به نام خدا
Endometriosis and Gynecologic cancers

M. S. Hosseini  Gyn-Oncologist

SHAHID BEHESHTI UNIVERSITY OF MEDICAL SCIENCES
IMAM HOSSEIN HOSPITAL
Endometriosis and ovarian cancers

Endometriosis appears to be associated with some epithelial ovarian cancers (EOC)

whether women with endometriosis are at risk for other types of cancers is unclear, but the overall risk appears to be low.
In a meta-analysis of 13 case-control studies including nearly 8000 women with EOC, women with a self-reported history of endometriosis had three times the risk of clear cell and double the risk of endometrioid and low-grade serous, but no change in risk of high-grade serous or mucinous EOC.
• A subsequent population-based study of nearly 50,000 Finnish women with endometriosis again reported an overall increased risk of ovarian cancer, endometrioid, clear cell, and serous types, in women with ovarian endometriomas overall standardized incidence ratio 2.56, (95% CI 1.98-3.27).

• The excess risk of ovarian cancer for women with ovarian endometriosis resulted in two additional cases per 1000 women followed for 10 years.

• In this study, there was no statistically significant association with isolated peritoneal endometriosis and ovarian cancer.
A subsequent population-based study of nearly 50,000 Finnish women with endometriosis again reported an overall increased risk of ovarian cancer (endometrioid, clear cell, and serous types) in women with ovarian endometriomas (i.e., ovarian endometriosis; overall standardized incidence ratio 2.56, 95% CI 1.98-3.27), but not for women with peritoneal or deep infiltrating endometriosis.
Activation of oncogenic KRAS and PI3K pathways and inactivation of tumor suppressor genes PTEN and ARID1A have been suggested as mechanisms for the transformation of ovarian endometriomas to malignancy.

The risk of malignant transformation of endometriosis has been estimated at 1 percent for premenopausal women, and 1 to 2.5 percent for postmenopausal women.

In a study of women with postmenopausal endometriosis, 35 percent (20 of 57) had different grades of metaplasia, hyperplasia, atypia, and endometrioid carcinoma arising in ovarian endometriosis.

Van Gorp T¹, Amant F, Neven P, Vergote I, Moerman P.

Abstract
For several decades, endometriosis has been suspected of playing a role in the aetiology of ovarian cancer. The literature concerning a possible histogenesis of ovarian cancer from benign endometriosis is reviewed in this chapter. Epidemiological evidence from large-cohort studies confirms endometriosis as an independent risk factor for ovarian cancer. Further circumstantial evidence for this link was found in the common risk factors for ovarian cancer and endometriosis. These risk factors influence retrograde menstruation and endometriosis in the same positive or negative way. Based on data in the literature, the prevalence of endometriosis in epithelial ovarian cancer has been calculated to be 4.5, 1.4, 35.9, and 19.0% for serous, mucinous, clear-cell and endometroid ovarian carcinoma, respectively. The risk of malignant transformation in ovarian endometriosis was calculated at 2.5% but this might be an underestimate. In addition, some authors described atypical endometriosis in a spatial and chronological association with ovarian cancer. Finally, molecular studies have detected common alterations in endometriosis and ovarian cancer. These data suggest that some tumours, especially endometrioid and clear-cell carcinomas, can arise from endometriosis. Moreover, endometriosis-associated ovarian cancer represents a distinct clinical entity, with a more favourable biological behaviour, given a lower stage distribution and better survival than non-endometriosis-associated ovarian cancer.

PMID: 15157647 DOI: 10.1016/j.bpo.2003.03.001 [Indexed for MEDLINE]
• Ovarian endometrioid carcinoma is often associated with and believed to arise from endometriosis (up to 42 percent of patients have evidence of ovarian or pelvic endometriosis.
• Endometrioid ovarian carcinoma is associated with carcinoma of the endometrium in 15 to 20 percent of cases.
Review Article

The Association between Endometriomas and Ovarian Cancer: Preventive Effect of Inhibiting Ovulation and Menstruation during Reproductive Life

Giovanni Grandi,1 Angela Tossi,2 Laura Cortesi,3 Laura Botticelli,2 Annibale Volpe,1 and Angelo Cagnacci1

1Department of Obstetrics Gynecology and Pediatrics: Obstetrics and Gynecology Unit, Azienda Ospedaliero Universitaria Policlinico of Modena, Via del Pozzo 71, 41124 Modena, Italy.
2Department of Oncology, Haematology and Respiratory Disease, Azienda Ospedaliero Universitaria Policlinico of Modena, Via del Pozzo 71, 41124 Modena, Italy.
3Department of Laboratory Medicine and Pathology, Azienda Ospedaliero Universitaria Policlinico of Modena, Via del Pozzo 71, 41124 Modena, Italy.

Correspondence should be addressed to Giovanni Grandi; grandi.gio@olec.it

Received 3 April 2015; Accepted 18 August 2015

Academic Editor: Ivo Metinohd-Herlebn

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Although endometriosis frequently involves multiple sites in the pelvis, malignancies associated with this disease are mostly confined to the ovaries, evolving from an endometrioma. Endometriomas present a 2.3-fold increased risk of transformation to clear-cell endometroid, and possibly low-grade serous ovarian cancer, but not in mucinous ovarian cancers. These last cancers are, in some aspects, different from the other epithelial ovarian cancers, as they do not appear to be decreased by the inhibition of ovulation and menstruation. The step by step process of transformation from typical endometriosis, through atypical endometriosis, finally to ovarian cancer seems mainly related to endocrine stress, inflammation, hyperestrogenism, and specific molecular alterations. Particularly, activation of oncogenic KRAS and PI3K pathways and inactivation of tumor suppressor genes PTEN and ARID1A are suggested as major pathogenic mechanisms for endometriosis associated clear-cell and endometrioid ovarian cancer. Both the risk for endometriomas and their associated ovarian cancers seem to be highly and similarly decreased by the inhibition of ovulation and retrograde menstruation, suggesting a common pathogenetic mechanism and common possible preventive strategies during reproductive life.

Endometriosis and risk of ovarian cancer: what do we know?

Milena Králíčková1,2,3, Antonio Simone Lagana3, Fabio Ghezzi4, Vaclav Vetvicka5

Received 8 April 2019 / Accepted 25 October 2019 / Published online: 19 November 2019

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Abstract

Purpose. Despite long and intensive research, endometriosis remains one of the leading causes of morbidity among premenopausal women. The majority of endometriosis-related ovarian carcinomas occur in the presence of atypical ovarian endometriosis. Nevertheless, despite the increased incidence of ovarian cancer in patients with endometriosis, our knowledge of the risk factors and mechanisms is still incomplete.

Method. Narrative overview, synthesizing the recent findings of literature retrieved from databases.

Results. Herein, we reviewed and summarized the most recent knowledge regarding endometriosis and ovarian cancer.

Conclusion. The evidence showing that patients with endometriosis have a higher risk of developing ovarian cancer is compelling. However, the question of how much higher the absolute risk is, is not fully clear.

Keywords. Endometriosis · Ovarian cancer · Immune imbalance · Neangiogenesis · Apoptosis

Introduction

Endometriosis is a chronic, estrogen-dependent, progressive disease characterized by the presence of endometrium-like tissue, glands, and stroma, outside the uterine cavity [1]. It most commonly involves ovaries, fallopian tubes, and the pelvic peritoneum. This disease is due to the ectopic implantation of endometriol-like cells, accompanied with their elevated proliferation and migration. It is the leading cause of morbidity among premenopausal women, and the complex pathogenesis of this enigmatic disorder remains controversial despite extensive research [2], which started almost 160 years ago [3]. This complex disease, affecting approximately 10% of women of reproductive age, has strong effects on the life of many women. It can cause spontaneous pregnancy loss and infertility in up to 50% of the women [4]. The main diagnostic tool for endometriosis is laparoscopy and histological confirmation on the surgical specimen, although ultrasound is able to identify both ovarian endometriomas (cysts) and deep infiltrating endometriosis [5]. The most commonly suggested causes of endometriosis are retrograd menstruation, genetic predisposition, lymphatic spread, immune dysfunction, metaplasia, or environmental causes [6,7]. Besides significant negative effects on women’s health and wellbeing [8], the risk of development of ovarian cancer cannot be overlooked [9].
Gynecologic Oncology: Original Research

Risk of Gynecologic Cancer According to the Type of Endometriosis

Lisa Sevvalainen, MD, Heini Lassus, MD, PhD, Anna Blut, MS, Aila Tiitinen, MD, PhD, Päivi Härkö, MD, PhD, Mika Gissler, MD, PhD, Eero Pukkala, MD, and Oskari Heikinheimo, MD, PhD

OBJECTIVE: To assess the risks of gynecologic cancer according to the type of endometriosis in women with surgically verified endometriosis.

METHODS: This is a population-based study of women with surgically verified endometriosis retrieved from the Finnish Hospital Discharge Registry 1987–2012 (N=49,933); the subtypes of ovarian (n=23,210), peritoneal (n=20,187), and deep infiltrating (n=2,372) endometriosis were analyzed separately. Gynecologic cancers were obtained from the Finnish Cancer Registry. The outcome measure was the standardized incidence ratio (95% CI) calculated as the ratio between the observed to the expected number of cancers and defined for each gynecologic cancer and further stratified according to the histology, follow-up time since surgery, and age at follow-up. The follow-up was 38,683 person-years, and the Finnish female population served as the reference.

RESULTS: Endometriosis was associated with increased risk of ovarian cancer (standardized incidence ratio 1.76 [95% CI 1.47–2.08]), especially with endometrioid (3.12 [2.15–4.30]) and clear cell (5.17 [3.20–7.89]) histologic type and to a lesser extent with serous type (1.37 [1.02–1.86]). The risk of ovarian cancer was highest among women with ovarian endometriosis and especially for endometrioid (4.72 [2.75–7.56]) and clear cell (10.1 [5.50–16.9]) ovarian cancer, occurring 5–10 years after the index surgery. The overall risk of ovarian cancer was not increased among women with peritoneal and deep infiltrating endometriosis. However, peritoneal endometriosis was associated with a twofold increase in risk of endometrioid histology. The risk of endometrial cancer was not altered in the entire cohort. The standardized incidence ratio for precancerous cervical lesions was 0.81 (0.71–0.92) and for invasive squamous cell carcinoma of the cervical cancer 0.46 (0.26–0.91).

CONCLUSION: The excess risk of ovarian cancer among women with ovarian endometriosis translates into two excess cases per 1,000 patients followed for 10 years. Acknowledging these risks is important when planning long-term management of women with endometriosis.

(OBSTET GYNECOL 2018;131:995–102) DOI: 10.1097/ACOG.0000000000002624

The association between endometriosis and cancer has been studied intensively. Endometriosis is characterized by chronic inflammation, tissue-specific excess production of estrogen, and resistance to progesterone, which characteristics may also predispose to cancer. In addition, endometriosis presents
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Lifetime Probability (%)[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1.0</td>
<td>1.3[1]</td>
</tr>
<tr>
<td>BRCA1 gene mutation</td>
<td></td>
<td>35 to 46[2,3]</td>
</tr>
<tr>
<td>BRCA2 gene mutation</td>
<td></td>
<td>13 to 23[2,3]</td>
</tr>
<tr>
<td>Lynch syndrome (hereditary nonpolyposis colon cancer)</td>
<td></td>
<td>3 to 14[4,5]</td>
</tr>
<tr>
<td>Other gene mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td></td>
<td>5.8[5]</td>
</tr>
<tr>
<td>RAD51C</td>
<td></td>
<td>5.2[7]</td>
</tr>
<tr>
<td>RAD51D</td>
<td></td>
<td>12[7]</td>
</tr>
<tr>
<td>Family history of ovarian or fallopian tube cancer</td>
<td>Uncertain[8]</td>
<td></td>
</tr>
<tr>
<td>(with negative testing for a familial ovarian cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
<td>2.67[9]</td>
</tr>
<tr>
<td>Endometriosis (increase in risk of clear cell,</td>
<td></td>
<td>2.04 to 3.05[10]</td>
</tr>
<tr>
<td>endometrioid, or low-grade serous carcinomas)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking (increase in risk of mucinous</td>
<td></td>
<td>2.1[11]</td>
</tr>
<tr>
<td>carcinoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrauterine device</td>
<td></td>
<td>0.68[12]</td>
</tr>
<tr>
<td>Past use of oral contraceptives</td>
<td></td>
<td>0.73[13]</td>
</tr>
<tr>
<td>Past breastfeeding (for &gt;12 months)</td>
<td></td>
<td>0.72[14]</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td></td>
<td>0.69[15]</td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td></td>
<td>0.71[16]</td>
</tr>
</tbody>
</table>
Screening for ovarian cancer

• While there appears to be an association between endometriosis and EOC, endometriosis is not considered a premalignant lesion, and screening is not recommended.

• There are no data indicating that prophylactic removal of endometriosis lesions reduces the risk of EOC.

• However, use of oral contraceptive pills decreases the risk of ovarian cancer in all users.
• Endometriosis-associated EOC appears to develop in younger women and has a better prognosis than most cases of EOC.

• In one retrospective series of 84 women with clear cell EOC, women with carcinoma arising in endometriosis lesions were younger (49 versus 59 years old) and had a better medial overall survival (196 versus 34 months) than women without endometriosis.
Ovarian remnant syndrome

• Patients with ORS may be affected by endometriosis or ovarian cancer.
• Thus, post-oophorectomy presentation consistent with either of these conditions requires evaluation.
• ORS with pelvic pain is often associated with endometriosis.
• Remnant ovarian tissue may contain endometriotic implants, or hormonal stimulation from functional ovarian tissue may stimulate endometriotic implants at other sites.

• The presence of malignancy in remnant ovarian tissue has been described in patients with a history of bilateral oophorectomy.

• In one series, 2 of 20 patients with ORS were reported to have ovarian adenocarcinoma, and a case of ovarian endometrioid carcinoma was noted in a patient 10 years after initial oophorectomy.
Endometriosis of rectovaginal or bowel disease

- In a study of 83 women undergoing surgical resection of intestinal endometriosis, 8 percent (7 of 83) had a concurrent malignancy.

- Four of the tumors were identified in endometriosis lesions (one clear cell carcinoma, one endometrial stromal sarcoma, and two endometrioid adenocarcinomas).

- Three other tumors arose from the ovary (one granulosa cell tumor, one mucinous carcinoma, and one adenocarcinoma).

- Of note, the majority of these women (71 percent) had an abdominal mass identified on physical examination or imaging, and thus malignancy was strongly suspected preoperatively.

- Additional surveillance for malignancy is not recommended for women with bowel endometriosis at this time.
The multistep process of vaginal cancer arising from deep infiltrating endometriosis: a case report

Jee Hyun Kim¹, Seung Hun Song¹, Gwangil Kim², Kyoung Ah Kim³ and Woo Ram Kim²

Abstract
Background: Malignant transformation of endometriosis in extravasation sites remains rare. Furthermore, the process is not definitely understood.

Case presentation: Herein, we report the case of a 40-year-old premenopausal nullipara woman who presented with vaginal bleeding and who was finally diagnosed with a vaginal cancer originating from endometriosis and with a synchronous endometrial cancer. A gynecologic examination revealed a multiple polypoid mass on the posterior vaginal fornix. Magnetic Resonance Imaging of the pelvis showed two masses abutting respectively on the anterior uterine wall and in the rectovaginal septum. The patient underwent a total laparoscopic excision of the rectovaginal mass, radical hysterectomy and low anterior resection of the rectum. The lesions were diagnosed as endometriosis, endometriosis-associated complex hyperplasia and endometrioid cancer. Furthermore, a synchronous endometrioid endometrial cancer was reported.

Conclusions: This case revealed the multistep process of malignant transformation of deep infiltrating endometriosis. The progression was individualized between implantation sites and in the same organ.

Keywords: Deep infiltrating endometriosis, Vaginal cancer originating from endometriosis, Synchronous endometrial cancer, Endometriosis-associated complex hyperplasia, Endometriosis-associated endometrioid cancer

Fig. 1 Multiple polypoid masses on the posterior vaginal fornix

Fig. 2 Magnetic Resonance Imaging of the pelvis finding of a multiple polypoid mass on the posterior vaginal fornix
Tumor markers

**CA 125**: Serum CA 125 values are elevated in approximately 50 percent of women with early-stage disease and in over 80 percent of women with advanced ovarian cancer.

The specificity of CA 125 is limited.

CA 125 levels are elevated in approximately **1 percent** of healthy women and fluctuate during the menstrual cycle.

CA 125 is also increased in a variety of benign and malignant conditions, including:
- Endometriosis
- Uterine leiomyoma
- Cirrhosis with or without ascites
- Pelvic inflammatory disease
- Cancers of the endometrium, breast, lung, and pancreas
- Pleural or peritoneal fluid due to any cause

Mean CA 125 levels further vary with ethnicity and smoking status (lower in non-white women and current smokers).
Human epididymal secretory protein E4 (HE4):

Like CA 125, human epididymal secretory protein E4 (HE4) is a promising biomarker for ovarian cancer.

In contrast to CA 125, HE4 levels do not appear to be elevated in women with endometriosis, and thus can be useful to rule out ovarian cancer in patients with endometriosis and a pelvic mass.

However, further study is warranted.
• CA125, HE4, risk ovarian malignancy algorithm (ROMA)

• **Risk malignancy index (RMI)**

RMI = UxMxserum CA125 (where U = 0 for an ultrasound score of 0, U = 1 for an ultrasound score of 1, and U = 3 for an ultrasound score of 2-5 and M = 1 for pre-menopausal women and M = 3 for post-menopausal women. If the patient underwent CT or MR prior to ultrasound, the parameters for the sonographic evaluations were identical to those described by Jacobs et al)

• **Ovarian cancer symptom index**

• The index is considered to be positive in women who report pelvic or abdominal pain, bloating, increased abdominal size, difficulty eating or early satiety occurring more than 12 times a month, with symptoms present for less than one year

• **Pelvic ultrasonography**

• **Multimodal screening**