-17].

Findings: Paper III indicated that women with endometriosis have a better prognosis after a malignancy diagnosis, particularly for breast cancer and ovarian cancer. It also indicated a worse prognosis for malignant melanoma. There was an interaction between endometriosis and age at malignancy diagnosis with a more pronounced effect on survival if the malignancy was diagnosed after the age of 54. In women with breast cancer we found an interaction with parity, with lower HR in nulliparous exposed women compared to parous exposed women.

Interpretations: The findings with better prognosis in women with endometriosis and ovarian cancer are consistent with previously published studies. However, our study only showed a better survival in ovarian cancer if the diagnosis was made after menopause. The findings might be due to the fact that there were very few women diagnosed with ovarian cancer before menopause. The strengths of this study are the same as for paper I and II regarding data on exposure and outcomes as well as the large number of women included and a long follow up time.
One weakness was the fact that we could not adjust for stage and histological subtype for the ovarian cancers since this information was not included in the NSCR before 2005. As for many other types of malignancies, stage has been shown to be an important prognostic factor in ovarian cancer [101-103]. In a case control study on endometriosis associated ovarian cancer, it was found that women with endometriosis and ovarian cancer have a better prognosis, mainly due to lower stage of disease, different distributions of histological subtypes, lower grade tumors and less residual tumor after surgery [15]. The authors suggested that women with endometriosis have a different kind of ovarian cancer which has different biological characteristics and therefore a better prognosis. Another explanation could be that women with endometriosis visit a gynecologist for examinations more often than other women and this increases the possibilities to detect an ovarian tumor in an earlier stage. We were only able to retrieve information on stage and histological subtype from a small percentage of the ovarian cancers and could therefore not make any conclusions regarding these issues.

Age at ovarian cancer diagnosis have been shown to be an important prognostic factor, also for women with endometriosis, with better prognosis when the malignancy is diagnosed at younger age [15, 103]. Our study results in paper I showed that women with endometriosis are diagnosed with ovarian cancer in younger ages than other

women. The results in paper III showed better survival only in the group diagnosed with ovarian cancer after the age of 54. This result is not consistent with previously published studies. However, the fact that we did not reach statistical significance in the age group below 55 years could be due to too few cases.

Paper III also showed a worse prognosis in women with endometriosis and malignant melanoma compared to women with malignant melanoma but no endometriosis diagnosis. One study have shown an increased risk for dysplastic naevi in women with endometriosis and also an increased risk of having a first degree relative with malignant melanoma [53]. The role of exogenous and endogenous reproductive hormones and risk of malignant melanoma is still somewhat unclear [88].

A prognostic importance of endometriosis on malignant melanoma has not previously been shown. The results should therefore be interpreted carefully. We showed that the worst prognosis for women with endometriosis and malignant melanoma was during the calendar period1990-1999. Danocrine, a testosterone derivative (17α-ethinyl testosterone), was very popular as endometriosis treatment during the 1980's and in the beginning of the 1990's. Though estrogens are known to inhibit invasion of malignant melanoma, dehydroepiandrosterone (DHEA) has been shown to enhance invasion [89]. Danocrine was not used anymore after the early 1990's and paper III shows a lower HR for women with endometriosis and malignant melanoma during the last time period, 2000-2005. Whether danocrine enhance invasion of malignant melanoma and thereby influences the prognosis of survival is not known.

The results from paper III also showed a statistically significant better survival in women with endometriosis for all malignancies combined. However, this should be interpreted with caution since the study also showed a better survival in breast cancer. Breast cancer is the most common type of malignancy and it is possible that it is the better survival in breast cancer that makes the better survival in all malignancies combined statistically significant..

6.2.3 One-sided oophorectomy and removal of all visible endometriotic lesions lower ovarian cancer risk (paper IV)

Endometriosis is a common disease and women with endometriosis often go through several types of treatments, both surgical and hormonal, during their lifetime. Whether or not any of these treatment could increase or decrease the risk of ovarian cancer is therefore of great clinical importance.

Studies have shown a protective effect of hysterectomy and tubal ligation on the risk of ovarian cancer. Whether or not this is true also for women with endometriosis is not known [10, 56, 91, 93, 94]. The surgical removal of an ovarian cyst has been shown to be protective against ovarian cancer, also in women with endometriosis [20]. The use of COC has been shown to be protective against ovarian cancer, also in women with endometriosis, but first after 10 years of usage [12]. One study have indicated that the use of danocrine could be associated with an increased risk of ovarian cancer [19].

Findings: The results regarding surgical treatment showed a strong reduction in risk for ovarian cancer after one-sided oophorectomy and when all visible endometriosis had been removed in both the univariate and multivariate analyses.
For hormonal treatments no statistically significant results were found except for a borderline significance for months of danocrine use and ovarian cancer risk in the univariate analysis.

Regarding the severity score the results in the univariate analysis showed an association between increasing severity score and increased risk of ovarian cancer. This could however not be verified in the multivariate analysis

Interpretations: The study showed a strong reduction in ovarian cancer risk if one-sided oophorectomy was performed or if all visible endometriosis was extirpated. These findings are in agreement with another study, showing a decreased risk of ovarian cancer if an ovarian cyst was removed [20]. The one-sided oophorectomy could of course be viewed as a variant or subgroup of all visible endometrosis removed, since the reason for performing an oophorectomy is that this ovary is affected by endometriosis.

A weakness with this study is the risk of misclassification regarding hormonal treatment. The information we had in the medical records were restricted to treatments prescribed by doctors in public hospitals and excluding information from general practitioners or private practice gynecologists. We have however no reason to believe that the lack of correct information would differ between cases and controls which makes the bias non-differential and may dilute the results.

The borderline significantly increased risk for ovarian cancer with use of danocrine in the univariate analysis is in agreement with one previously published study [19]. Treatments with gestagens or GnRH-agonists have never been associated with ovarian cancer and this is confirmed in study IV.
COC have been shown in several studies to be protective against ovarian cancer. Most of the studies have focused on risk reduction after 5- 10 years of use [12, 18]. Studies have indicated a protective effect of COC use also after a shorter time period with an increased risk reduction the more year of COC use[94]. It also seems like the protective effect of COC use remains several years after the treatment has ended [18, 94]. We could not show a protective effect of COC use probably due to the fact that we have too few women included and not so many long time users of COC.

The purpose of the creation of the severity score was to identify those women with an increased risk of ovarian cancer. The idea came from a study on risk of lymphoma in patients with rheumatoid arthritis. This study focused on whether or not the treatment of rheumatoid arthritis could influence the risk of lymphoma and a scoring system was created to measure level of severity of disease and inflammation. The results showed that it was the severity of the rheumatoid arthritis and increased inflammation that was associated with lymphoma and not the treatment [104]. To our knowledge, a similar scoring system concerning endometriosis and risk of malignancy has not been done before. Our score included:

1. *age at endometriosis diagnosis*
2. *symptoms of endometriosis*
3. *number of visits to the doctor*
4. *number of surgical procedures*
5. *classification of stage of endometriosis*
6. *blood tests showing signs of inflammatory activity*

There are several weaknesses with this scoring system. For instance the true age at onset of endometriosis cannot be assessed. The pelvic pain was often difficult to score since the degree didn't always appear in the records, for instance about pain at intercourse. The degree of pain and discomfort has not been clearly correlated to the stage of the disease or to the number and size of the lesions. We found that the number of visits to the doctor could vary a lot, for instance women with infertility problems have many visits while women with an endometriotic cyst only had a few visits and was "cured" after surgery. Both infertility and endometriotic cysts are risk factors for ovarian cancer, but number of visits to the doctor does not seem to be a good indicator. Number of surgical procedures did not vary a lot. Almost all women had 1-3 procedures.
Another weakness has to do with the classification of endometriosis stage. We used the classification of the American Society for Reproductive Medicine, that was originally designed to be a tool in assessing infertility problems [99]. The classification gives a high scoring to adhesions and low scoring to peritoneal endometriosis. This does not necessarily coincide with the severity of the disease and risk of cancer development.

Despite the weaknesses, we have no reason to believe that information from the medical records on these issues would have been reported or included differently between cases and controls. The needs for an instrument to discriminate those at risk from those that are not are of course invaluable to both patients and clinicians. Our scoring system showed a statistically significant association with an increased risk of ovarian cancer with increasing points of the severity score, however, only in the univariate and not in the multivariate analyses. A further development of a scoring system is important to be able to identify endometriosis women at risk of ovarian cancer.

6.3 FUTURE RESEARCH

This thesis shows an increased risk for several types of malignancies in women with endometriosis. It is easier to understand the biological mechanisms behind ovarian endometriosis developing into or causing a cancer growth in the ovary then to explain the increased risks of i.e. thyroid cancer, malignant melanoma or non-Hodgkins lymphoma. A genetic explanation with one or more inherited genes causing both endometriosis and different types of malignancies can not be excluded. The deficiency in the immune system that in one end allows the endometriosis disease to develop and in the other end allow malignancies to appear might be another explanation. Future research is needed to clarify the association between endometriosis and these types of malignancies.

Endometriosis is a common disease. However, although ovarian cancer is not a very common malignancy, it has a poor prognosis. Our data show the risk of developing ovarian cancer to be 19/100 000 person years for Swedish women and this risk increases to 27/100 000 person years if the woman has endometriosis. This might not seem like a large increase in risk but the key issue here is to identify those women with endometriosis that are at risk of developing ovarian cancer. Our studies shows that

young age at endometriosis diagnosis, long-standing endometriosis and endometriosis in the ovaries are all risk factors. How can women with endometriosis that are at increased risk of ovarian cancer be identified? But to be able to advice women about a risk and if possible profylactically provide for instance oophorectomy in women who have finished their child bearing period, more research is needed.

Is there a precursor state where atypical cells can develop into a malignancy and can this be identified and treated? More efforts are needed to try and identify atypical cells in endometriosis and to establish their possible malignant potential.

The better prognosis after a malignancy diagnosis; for all malignancies combined and for breast and ovarian cancer separately, but the worse prognosis in malignant melanoma raises questions about the biology behind these diseases and the impact of endometriosis. Why do women with endometriosis have increased risks for so many different kinds of malignancies? Could the immune system failure, that allows endometriosis development, be an advantage or sometimes a disadvantage in fighting a malignancy? It is difficult for the moment to see how the survival results could be directly useful for clinical management of endometriosis patients. The results require further exploration in tumor biology and cancer epidemiology to better understand the association between endometriosis and malignancies.

The most important limitation to study IV was the number of cases available in a small country like Sweden. An extended study is needed to properly assess the association between hormonal treatment of endometriosis and future risk of ovarian cancer. A Scandinavian study to increase power is under consideration. Denmark and Norway have population based national registers for cancer and other diseases, similar to the Swedish registers.

In paper IV we only looked at one-sided oophorectomy and future risk of ovarian cancer. It would have been interesting from a clinical point of view to study the difference in risk of ovarian cancer when a complete oophorectomy is performed compared to an extirpation/resection of only the endometriotic tissue/cyst in the ovary, leaving the part of the ovary that is considered to be healthy in place

7 CONCLUSIONS

- Women with endometriosis have an increased risk of some malignancies, especially ovarian cancer.(Paper I)

- The risk increases with early diagnosed or long-standing disease or if the endometriosis is located to the ovaries. (Paper I)

- Hysterectomy may have a protective effect against ovarian cancer in women with endometriosis. (Paper I)

- The increased risk for malignancy is not related to parity. (Paper II)

- Women with endometriosis might have a better survival after a diagnosis of a malignancy than other women without endometriosis, especially for breast cancer and ovarian cancer. (Paper III)

- The prognosis after a diagnosis of malignant melanoma is worse for women with endometriosis than for women without this disease. (Paper III)

- The future risk of ovarian cancer is extensively reduced if one-sided oophorectomy is performed or if all visible endometriosis is removed. (Paper IV)

- The risk for ovarian cancer seems to be increased after danocrine treatment of women with endometriosis. (Paper IV)

8 SVENSK SAMMANFATTNING

8.1 BAKGRUND

Endometrios är en av de vanligaste gynekologiska sjukdomarna och drabbar ca 10 % av alla kvinnor i fertil ålder. Det är en kronisk, inflammatorisk, östrogenberoende sjukdom som orsakas av implantation av avstött livmoderslemhinna utanför själva livmodern. Sjukdomen ger som främsta symtom smärtor vid menstruation, ägglossning och samlag men är också en vanlig orsak till infertilitet.

Endometrios betraktas som en godartad sjukdom men har många egenskaper gemensamt med en malignitet. Ända sedan 1920-talet har det förekommit flera rapporter om endometrios och cancer som uppstått på samma plats. Man uppskattar att vid endometrios i äggstocken utvecklas cancer i 0,7-5,0 % av fallen.
Epidemiologiska studier har visat en ökad risk för bl a bröstcancer, äggstockscancer, non-Hodkin's lymfom, malignt melanom och cancer i sköldkörteln hos kvinnor med endometrios.

Barnafödande påverkar risken att insjukna i flera olika typer av maligniteter. Äggstockscancer, bröstcancer och cancer i livmodern är exempel på sådana cancrar där risken att få dessa sjukdomar påverkas av om kvinnan fött barn eller inte. Endometrios är en vanlig orsak till infertilitet. Huruvida den ökade risken för vissa typer av maligniteter hos kvinnor med endometrios beror på minskat barnafödande eller på endometriossjukdomen i sig är inte känt.

Ett fåtal mindre studier har visat att endometrios kan ha en positiv effekt på överlevnaden hos kvinnor med äggstockscancer. Om endometrios också påverkar överlevnaden i andra maligniteter är inte tidigare undersökt.

Kvinnor med endometrios genomgår oftast flera kirurgiska och hormonella behandlingar under livet för att avlägsna den sjuka vävnaden, dämpa symptomen och förbättra fertiliteten. Om behandlingen av endometrios skyddar mot eller ökar risken för äggstockscancer är endast mycket sporadiskt undersökt. P-piller har i flera studier vistas ha en skyddande effekt mot äggstockscancer och åtminstone en studie har visat att detta gäller också för kvinnor med endometrios. En tidigare studie har visat att behandling med danocrine kan ge ökad risk för äggstockcancer. Behandling med gulkroppshormon eller sk GnRH-agonister har inte visats medföra någon ökad risk för äggstockscancer, men detta har inte studerats närmare.
När det gäller kirurgisk behandling har borttagande av livmodern och sterilisering vistas skydda mot äggstockcancer. Om detta gäller även för kvinnor med endometrios är något oklart. En studie har visat att om man operar bort en cysta på äggstocken så minskar detta risken att drabbas av äggstockcancer även hos kvinnor med endometrios.

8.2 SYFTE

Syftet med denna avhandling var att studera sambandet mellan endometrios och malignitet.
I delarbete I ville vi studera om kvinnor med endometrios har en ökad risk att insjukna i en malignitet jämfört med Sveriges kvinnliga befolkning i övrigt. Delarbete II syftade till att undersöka hur barnafödande påverkar risken att utveckla en malignitet hos

kvinnor med endometrios. I tredje delarbetet studerades huruvida kvinnor med endometrios har en bättre eller sämre överlevnad i en malignitet jämfört med andra kvinnor. Slutligen studerade vi i delarbete IV om den hormonella eller kirurgiska behandlingen av endometrios ökar eller minskar risken att insjukna i äggstockscancer.

8.3 MATERIAL OCH METOD

Samtliga delarbeten i denna avhandling baseras på data från de stora populationsbaserade register som finns att tillgå i Sverige. Data från olika register avseende samma individ kopplas samman med hjälp av personnumret. Delarbete I-III är kohortstudier och delarbete IV är en fall-kontroll studie som utgår från en kohort. Endast kvinnor som vårdats i slutenvård på offentligt sjukhus är med i studierna

Följande populationsbaserade register har använts till delarbetena i denna avhandling:

Patientregistret
Detta register startades 1964 och sedan 1987 har det nära 100 % täckning av all slutenvård i offentlig regi. Information från detta register inkluderar bl a kön, län, datum och diagnos vid utskrivning, vilket sjukhus man vårdats på och vilka kirurgiska åtgärder som utförts. Utskrivningsdiagnoserna är kodade enligt ICD 8-10.

Cancerregistret

Cancerregistret grundades 1958 och syftet var att skapa ett nationellt populationsbaserat register över cancersjukdomar. Detta skulle användas till övervakning över förekomsten av och trender över tid för olika maligniteter, statistik och forskning. Sedan 1980-talet finns sex regionala onkologiska centra som hjälper till att samla in data från sjukhus avseende maligna diagnoser och som sedan sänder in detta till Socialstyrelsen för sammanställning. Registret innehåller information om kön, län, malignitetsdiagnos, diagnosdatum, vilket sjukhus och klinik som patienten vårdats på, lokalisation av tumören och TNM-klassifikation. Malignitetsdiagnoserna kodas enligt ICD-7-10 men översätts alltid till ICD-7 för att möjliggöra jämförelser över tid. Sedan 2005 innehåller också registret information om stadium vid diagnos och histologisk undergrupp även för gynekologiska cancrar.

Fler-generationsregistret

Alla individer födda i Sverige sedan 1932 och/eller skrivna i Sverige från och med 1961och framåt finns med i fler-generationsregistret. Detta register startades 2000. I registret är alla individer sammankopplade med sina föräldrar, syskon och barn. Detta gör att information avseende hur många barn en kvinna fött och kvinnans ålder vid första barnets födelse enkelt kan fås fram ur registret.

Dödsorsaksregistret

Dödsorsaksregistret har funnits i sin nuvarande form sedan 1961 och har sedan 1997 nära 100 % täckning av alla dödsfall. Tidpunkt och orsak till en svensk medborgares död i Sverige eller utomlands registreras. Dödsorsakerna kodas enligt ICD 7-10.

8.4 DELARBETE I

I denna kohortstudie inkluderades 64 492 kvinnor som slutenvårdats på sjukhus med diagnosen endometrios mellan åren 1969 och 2000. Under uppföljningstiden registrerades 3 349 nydiagnostiserade fall av malignitet. Som kontrollgrupp användes data på cancerinsjuknande i den totala svenska kvinnliga befolkningen under samma tidsperiod. SIR användes som mått på relativ risk. Studien visade att kvinnor med endometriois har en ökad risk för äggstockscancer (SIR 1.43), endokrina tumörer (SIR 1.36), non-Hodgkin's lymfom (SIR 1.24) och hjärntumörer (SIR 1.22). Om kvinnan hade endometrios i äggstockarna, hade fått endometriosdiagnosen i unga år eller haft endometrios i mer än tio års tid ökade risken för äggstockscancer ytterligare. Kvinnor med endometrios insjuknade också tidigare i livet i äggstockscancer än andra kvinnor och att operera bort livmodern verkade vara associerat med en minskad risk för att drabbas av äggstockscancer.

8.5 DELARBETE II

I denna kohortstudie inkluderades 63 630 kvinnor som slutenvårdats på sjukhus med diagnosen endometrios mellan åren 1969 och 2002, och som dessutom fanns med i fler-generationsregistret. Från fler-generationsregistret hämtades information om antal födda barn och ålder vid första barnets födelse. Under uppföljningstiden registrerades 3 822 nydiagnostiserade maligniteter. Som kontrollgrupp användes data på cancerinsjuknande i relation till paritet i den totala svenska kvinnliga befolkningen under samma tidsperiod. SIR användes som mått på relativ risk. Studien visade att kvinnor med endometrios har en ökad risk för endokrina tumörer (SIR1.38), äggstockscancer (SIR 1.37), njurcancer (SIR 1.36), cancer i sköldkörteln (SIR 1.33), hjärntumörer (SIR 1.27), malignt melanom (SIR 1.23) och bröstcancer (SIR 1.08). Det fanns inga statistiskt signifikanta skillnader i SIR mellan de kvinnor som ej fött barn jämfört med de som fött barn för någon av de maligniteter som inkluderats i studien.

8.6 DELARBETE III

Det tredje delarbetet är en kohort studie avseende endometriossjukdomens effekt på överlevnaden efter en malignitetsdiagnos. I studien inkluderades 4 278 kvinnor med endometrios och en malignitetsdiagnos (exponerade kvinnor) och 41 831 kvinnor med en malignitetsdiagnos men inte endometrios (oexponerade kvinnor). HR användes som mått på relativ risk. Studien visade bättre överlevnad för de exponerade kvinnorna när det gällde alla maligniteter tillsammans (HR 0.92), men också för bröstcancer (HR 0.86) och för kvinnor diagnostiserade med äggstockscancer efter 54 års ålder (HR 0.62). När det gällde malignt melanom hade kvinnor med endometrios en sämre prognos än andra kvinnor (HR 1.52).

8.7 DELARBETE IV

I denna fall-kontroll studie undersöktes om kirurgisk eller hormonell behandling av endometrios kan öka eller minska risken att insjukna i äggstockscancer. Medicinska journaler från 220 kvinnor med endometrios och äggstockscancer (fall) och 416 journaler från kvinnor med enbart endometrios (kontroller) gicks igenom noggrant. Information om medicinsk och kirurgisk behandling av endometriossjukdomen, ålder

vid diagnos, rökning, övervikt, ärftlighet med mera insamlades i en databas. OR användes som mått på relativ risk. Studien visade att risken för äggstockscancer minskade dramatiskt om ena äggstocken tagits bort i samband med operationen av endometriosen. Liknande riskreduktion fanns också då man avlägsnat all annan synlig endometrios kirugiskt. När det gällde den medicinska behandlingen fanns endast ett antytt samband mellan antal månader man använt danocrine och äggstockscancer, detta samband var dock inte statistiskt signifikant.

8.8 SLUTSATSER

- Kvinnor med endometrios har en ökad risk för flera maligniteter, ffa äggstockscancer. Risken att insjukna i äggstockscancer ökar ytterligare om kvinnan har endometrios på äggstocken, insjuknar i endometrios i unga år eller har haft endometrios i minst 10 år. Att operera bort livmodern kan ha en skyddande effekt mot äggstockscancer.

- Den ökade risken för en malignitet är dock inte relaterad till paritet.

- Kvinnor med endometrios har en bättre prognos efter att ha fått en malignitetsdiagnos jämfört med andra kvinnor utan endometrios, ffa vid bröstcancer och äggstockscancer. Vid malignt melanom är prognosen sämre för kvinnor med endometrios jämfört med andra kvinnor.

- Risken att insjukna i äggstockscancer minskas kraftigt om all synlig endometrios avlägsnas kirurgiskt, inklusive om ena äggstocken opereras bort.

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APPENDIX

”Severity score”

1.1 Number: ……

1.4 Case = 1 Control = 2

40. Age at diagnosis: <25 = serious = 10 p
26-35 = moderate = 5 p
36-50 = mild = 2 p
>50 = minimal = 1p

Points…….

41.Symptoms of endometriosis (Pelvic symptom score enl I Brosens et al , 1993)

A.Dysmenorrhea
0= no dysmenorrhea or amenorrhea
1= mild with some loss of work capacity
2= moderate have to lay down part of day or stay home from work
3= serious, have to stay in bed for one or more days, can not work

B.Dyspareunia
0= no dyspareunia
1= mild, tolerable discomfort
2= moderate, intercourse painful, interrupt intercourse because of this
3= serious, avoid intercourse because of pain

C.Pelvic pain
0= no pain
1=mild, pain sometimes
2= moderate, pain most days of the menstrual cycle
3= serious , pain most days or need of strong analgetics

Points (sum):…….

42.1 Total number of doctors visits due to endometriosis: ……

42.2 1-3 visits = 0p
4-8 visits = 3 p
>8 visits = 5 p **Points:……..**

43.1 Total number of operations due to endometriosis: ……..

43.2 1-3 op = 0 p
4-8 op = 3p
>8 op= 5p **Points:**……

44. Classificationsmodel according to American Society for Reproductive Medicine, revised classification of endometriosis, 1996.

Stage at first time surgery for endometriosis:

1= stage 1, minimal 1-5 p or stage 2, mild 6-15 p **= 1 p**
2= stage 3, moderate 16-40 p **= 2p**
3= stage 4, serious >40p **= 3p**
4= data not available

45. Blood tests

45.1 ESR=
45.2 0= normal, <=20 (highest value)
1= 21-50
2= >50

45.3 CRP=

45.4 0=normal <8 (highest value)
1= 9- 30
2= >30

Points : 0p= normal tests
2p = once elevated value
5p= more than once elevated value

46. Total score

	Points
Age at diagnosis	
Symptom at diagnosis	
Doctor visits	
Number of operations	
Class. accord. to ASRM	
Blood tests	
Total score	