Association between endometriosis and cancer: A comprehensive review and a critical analysis of clinical and epidemiological evidence

Edgardo Somigliana a,b, Paola Vigano’a,b,c, Fabio Parazzini a,b,d, Sandra Stoppelli c, Erika Giambattistac, Paolo Vercellinia,b,c,*

a Department of Obstetrics, Gynecology and Neonatology, Ospedale Maggiore Policlinico, Mangiagalli and Regina Elena, Via Commenda 12, 20122 Milan, Italy
b CROG Center for Research in Obstetrics and Gynaecology, Viale Caldara 39, 20122 Milan, Italy
c Università degli Studi di Milano, Milan, Italy
d Mario Negri Institute for Pharmacological Research, Milan, Italy

Received 11 July 2005
Available online 13 February 2006

Abstract

Objective. This review was aimed to critically evaluate observational, cohort, and case–control studies performed so far in order to assess the association between endometriosis and malignant diseases. Based on the observations herein presented, clinical indications that might avoid physicians’ mismanaging of affected patients are proposed.

Methods. Search strategies included online searching of the MEDLINE database and hand searching of relevant publications and reviews. Additional reports were collected by systematically reviewing all references from retrieved papers.

Results. Endometriosis is not associated with an increased risk of cancer in general. Data from large cohort and case–control studies indicate an increased risk of ovarian cancers in women with endometriosis. The observed effect sizes are modest varying between 1.3 and 1.9. Evidence from clinical series consistently demonstrates that the association is confined to the endometrioid/clear-cell histotypes. Available studies are characterized by several limitations, some of which potentially bias results towards the null hypothesis whereas others leading to overestimate the association. Evidence for an association with melanoma and non-Hodgkin’s lymphoma is increasing but still to be verified whereas an increased risk for other gynecological cancer types is not supported.

Conclusions. Epidemiological findings on the association between endometriosis and cancer are still elusive. At present, endometriosis should not be considered a medical condition associated with a clinically relevant risk of any specific cancer. On the basis of the present findings, modifications of the standard treatment options for the disease are not justifiable.

© 2005 Elsevier Inc. All rights reserved.

Keywords: Endometriosis; Cancer; Epidemiology

Contents

Introduction ............................................................... 332
Evidence from clinical series. ............................................................... 332
Malignant tumor arising in endometriosis; criteria and frequency ............................................................... 332
Endometriosis as a preneoplastic condition: histologic changes and molecular evidence ............................................................... 332
Characteristics of endometriosis-associated ovarian carcinomas ............................................................... 333
Non-ovarian cancers arising from endometriosis ............................................................... 334
Evidence from population-based cohort studies ............................................................... 334

* Corresponding author. Department of Obstetrics, Gynecology and Neonatology, Ospedale Maggiore Policlinico, Mangiagalli and Regina Elena, Via Commenda 12, 20122 Milan, Italy. Fax: +39 02 55185028.
E-mail address: paolo.vercellini@unimi.it (P. Vercellini).

0090-8258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2005.11.033
Introduction

Endometriosis is a common gynecological disorder in which endometrial tissue (glandular epithelium and stroma) is found at locations outside the uterine cavity [1]. Although this disease is generally regarded as a benign condition, it shows some characteristics reminiscent of malignancy, such as development of local and distant foci and attachment to and invasion of other tissues with subsequent damage to the target organs [2].

In the last decade, based on epidemiological and biological studies, endometriosis has been associated with a definite increase in risk of various malignancies [3–6]. This aspect has important clinical implications, requiring modifications in current therapeutic management if endometriosis is recognized as a cancer precursor lesion.

This review aims to represent a comprehensive and systematic tool for those approaching this problem. Observational, cohort, and case-control studies that have evaluated the malignant potential of endometriosis are herein described. Search strategies included online searching of the MEDLINE database and hand searching of relevant publications and reviews from January 1990 to July 2005. Keywords included: endometriosis combined with cancer or tumor. Additional reports were collected by systematically reviewing all references from retrieved papers. Both prospective and retrospective studies have been included. In order to give the reader a useful instrument, these studies have been critically analyzed with a specific focus on their problems and limitations. The significance of the reported findings in relation to the strategies for the treatment of endometriosis is discussed.

Evidence from clinical series

Malignant tumor arising in endometriosis; criteria and frequency

In 1925, Sampson first proposed the criteria still in use to identify malignant tumors raised from endometriosis: (1) clear evidence of endometriosis close to the tumor, (2) the carcinoma must be seen to arise in endometriosis, and not to be invading it from some other sources, (3) presence of tissue resembling endometrial stroma surrounding characteristic glands [7]. The demonstration of a histologically-proven transition from benign endometriosis to cancer has been later added by Scott as an additional criterion [8]. The application of all these stringent criteria, including that proposed by Scott, has rarely been fulfilled [9–14], thus providing support to the idea that the malignant transformation of endometriosis is a rare event. On the other hand, whereas the application of these four criteria reasonably allows to identify cases for whom a malignant transformation is unquestionable, their stringent use may lead to underestimate the real frequency of this phenomenon. Indeed, (1) the tumor might have obliterated the tissue of origin, eliminating any histological evidence of endometriosis, (2) the demonstration of a histological contiguity between endometriosis and malignant tumors requires the extensive sectioning of the ovaries. Unfortunately, currently available series on the association between endometriosis and cancer are retrospective, and thus probably unable to properly address this point.

Few large retrospective series have evaluated the prevalence of ovarian malignancy among patients operated for endometriosis. Mostoufizadeh and Scully reported eight cancers in 950 cases (0.8%) of ovarian endometriosis [15]. A similar prevalence (0.9%) has been more recently documented by Stern et al. in a series of 1000 patients with the disease [13]. This latter prevalence raised to 3.8% if “arising in” was defined according to Sampson’s criteria only, thus without the histological demonstration of a contiguity between the two entities [7,8]. Furthermore, given the limitations inherent to retrospective studies, the same prevalence differed significantly according to the pathologists who performed the analysis. This rate was as high as 8.9% (27 out of 305) if pathologists with a specific gynecologic experience were involved. Conversely, this percentage dropped to 1.3% (9 out of 695) if reports from other pathologists were considered [13].

A prospective, sufficiently large and unbiased series evaluating the frequency of ovarian cancer concomitant to endometriosis is currently not available.

Endometriosis as a preneoplastic condition: histologic changes and molecular evidence

Whether or not endometriosis should be considered a preneoplastic disease represents a major and controversial
issue. Similarly to its eutopic uterine counterpart, studies on the epithelial lining of cystic ovarian endometriosis have documented the presence of metaplastic, hyperplastic, or atypical changes. The precise prevalence of these alterations in endometriosis and their significance in terms of risk to undergo malignant transformation are not defined [12,14,16–19].

Data on metaplasia are scanty and controversial. An increased prevalence of metaplasia in endometriotic lesions of patients with endometriosis-associated ovarian cancers (100% in the 54 cases associated with cancer versus 63% among 257 patients without cancer) has been reported by Fukunaga et al. [19] while Prefumo et al. failed to observe this association [14,19]. Of note, the prevalence of metaplasia in women without cancer resulted quite different in these two studies (63% and 12%) even if they have used the same morphological criteria. This difference is difficult to explain and may be due, at least in part, to a different study population and/or to selection biases [20]. Moreover, the presence of neoplasm per se might induce metaplasia in the adjacent endometriosis [19]. Overall, there is insufficient evidence supporting metaplasia of endometriotic lesions as a preneoplastic condition.

Data on atypia are more univocal. Prefumo et al. [14] have documented a highly significant increased presence of severe atypia in endometriotic lesions in patients with endometriosis-associated ovarian cancer when compared to patients with endometriosis alone (100% of 14 cases compared to 2% of 325 controls). These results are in line with those reported by Fukunaga et al. who documented severe atypia in 61% of 54 endometriosis-associated cancers and in 2% of 255 endometriosis patients without cancer [12]. A high frequency of severe atypia was also reported by Ogawa et al. who have observed this type of lesion in 29 out of 37 cases (78%) with endometriosis-associated ovarian tumor. These same authors have observed the transition from typical to atypical endometriosis in 22 cases, and the transition from atypical endometriosis to carcinoma in 23 cases. A direct transition from typical endometriosis to carcinoma was observed only in one case [21].

Finally, data on endometriotic hyperplasia, although very limited, also support a possible association with the malignant transformation. Complex hyperplasia, but not simple hyperplasia, has been more frequently observed in endometriotic lesions of women with ovarian cancer than in those without malignancy (50% of 14 cases compared to 1% of 325 controls). However, as complex hyperplasia is frequently associated with atypia, the possibility to ascertain the role of this histological feature as an independent cancer precursor lesion is quite complicated [14,17].

Overall, these data suggest that carcinoma may arise from endometriosis through a multi-step phenomenon where typical endometriosis may change into severe atypia with or without hyperplasia and then into carcinoma. Nevertheless, conclusive evidence supporting this model is lacking. Studies prospectively evaluating the risk of cancer in patients with endometriotic atypia and/or complex hyperplasia are extremely scarce and inconclusive [14,17,19]. A major limit in investigating the potential malignant transformation of these lesions is that, during a surgical intervention for endometriosis, excision of endometriomas is generally complete and, consequently, it may be argued that atypical lesions are practically absent after surgery. As previously done for endometrial hyperplasia [22], a long-term survey of untreated cases of endometriotic hyperplasia-atypia with the aim to assess the real malignant potential of these lesions would represent an optimal study design. For ethical reasons, this study is obviously unfeasible.

Molecular findings are presently not sufficient to support the idea of endometriosis as the precursor lesion of some ovarian tumors. According to some studies, about 50% of endometriosis lesions would harbor somatic genetic changes in chromosomal regions supposed to contain genes involved in ovarian tumorigenesis, especially for the endometrioid histotype [23]. Common aberrant genetic events have been detected in cases of endometriosis concomitant with cancers supporting the progression model of carcinogenesis from the benign precursor to the ovarian tumour [24–26]. However, these data were unequivocally replicated [27]. Furthermore, gene mutational studies are very few in this context. Isolated studies have found somatic mutations at PTEN gene and modifications of the protein level in about 20% of endometriotic cysts [28,29]. Along this line, a very elegant study in genetically engineered mice has shown that, in mice harboring an oncogenic allele of K-ras resulting in the development of benign lesions reminiscent of endometriosis, a conditional deletion of PTEN caused the progression towards the ovarian endometrioid tumor [30]. Therefore, although these studies tend to sustain the possibility that endometriotic tissue may harbor mutations in genes critical to cancer development, the real frequency of these genetic alterations is presently completely unknown.

**Characteristics of endometriosis-associated ovarian carcinomas**

The frequency of endometriosis remains a debated issue [7,8]. Diagnosis of the disease is typically made by direct visualization of the pelvis during a laparoscopic surgical examination as non-invasive diagnostic tools have a relatively low sensitivity. This aspect represents a major limit in determining the precise prevalence of the disease in the general population considering that an unknown but probably large proportion of affected patients are asymptomatic. Thus, the reported surgically-diagnosed annual incidence of 1.3–1.6 per 1000 women aged 15–49 years may represent an underestimation of the real frequency [31]. This problem complicates the evaluation of the frequency of association between endometriosis and ovarian cancer, which is made even more complex considering that most patients with an ovarian tumor are in postmenopausal age, when diagnosis of endometriosis is quite difficult.

Keeping in mind these limitations, endometriosis was found to be concomitantly present to ovarian tumors in 4–29% of cases operated for the malignancy (Table 1) [4,11,12,21,32–38]. These percentages do not appear to be very different from the 10% supposed prevalence of the disease in the reproductive age [39]. On the other hand, a consistent body of evidence has documented a clear association between endometriosis and...
endometrioid and/or clear cell ovarian carcinomas (Table 1). This observation represents one of the most important issues supporting a possible causal relationship between endometriosis and ovarian cancer.

A novel aspect in the field of endometriosis is represented by its anatomical asymmetric distribution [14,40–42]. In patients with a monolateral endometrioma, the proportion of left-sided lesions varies between 57% and 64% [14,40,42]. This asymmetrical distribution, not found for non-endometriotic benign cysts [43], is thought to be compatible with the anatomical difference between the two hemipelvis which would facilitate the permanence of the refluxed endometrium in the left side. Interestingly, a preponderance of left-sided endometriosis tended to be younger and to be diagnosed in earlier stages without concomitant endometriosis. Patients with endometriosis are frequently asymptomatic until advanced stages. The typical symptoms of endometriosis might facilitate earlier diagnosis whereas ovarian cancers are frequently asymptomatic until advanced stages.

### Non-ovarian cancers arising from endometriosis

There are a paucity of studies, usually case reports, describing malignancies arising from extraovarian endometriosis. Combining all literature reports, Heaps et al. identified 44 cases of malignant tumors arising in endometriosis from extragonadal sites [10]. Frequent locations were the pelvis, the rectovaginal septum, and the colon/rectum and they were typically diagnosed as endometrioid carcinomas (66%). The second more frequent diagnosis was represented by sarcomas (25%). Surprisingly, only 2 cases of clear cell carcinoma were identified (5%). Although based on a smaller series, this figure has been subsequently confirmed [49,50]. The low frequency of the clear cell histotype is in contrast with findings reported for ovarian endometriosis but reasons to explain this discrepancy are unknown.

### Evidence from population-based cohort studies

Few cohort studies have evaluated the subsequent cancer risk after long-term follow-up in women with a diagnosis of endometriosis.

#### The Swedish studies

Beginning in 1964, the Swedish National Board of Health and Welfare started collecting data on individual hospital discharges in an inpatient register. Since each record contains precise medical data including diagnosis of endometriosis, this tool has been used to investigate the potential association between endometriosis and cancer. The frequency of cancer in the general population adjusted for age was used as a referral group. A cohort study and its following expansion and two cohort nested case–control studies [51,52] have so far derived from this register.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Ovarian cancer histotype</th>
<th>Endometrioid</th>
<th>Clear cell</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors</td>
<td>Serous</td>
<td>Mucinous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aure et al. [32]</td>
<td>0% (0/357)</td>
<td>1% (1/203)</td>
<td>9% (20/212)</td>
<td>24% (14/59)</td>
<td>4% (35/831)</td>
</tr>
<tr>
<td>Kurman and Craig [33]</td>
<td>6% (7/118)</td>
<td>4% (2/47)</td>
<td>11% (4/37)</td>
<td>8% (2/28)</td>
<td>2% (2/176)</td>
</tr>
<tr>
<td>Russel [34]</td>
<td>3% (7/233)</td>
<td>4% (3/69)</td>
<td>28% (20/72)</td>
<td>48% (16/33)</td>
<td>2% (2/176)</td>
</tr>
<tr>
<td>Vercellini et al. [4]</td>
<td>4% (8/220)</td>
<td>6% (6/94)</td>
<td>26% (30/114)</td>
<td>21% (8/38)</td>
<td>12% (11/88)</td>
</tr>
<tr>
<td>De La Cuesta et al. [11]</td>
<td>0% (0/10)</td>
<td>6% (1/18)</td>
<td>39% (9/23)</td>
<td>41% (7/17)</td>
<td>4% (1/28)</td>
</tr>
<tr>
<td>Toki et al. [35]</td>
<td>10% (9/88)</td>
<td>9% (3/33)</td>
<td>30% (16/54)</td>
<td>50% (22/44)</td>
<td>0% (0/16)</td>
</tr>
<tr>
<td>Jimbo et al. [36]</td>
<td>9% (8/92)</td>
<td>3% (1/35)</td>
<td>23% (3/13)</td>
<td>41% (13/32)</td>
<td>8% (2/28)</td>
</tr>
<tr>
<td>Fukunaga et al. [12]</td>
<td>10% (6/63)</td>
<td>6% (2/35)</td>
<td>42% (13/31)</td>
<td>54% (27/50)</td>
<td>6% (2/3)</td>
</tr>
<tr>
<td>Ogawa et al. [21]</td>
<td>7% (4/60)</td>
<td>0% (0/17)</td>
<td>43% (3/7)</td>
<td>70% (30/43)</td>
<td>8% (2/3)</td>
</tr>
<tr>
<td>Vercellini et al. [37]</td>
<td>3% (2/61)</td>
<td>3% (1/30)</td>
<td>20% (13/66)</td>
<td>14% (5/35)</td>
<td>6% (1/17)</td>
</tr>
<tr>
<td>Oral et al. [38]</td>
<td>4% (3/70)</td>
<td>6% (2/35)</td>
<td>22% (4/18)</td>
<td>9% (1/11)</td>
<td>8% (4/49)</td>
</tr>
</tbody>
</table>

Those studies evaluating association with at least endometrioid, clear cell, and seromucinous histotypes have been included. a Only Stage I cancers were included.
In the first study [5], the records of 20,686 women who were hospitalized for endometriosis from 1969 to 1983 were linked against the National Swedish Cancer Registry through 1989 to detect all subsequent diagnoses of cancer. The mean follow-up was 11.4 years and the cohort contributed 216,851 woman years. Standardized incidence ratios (SIR) and relative 95% Confidence Interval (95% CI) were computed using age- and period-specific incidence rates derived from the Swedish population. A total of 738 malignancies was detected among the study subjects, resulting in an overall SIR of 1.2 (95% CI, 1.1–1.3). Significant risk increases were observed for cancer of the breast (SIR = 1.3; 95% CI, 1.1–1.4), of the ovary (1.9; 95% CI, 1.3–2.8), and for all hematopoietic malignancies (SIR = 1.4; 95% CI, 1.0–1.8). This latter increase was largely determined by an excess risk of non-Hodgkin’s lymphoma (SIR = 1.8; 95% CI, 1.2–2.6), which was limited to patients admitted after age 40. The risk of ovarian cancer was particularly elevated among subjects with a long-standing history (≥10 years) of ovarian endometriosis (SIR = 4.2; 95% CI, 2.0–7.7) [5]. The expansion of this study [53] enrolled a total of 64,492 women after a hospital discharge diagnosis of endometriosis from 1969 to 2000 but the previously reported increased overall cancer risk was not confirmed (SIR = 1.0; 95% CI, 0.9–1.0). Conversely, this study still documented an increase in risk for ovarian cancer (SIR = 1.4; 95% CI, 1.2–1.7) and for non-Hodgkin’s lymphoma (SIR = 1.2; 95% CI, 1.0–1.5). Supporting a trend found in the original study, the risk of cervical cancer resulted decreased (SIR = 0.6; 95% CI, 0.5–0.8).

Using the same register, data involving 15,844 women who underwent gynecologic operations between 1965 and 1983 were analyzed to assess the risk of breast cancer in relationship to indication for surgery. Endometriosis as the sole indication for surgery was associated with a more than 3-fold increase in risk (Table 3) [51].

Finally, Borgfeldt and Andolf [52] evaluated whether women born before 1970 and discharged from hospital during the period 1969–1996 with a diagnosis of ovarian cyst (n = 42,217), functional ovarian cyst (n = 17,998), or endometriosis (n = 28,163) had an increased risk of developing gynecologic cancers. For each case, three controls were matched. Women with endometriosis had an overall increased risk for gynecologic malignancy (odds ratio, OR = 1.1; 95% CI, 1.0–1.3), and specifically for ovarian cancer (OR = 1.3; 95% CI, 1.0–1.7). The risk was even more pronounced after more than 10 years from the diagnosis of endometriosis (OR = 1.5; 95% CI, 1.0–2.1) and was inversely related to parity, being almost 2-fold in nulliparous subjects (OR = 1.9; 95% CI, 1.2–3.0). Finally, women with endometriosis had a decreased risk of both cervical (OR = 0.6; 95% CI, 0.4–0.9) and endometrial cancer (OR = 0.6; 95% CI, 0.4–0.8), whereas no change in breast cancer risk was found (OR = 1.1; 95% CI, 1.0–1.2).

The Iowa Women’s Health Study

The Iowa Women’s Health Study is a prospective study designed to identify risk factors for cancer and other chronic diseases in postmenopausal women [6]. This large cohort of postmenopausal women is linked annually to the Iowa Cancer Registry to determine if they have developed a malignancy. Self-reported history of endometriosis diagnosis was recorded on a baseline questionnaire and its association with cancer evaluated. Of the 37,434 women at risk, 1392 (3.8%) reported at baseline that they had ever been diagnosed with endometriosis. Endometriosis was not associated with risk of all cancers combined [Relative Risk (RR) 0.9 (95% CI, 0.8–1.0)]. Unfortunately, the power of this study was insufficient to draw conclusions on the risk of ovarian cancer. The only specific cancer type found to be associated was the non-Hodgkin’s lymphoma with a 1.8 RR (95% CI, 1.0–3.0) even after adjustment for transfusion history, marital status, and alcohol intake (RR = 1.7; 95% CI, 1.0–2.9), known risk factors for this type of tumor.

Cohort studies enrolling infertile women

Since endometriosis is associated with infertility, association between the disease and cancer should be interpreted with caution since an increased risk may be due to nulliparity rather than to endometriosis per se. This bias may be particularly relevant for ovarian and breast cancer. In this context, interesting findings were derived from cohort studies specifically enrolling infertile women. Venn et al. evaluated the incidence of gynecologic malignancies in a cohort of 29,700 infertile women using data from 10 Australian infertile clinics. The authors failed to observe an increased risk of breast cancer (SIR = 1.0; 95% CI, 0.7–1.5). The recruited sample size did not allow reliable analysis for uterine and ovarian cancers [54].

More recently, a large U.S. study has assessed the risk of ovarian cancer according to the different causes of infertility (endometriosis, ovulation disorders, tubal disease and pelvic adhesions, male factors or uterine/cervical disorders, and unexplained causes/incomplete work-ups) among 12,193 women recruited between 1965 and 1988 in five different centers [55]. Infertile patients were found to have a significantly higher risk of ovarian cancer (SIR = 2.0; 95% CI, 1.4–2.6); the risk was higher for patients with primary (SIR = 2.7; 95% CI, 1.8–4.0) rather than secondary infertility (SIR = 1.4, 95% CI, 0.9–2.3). Among infertile women, patients with endometriosis had the highest risk with an SIR of 2.5 (95% CI, 1.3–4.2) compared to the general population and an SIR of 4.2 (95% CI, 2.0–7.7) for the group with primary infertility. When comparisons by cause of infertility were performed within the infertile population, the SIR for ovarian cancer resulted 1.3 (95% CI, 0.6–2.6) in women with endometriosis. When restricting the analysis only to women with endometriosis and primary infertility, the SIR raised to 2.7 (1.1–6.7). This group of patients might represent those with more advanced stages of the disease. Data from the same series of patients have been successively analyzed with the specific aim to assess the risk of cancers in extraovarian sites [56]. A statistically significant association between endometriosis and melanoma (RR = 2.1; 95% CI, 1.0–4.4) has emerged. The risk for non-Hodgkin’s lymphoma was not increased (data not reported) although the small number of events did not allow definitive conclusions.
Endometriosis and ovarian cancer

Case–control studies

The association between endometriosis and ovarian cancer has been also investigated using a case–control study design.

In a large population-based case–control study, cases 20–69 years of age with a recent diagnosis of epithelial ovarian cancer (n = 767) were compared with community controls (n = 1367) [57]. After adjustment for reproductive and contraceptive factors that reduce the risk such as age, number of pregnancy, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, and breast-feeding, women with ovarian cancer resulted 1.7-fold more likely (95% CI, 1.2–2.4) to report a history of endometriosis.

Ness et al. [58] pooled data on infertility and fertility drug use from eight case–control studies conducted between 1989 and 1999 in the United States, Denmark, Canada, and Australia to examine the relationship between infertility and relative treatments and ovarian cancer. Included in the analysis were 5207 cases and 7705 controls. Endometriosis and unknown cause of infertility resulted independently associated with elevation in ovarian cancer risk after adjustment for standard confounding factors [Odds Ratios (OR) 1.7 (95% CI, 1.1–2.7) and 1.2 (95% CI, 1.0–1.4), respectively].

Finally, Modugno et al. [59] pooled data on the history of endometriosis from 4 population-based, ovarian cancer case–control studies that recruited women from 4 regions of the United States from 1993 through 2001. Of the 2098 cases and 2953 control subjects included in the combined analysis, 177 cases (8.5%) and 184 control subjects (6.3%) reported a history of endometriosis. After adjustments for study site, duration of oral contraceptives use, parity, age, tubal ligation, and family history of ovarian cancer, women with endometriosis resulted more likely to develop ovarian cancer than women without a history of the disease (adjusted OR = 1.3; 95% CI, 1.1–1.6). As expected, cases were less likely to have born children, to have had a tubal ligation, and have used oral contraceptives. Compared with never users of oral contraceptives, the use for >10 years was associated with a substantial reduction in risk among women with endometriosis (adjusted ORs for <10 years and >10 years of use were 0.58 and 0.21, respectively). Among women without endometriosis, the adjusted ORs were 0.70 and 0.47, respectively.

Endometriosis and ovarian cancer: limitations of the studies

Data from the majority of the available cohort and case–control studies tend to suggest an association between endometriosis and ovarian cancer, although it is difficult to precisely estimate the effect size as the observed increase in risk ranges from 30 to 90% (Table 2) [5,52,55,57–59]. The magnitude of this association does not clearly support causality. In epidemiology, a relative risk of less than two is considered to indicate a weak association and weak associations are more likely to be explained by unrelated biases [60]. Some limitations of available studies have to be considered: (1) confounders have not always been controlled adequately. It is well known that parity and oral contraceptive use represent strong preventive factors [61]. Measures of association should at least be controlled for these two factors. Adjustments for these two confounders have been performed only in 3 out of the 7 available epidemiological studies [57–59]. Of note, it cannot be ruled out that some medical treatment options of endometriosis may also influence the hazard of ovarian cancer. A recent study has suggested that danazol, an antiandrogenic medication that was commonly used in the treatment of endometriosis in the past, may increase the risk of ovarian cancer [62]; (2) studies assume that the identification of endometriosis in the past, may increase the risk of ovarian cancer. Hence, some limitations may have biased results towards the null hypothesis whereas others may have led to overestimate the association.

Endometriosis and other cancers

Breast cancer

The potential association between endometriosis and breast cancer remains unclear. This issue is of particular importance given the relatively high incidence of both conditions: even a minor increase in breast cancer risk would have a major clinical impact. Data from previously mentioned cohort studies on the

Table 2

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study design</th>
<th>Entity of the association</th>
<th>OR, SIR, or RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brinton et al. [5]a</td>
<td>Cohort</td>
<td></td>
<td>1.9</td>
<td>1.3–2.8</td>
</tr>
<tr>
<td>Ness et al. [57]</td>
<td>Case–control</td>
<td>1.7</td>
<td>1.2–2.4</td>
<td></td>
</tr>
<tr>
<td>Ness et al. [58]</td>
<td>Case–control</td>
<td>1.7</td>
<td>1.1–2.7</td>
<td></td>
</tr>
<tr>
<td>Berglund et al. [53]a</td>
<td>Cohort</td>
<td>1.4</td>
<td>1.2–1.7</td>
<td></td>
</tr>
<tr>
<td>Brinton et al. [55]</td>
<td>Cohort</td>
<td>1.3</td>
<td>0.6–2.6</td>
<td></td>
</tr>
<tr>
<td>Borgfeldt and Andolf [52]</td>
<td>Case–control</td>
<td>1.3</td>
<td>1.0–1.7</td>
<td></td>
</tr>
<tr>
<td>Modugno et al. [59]</td>
<td>Case–control</td>
<td>1.3</td>
<td>1.1–1.6</td>
<td></td>
</tr>
</tbody>
</table>

OR: odds ratio, SIR: standardized incidence ratio, RR: relative risk, CI: confidence interval.

a The study from Berglund et al. [53] is an extension of the study from Brinton et al. [5].
association of endometriosis and cancer are inconclusive, since an increase in risk was initially found in the Swedish studies [5,51,52] but not in studies from other countries [6,54].

Two case–control studies have specifically focused on this possible association [63,64]. One of these studies has reported an elevated OR of borderline significance in premenopausal women (OR = 4.3; 95% CI, 0.9–20.4) but an OR <1 in postmenopausal women [63]. The second study did not find significant variation in breast cancer risk in association with a history of surgery for endometriosis (OR = 1.1; 95% CI, 0.7–1.8).

Data on the association between endometriosis and breast cancer should be interpreted with caution, because of the small number of subjects reporting the condition, the trend towards a protective effect in postmenopausal women observed in some studies [63,64], and the lack of consistency among studies. Available epidemiological findings are summarized in Table 3.

### Table 3

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study design</th>
<th>Entity of the association</th>
<th>OR, SIR, or RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moserson et al. [23]</td>
<td>Case – control</td>
<td>4.3</td>
<td>0.9–20.4</td>
<td></td>
</tr>
<tr>
<td>Schairer et al. (A) [51]</td>
<td>Cohort</td>
<td>3.2</td>
<td>1.2–8.0</td>
<td></td>
</tr>
<tr>
<td>Schairer et al. (B) [51]</td>
<td>Cohort</td>
<td>3.0</td>
<td>0.7–4.1</td>
<td></td>
</tr>
<tr>
<td>Brinton et al. [5]</td>
<td>Cohort</td>
<td>1.3</td>
<td>1.1–1.4</td>
<td></td>
</tr>
<tr>
<td>Weiss et al. [64]</td>
<td>Case – control</td>
<td>1.1</td>
<td>0.7–1.8</td>
<td></td>
</tr>
<tr>
<td>Venn et al. [54]</td>
<td>Cohort</td>
<td>1.0</td>
<td>0.7–1.5</td>
<td></td>
</tr>
<tr>
<td>Olson et al. [6]</td>
<td>Cohort</td>
<td>1.0</td>
<td>0.8–1.2</td>
<td></td>
</tr>
<tr>
<td>Borgfeldt and Andolf [52]</td>
<td>Case – control</td>
<td>1.1</td>
<td>1.0–1.2</td>
<td></td>
</tr>
<tr>
<td>Brinton et al. [56]</td>
<td>Cohort</td>
<td>0.8</td>
<td>0.6–1.1</td>
<td></td>
</tr>
<tr>
<td><strong>Cervical cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brinton et al. [5]</td>
<td>Cohort</td>
<td>0.7</td>
<td>0.4–1.3</td>
<td></td>
</tr>
<tr>
<td>Berglund et al. [53]</td>
<td>Cohort</td>
<td>0.6</td>
<td>0.5–0.8</td>
<td></td>
</tr>
<tr>
<td>Borgfeldt and Andolf [52]</td>
<td>Case – control</td>
<td>0.6</td>
<td>0.4–0.9</td>
<td></td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brinton et al. [5]</td>
<td>Cohort</td>
<td>1.1</td>
<td>0.6–1.9</td>
<td></td>
</tr>
<tr>
<td>Olson et al. [6]</td>
<td>Cohort</td>
<td>1.2</td>
<td>0.6–2.5</td>
<td></td>
</tr>
<tr>
<td>Borgfeldt and Andolf [52]</td>
<td>Case – control</td>
<td>0.6</td>
<td>0.4–0.8</td>
<td></td>
</tr>
<tr>
<td>Brinton et al. [56]</td>
<td>Cohort</td>
<td>0.8</td>
<td>0.3–1.9</td>
<td></td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wyshak et al. [65]</td>
<td>Case – control</td>
<td>3.9</td>
<td>1.2–12.4</td>
<td></td>
</tr>
<tr>
<td>Frisch et al. [66]</td>
<td>Case – control</td>
<td>1.1</td>
<td>0.5–2.3</td>
<td></td>
</tr>
<tr>
<td>Holly et al. [69]</td>
<td>Case – control</td>
<td>0.9</td>
<td>0.5–1.4</td>
<td></td>
</tr>
<tr>
<td>Brinton et al. [5]</td>
<td>Cohort</td>
<td>1.0</td>
<td>0.7–1.5</td>
<td></td>
</tr>
<tr>
<td>Olson et al. [6]</td>
<td>Cohort</td>
<td>0.7</td>
<td>0.2–1.8</td>
<td></td>
</tr>
<tr>
<td>Brinton et al. [56]</td>
<td>Cohort</td>
<td>2.1</td>
<td>1.0–4.4</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Hodgkin’s lymphoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brinton et al. [5]</td>
<td>Cohort</td>
<td>1.8</td>
<td>1.2–2.6</td>
<td></td>
</tr>
<tr>
<td>Olson et al. [6]</td>
<td>Cohort</td>
<td>1.7</td>
<td>1.0–2.9</td>
<td></td>
</tr>
<tr>
<td>Berglund et al. [53]</td>
<td>Cohort</td>
<td>1.2</td>
<td>1.0–1.5</td>
<td></td>
</tr>
</tbody>
</table>

OR: odds ratio, SIR: standardized incidence ratio, RR: relative risk, CI: confidence interval.

a The study from Berglund et al. [53] is an extension of the study from Brinton et al. [5].

Three possible explanations for the slight, if any, increase in breast cancer risk among women with endometriosis, especially premenopausal ones, can be hypothesized: (1) the two diseases may share a common pathogenetic insult. Of note, both conditions have an hormonal-dependent etiology; (2) endometriosis, a possible cause of infertility, is particularly evident in nulliparous women or in women who have delayed childbearing, both risk factors for breast cancer; (3) treatment of endometriosis with medications such as danazol, progestational agents, and oral contraceptives could have an adverse effect on the breast.

### Cervical and endometrial cancer

The documentation of a reduced risk of cervical cancer in patients with endometriosis using the National Swedish Cancer Register is unexpected (Table 3) [5,52,53]. If confirmed, this association could be interpreted in terms of increased number of referrals to a gynecologist from patients with endometriosis, and the consequent more regular performance of cervical smears.

The relationship between endometriosis and endometrial carcinoma is potentially interesting because it could suggest a “baseline” genetic predisposition of the endometrium of some women to undergo malignant transformation. In other words, the eutopic endometrium, and not endometriosis per se, would be the origin of eutopic and ectopic adenocarcinomas. However, no association has been found between endometriosis and endometrial carcinoma in population-based studies (Table 3) [5,6].

### Melanoma

An association between melanoma and endometriosis has been repeatedly reported by a single research group (Table 3) [65–68]. In general, these studies collected a limited number of subjects, concerned dysplastic nevi, a well-known precursor of melanoma, rather than the cancer itself and were characterized by too many subanalyses in relation to the casistics evaluated. Based on one of these studies, among 7559 female college and university alumnae, a higher number of subjects with melanoma reported procedures related to the reproductive system, including surgery for endometriosis (OR = 3.2; 95% CI, 1.0–10.1 versus the non-melanoma skin cancer group, and OR = 3.9; 95% CI, 1.2–12.4 versus women with neither malignancies).

However, when the reproductive history of a group of women attending the Pigmented Lesion Unit of the Massachusetts General Hospital was investigated [66], the risk of endometriosis was not increased in the group of women with melanoma and without dysplastic nevi (OR = 1.1; 95% CI, 0.5–2.3).

Results from large independent observational studies are controversial in this regard (Table 3). Holly et al. [69] investigated oral contraceptive use and reproductive factors in a population-based case–control study of 452 women aged 25–59 years with a cutaneous malignant melanoma and 930 controls. No consistent association was observed between melanoma risk and oral contraceptive use as well as any considered reproductive factors, including endome-
Endometriosis (OR = 0.9; 95% CI, 0.5–1.4). These findings were subsequently confirmed in the first study by Brinton et al. [5] (SIR 1.0, 95% CI, 0.7–1.5) and in the Iowa Women’s Health Study [6] (RR 0.7, 95% CI, 0.2–1.8), but in the latter report, number of expected cases was very low. However, the most recent study by Brinton et al. has again proposed this possible association [56]. As previously mentioned, a statistically significant increased risk of melanoma in the order of 2-fold was documented in infertile women with endometriosis when compared to patients with other causes of infertility.

Non-Hodgkin’s lymphoma

The association between non-Hodgkin’s lymphoma and endometriosis is intriguing. The two largest population-based cohort studies have independently documented this association [4,5] (Table 3). However, the statistically significant results from these studies are based on a small number of observed cases and need further confirmation. Case–control studies aimed to verify this association are lacking.

Potential explanations for an increased risk of non-Hodgkin’s lymphoma in women with endometriosis are currently speculative. Three different explanations for this association have been suggested [6]: (1) humoral immunity abnormalities have been documented in women with endometriosis. More specifically, there may be a link between B-cell activation in endometriosis and development of B-cell lymphoma; (2) the association may be consequent to medications prescribed to treat endometriosis; (3) the link between the two conditions may be due to a common etiological agent [6].

Discussion

Endometriosis does not appear to be associated with an increased risk of cancer in general. In contrast, evidence is accumulating suggesting a link between endometriosis and specific cancer types, but still definitive conclusions are difficult to draw. Besides the possible malignant transformation of ectopic endometrium, the main question remains “how often does this occur?”. Moreover, the issue is not limited to degeneration of genital tissues, but includes the risk of developing some specific cancers in distant organs apparently not affected by endometriosis. Even if further evidence is required, some epidemiological data support an association with melanoma and non-Hodgkin’s lymphoma [6,56].

However, to date, the main scientific interest has been focused on the relationship between endometriosis and epithelial ovarian cancer. Data from large cohort and case–control studies tend to suggest an association between the two diseases although, in general, most of the observed effect sizes are modest [5,52,55,57–59]. Insights from clinical series also indicate a connection between endometriosis and ovarian cancer which is represented by the consistently demonstrated association between endometriosis and endometrioid and clear-cell histotypes [4,11,12,21,32–38]. Thus, there is no doubt that current evidence is robust enough to sustain a link between endometriosis and ovarian cancer. However, the demonstration of an association between two conditions cannot be used to infer causality. Two possible scenarios may be envisioned to explain this link:

1. Endometriotic cells might undergo somatic mutational events involving tumor suppressor genes and/or oncogenes able to confer to the cells the malignant potential characteristics of cancer. According to this view, endometriosis would be the precursor of some, if not all, ovarian cancers of endometrioid and clear cell histologic types. Support to the idea of the ectopic tissue as the benign precursor of some ovarian cancers comes from those cases of evident histologically-proven transition from the benign disease to the malignant entity [12,14]. Moreover, the asymmetric distribution of endometrioid ovarian cancers [37], a topographical feature that has been repeatedly reported for endometriosis [40] gives further support to this hypothesis.

2. Alternatively, endometriosis and ovarian carcinoma might represent two distinct biological entities characterized by a different set of causative molecular events and their relative frequent coexistence may derive from the sharing of some risk factors or antecedent mechanisms (genetic predisposition, immune dysregulation, environmental factors). In this regard, nulliparity and menstrual characteristics (early age at menarche, regular menstrual cycles) are well known determinants of the risk for both the conditions [70–76]. Other common risk factors are a diet rich in saturated fats and alcohol and coffee consumption [33,74]. Unfortunately, very few studies have analyzed the role of different risk factors on various histologic subtypes of ovarian cancer; the only important reported difference is the suggested risk effect of the use of hormone replacement therapy (HRT) on endometrioid, but not other histologic types of ovarian cancer. The use of this therapy is known to increase the risk of persistence of endometriosis after menopause [77–86].

At present, we are unable to disentangle this issue; the idea that, in rare cases, the ectopic tissue undergoes malignant transformation cannot be refuted but we are unable to quantify the entity of this process and consequently to infer that causality should be advocated to explain the increased risk of specific histotypes of ovarian cancer in women with endometriosis. Biological findings are sometimes useful to unravel this kind of issues but, as already mentioned, molecular knowledge is presently not very helpful in this field.

On this basis, it cannot be concluded that “women with endometriosis should be considered at high risk for the development of ovarian cancer” [3] for the malignant potential of the disease. Consequently, from a clinical point of view, it is questionable whether a systemic and serial surgery may be justifiable in women with endometriosis based on the assumption that eradication of visible lesions would abolish this increase in risk. More importantly, it has never been demonstrated that a surgical aggressiveness towards endometriotic lesions might lower future ovarian cancer risk. On the other hand, it is well known that oral contraceptives have a
protective effect of on ovarian cancer risk in general. Recent evidence also supports a specific protective effect in women with endometriosis [59]. Oral contraceptive use is associated with a substantial and duration-dependent reduction in risk, with an observed 80% lower occurrence of ovarian cancer in women with endometriosis who use the drug for >10 years. Hence, the prescription of oral contraceptives for long periods of time seems wise in women with recurrent endometriosis. This approach is based on robust data and seems preferable to the uncertain results of a repetitive surgery that, in these patients, is sometimes associated with major morbidity due to severely distorted anatomical conditions.

Another area of speculation is the role of HRT with unopposed estrogen or of selective estrogen receptor modulators (SERMs) such as tamoxifen in the genesis of endometriosis-associated cancer. Estrogenic stimulation with unopposed estrogen produces a 20% rate of endometrial hyperplasia and treatment with tamoxifen as an estrogen agonist in endometrial tissue may cause a spectrum of proliferative endometrial lesions including hyperplasia. The behaviour of the ectopic tissue in this regard might be similar to that of the eutopic tissue in which complex hyperplasia can definitively progress to frank cancer in 10% of the cases. Unfortunately, clinical data are extremely scanty. Modesitt et al. observed that among 21 women with extraovarian cancer arising in endometriosis 62% received HRT [49]. No other case series on this topic is currently available. Some reports of patients developing malignant transformation of endometriosis after abdominal hysterectomy and bilateral salpingo-oophorectomy while on long-term unopposed HRT have been published [87 – 89]. Similarly, a possible association between tamoxifen therapy and malignant transformation of endometriosis has been proposed based on the occurrence of sporadic cases [90,91].

Overall, the following therapeutic suggestions can currently be proposed:

(a) No “prophylactic surgery” should be offered systematically in women with endometriosis. Combined oral contraception, a demonstrated strong protective factor against ovarian cancer, should be favored;

(b) Before prescribing unopposed estrogen replacement therapy to women with endometriosis who underwent hysterectomy, information should be given on the potential risk of neoplastic degeneration of residual endometriotic foci. Administration of progesterone to women who are receiving HRT after a definitive operation for endometriosis might be wiser. Similarly, tamoxifen should not be precluded to women with a history of endometriosis who need tamoxifen as an adjuvant therapy in the treatment of breast cancer. Evidence supporting a favoring effect of tamoxifen on malignant transformation of endometriosis is only based on inferences and the entity of the potential risk is completely unknown.

For other types of tumors, since evidence supporting an association is scanty and debated, no modifications in the standard, age-related diagnostic evaluations for the early detection of cancer are suggested. Although an increase in breast cancer risk in patients with endometriosis has been suggested in some studies [5,51,52], data are not robust enough to suggest major modifications in the standard, age-related diagnostic evaluations for the early detection of this cancer. Similarly, women with endometriosis should undergo the usual dermatologic surveillance suggested for the general population, as there is no definitive evidence of an association with malignant melanoma [5,6]. General practitioners and gynecologists should be aware of the possibility that women with endometriosis are at increased risk of non-Hodgkin’s lymphomas, and consequently, should seek prompt evaluation in case of recurrent infections, unexplained fever, persistent cough, or weight loss. However, because the total number of patients that develop non-Hodgkin’s lymphoma in the general population is relatively small, no major invasive or expensive diagnostic investigations seem warranted in women with endometriosis undergoing routine screening programs.

The set-up of nation-based register of women diagnosed with endometriosis is badly needed. Researchers and experts in the field should join their efforts to increase the awareness of endometriosis as a social problem among responsible of major Health Institutions, which are the only possible source of funding needed to support extensive, long-term cohort studies. Further research could help greatly in definitively disentangling the issue of the type of relationship between endometriosis and cancer, and in programming the opportune treatment and follow-up modalities.

References


Prevalence of ovarian endometriosis as suggested by a nested case–control study. Gynecol Oncol 2001;83:100–8.


