Endometriosis and Endometriosis-Associated Ovarian Cancer (EAOC)

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1 Introduction

Endometriosis is a gynecologic disease that affects over 10% of women of reproductive age causing pelvic pain, dysmenorrhea, and infertility, resulting in significant disability and reduced quality of life [1, 2].

In endometriosis the endometrial glands, stroma, and blood vessels develop outside the uterus, most commonly in the ovary, often creating cystic cavities lined by endometrial tissue (ovarian endometriotic cysts). Hormonal-related cyclic changes may involve the ectopic endometrial tissue the shedding of which may fill the closed cavity of the cyst with blood irritating the epithelial lining and producing an inflammatory reaction. The endometrioid tissue lining may also react by epithelial atypical hyperplasia and even neoplasia, in a manner somehow similar to that in the uterine cavity and under the same hormonal influences. It should be mentioned that

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endometriosis develops during the reproductive period of a woman's life being absent before puberty and in late menopause, except for the iatrogenic effect of hormone therapy.

The diagnosis of endometriosis requires histologic evidence of the presence of endometrial glandular and stromal tissue outside of the uterus. Microscopically, the tissue may exhibit estrogen-related changes (cell proliferation) and, during pregnancy or with progestin therapy, secretory changes and even stromal decidualization. The vicinity of steroid hormone-secreting Graafian follicles may enhance their effect on the ovarian endometriotic foci.

The most frequent sites affected by the endometriosis are the ovaries, posterior cul-de-sac, fallopian tubes, bladder, and large and small bowel, but endometriosis may affect almost any organ in the body such as the lung and even the brain.

2 Pathogenesis

Several hypotheses have been suggested as the etiology of the endometriosis. The most accepted is the theory of retrograde menstruation whereby the retrograde menstrual flow through the fallopian tubes into the peritoneal surface seeds these surfaces and organs leading to attachment of endometrial cells and their proliferation at distant pelvic and abdominal sites and peritoneal cavity. Second hypothesis, coelomic metaplasia, assumes that metaplastic changes in the peritoneum, under stimuli from the estrogen stimulation, environment, infections, or other agents, transform the mesothelium into endometrial cells to develop endometriosis. Very recent genetic studies have suggested that endometriosis is a clonal disease in the epithelium and its development is independent of stroma, providing new insight into the genesis of endometriosis.

3 The Relationship of Endometriosis and Ovarian Cancer

The association between endometriosis and ovarian cancer has perplexed clinicians and scientists for many years since it was first reported by Sampson in 1925 [3]. Today endometriosis is classified in typical and atypical, based on the degree of histological atypia. At the present time, it is, however, unclear if atypical endometriosis is a true precursor of endometriosis-associated ovarian cancer (EAOC) or whether it represents an inflammatory and reactive histologic background [4]. The clear cell carcinoma and endometrioid carcinoma are the most frequent histologic types associated with endometriosis; however, even serous and mucinous subtypes have been found in association with endometriosis occasionally.

Several excellent reviews have summarized the current evidence on endometriosis and EAOC including theories on possible pathogenesis of ovarian cancer arising from endometriosis, yet to date there is no clear mechanism and uniform hypothesis

that would explain the risk of ovarian cancer in women with endometriosis and the etiology of EAOC.

The significance of this relationship was reported by Britton in a large Swedish study of 20,686 women hospitalized because of endometriosis and followed for 11.4 years and is further confirmed by Brinton et al. in 2004 with a retrospective cohort study conducted in the United States [5], analyzing the correlation of endometriosis causing primary infertility and ovarian cancer, resulting in an SIR of 4.19 (95% CI 2.0–7.7) and a risk ratio of 2.72 (95% CI 1.1–6.7) compared with patients with secondary infertility and no endometriosis. Further analysis within the cohort of primary infertility patients with endometriosis in 2005 by Brinton et al. again revealed elevated relative risks (95% CI) of 2.9 (1.2–7.1) for ovarian cancer, 2.4 (0.7–8.4) for colon cancer, 4.65 (0.8–25.6) for thyroid cancer, and 2.3 (0.8–6.7) for melanomas [6]. These Swedish cohort studies were expanded by Melin et al. in 2006 to evaluate whether risk ratios were consistent with longer follow-up [7]. The cohort was 64,492 endometriosis patients discharged from hospitalization identified through the Swedish Inpatient Registry from 1969 to 2000. When cross-referenced with the national Swedish Cancer Registry, 3349 patients were identified to have developed ovarian cancer. With extended follow-up and calculation of updated standardized incidence ratios, there was no risk for overall cancer (1.04), but an increase was noted in ovarian cancer (1.43 [95% CI 1.2–1.7]), endocrine tumors (1.36 [95% CI 1.2–1.6]), non-Hodgkin lymphoma (1.24 [95% CI 1.0–1.50]), and brain tumors (1.22 [95% CI 1.0–1.4]). Importantly, the risk for women with early diagnosis and long-standing endometriosis was most pronounced, with standardized incidence ratios (SIRs) of 2.01 and 2.23, respectively [8]. Of note, women with a history of hysterectomy at or before time of endometriosis diagnosis did not show an elevated risk [9]. Again, both studies of the Swedish cohorts may be skewed to reflect malignant incidence ratios for cases of more severe endometriosis, because the cohorts were hospitalized patients with more advanced stages of endometriosis. Also, because records of hospitalized patients were retrospectively cross-referenced with a separate cancer patient registry, there is the possibility of negating or including cases erroneously.

Olsen et al. completed the largest study that did not support the increased ovarian cancer risk in endometriosis patients [9]. Analyzing a group of 37,434 postmenopausal women, a cohort of 1392 postmenopausal patients who self-reported the diagnosis of endometriosis was isolated. After an average 13-year follow-up, no significant increased risk was found for all cancers, breast cancer, or ovarian cancer, but there was a significant association with increased risk of non-Hodgkin lymphoma, with an age-adjusted risk ratio of 1.8 (95% CI 1.0–3.0). This study involved acceptable long-term follow-up; however, several factors must be taken into account. The study was underpowered, as the cohort was smaller and included only three ovarian cancer cases. Furthermore, the endometriosis was not histologically confirmed, and, because all of the patients were postmenopausal, it is possible that younger patients may have already developed ovarian cancer and died. Table 1 summarizes the epidemiologic studies of ovarian cancer risk in endometriosis patients.

Table 1 Epidemiologic studies assessing ovarian cancer risk in endometriosis patients

Author	Study type	Cohort size	Mean follow-up (years)	Ovarian malignancies identified	Ovarian cancer in endometriosis patients (SIR/OR)	
Brinton et al., 1997 [19]	Cohort	20,686 endometriosis patients	11.4	29	Overall cancer risk	
					Ovarian cancer	1.2
					Ovarian cancer with ≥10 years	1.9
					Follow-up	2.5
					Ovarian cancer with long-standing endometriosis	4.2
Brinton et al., 2004 [20]	Cohort	12,193 infertility patients		45	Ovarian cancer	2.5
Brinton et al., 2005 [5]	Cohort			2491	2.53 (1.19–5.38)	
Ness et al., 2000 [17]	Case control			66	Ovarian cancer	1.7
Borgfeldt and Andolt 2004 [19]	Nested case control	28,163		81	Ovarian cancer	1.3
Modugano et al., 2006 [21]	Case control			177	1.3 (1.1–1.6)	
Melin et al., 2006 [7]	Cohort	64,492	12.7	122	Overall cancer risk	1.04
					Ovarian cancer	1.43
					Ovarian cancer early	2.0
					Diagnosed endometriosis	2.2
					Ovarian cancer with long-standing endometriosis	
Olson et al., 2002 [8]	Cohort	1392	13	3	No increased risk for overall or ovarian cancer	
Kobayashi et al., 2007 [22]	Cohort	6398	12.8	46	Ovarian cancer	8.95
					Ovarian cancer >50 years old	13.2

Reciprocal analysis of the prevalence of endometriosis found in ovarian cancer patients also supports the clinical correlation. In a review of 29 studies from 1973 to 2002 on the prevalence of endometriosis in epithelial ovarian cancers organized by location of disease, the following three groups were compiled: (1) histologic proof of transition from ovarian endometriosis to cancer as defined by Sampson [10], (2) ovarian cancers with endometriosis in the same ovary, and (3) ovarian cancers with concomitant pelvic endometriosis. The second category was considered to be the best estimation of endometriosis in the different histologic subtypes, yielding a prevalence of 4.5% in serous, 1.4% in mucinous, 35.9% in clear cell, and 19% in endometrioid carcinomas [11, 12].

These data were further corroborated by Valenzuela et al. in 2007 [13]; among 22 cases of ovarian endometrioid adenocarcinomas of the ovary, three patients were found to have concomitant endometriosis as defined by the Sampson criteria. The review by Van Gorp et al. calculated an ovarian cancer prevalence of 0.9% in all cases of endometriosis, 2.5% when present in the same ovary, and 4.5% when coexistent with any pelvic endometriosis [11]. Malignant extraovarian endometriosis is estimated to account for 25% of all malignant transformations of endometriosis and 80% of the endometrioid subtype [14–16].

Looking at the trend of ovarian cancer in endometriosis is more difficult because endometriosis is not always aggressively resected and confirmed by histopathologic studies. Only a limited number of the studies controlled for confounding factors for both diseases, such as parity, infertility, tubal ligation, ovarian hyperstimulation, and duration of endometriosis; Ness et al. completed two case–control studies confirming the association between endometriosis and ovarian cancer [17, 18]. In a group of 767 women with ovarian cancer and 1367 control subjects, with adjustments made for age, parity, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, and breast-feeding, overall women with breast cancer were 1.7-fold more likely to report an endometriosis history [17]. Furthermore, in a pooled study of 13,000 women, ovarian cancer was more likely among subfertile women, especially with infertility resulting from endometriosis, showing an odds ratio of 1.9 (95% CI 1.2–2.9) [18].

In 2012, Pearce et al. suggested that ovarian cancer risk associated with endometriosis varies according to histologic subtype of ovarian cancer [23]. In a pooled analysis of 13 case–control studies from the Ovarian Cancer Association Consortium database, the investigators assessed self-reported endometriosis data from a total of 23,144 women—13,326 controls, 7911 with invasive ovarian cancer, and 1907 with borderline ovarian cancer. When stratified by age (5-year categories) and ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other) and adjusted for duration of oral contraceptive use (ranging from 0 to ≥10 years), self-reported history of endometriosis was associated with a significantly increased risk of invasive clear cell, invasive low-grade serous, and invasive endometrioid ovarian cancer subtypes. No association was found between a history of endometriosis and invasive mucinous, invasive high-grade serous, or borderline (both serous and mucinous) ovarian cancer [23, 24].

Over the last few years, a new paradigm for ovarian cancer pathogenesis has emerged that presupposes two distinct types of ovarian epithelial carcinoma with distinct molecular profiles: type I and type II carcinomas. Type I tumors include endometrioid, clear cell carcinoma, and low-grade serous carcinoma and mostly arise via defined sequence either from endometriosis or from borderline serous tumors, mostly presenting in an early stage. Histologic evidence of endometriosis is found in 23–36% of type I endometrioid and clear cell ovarian cancers [25]. Together these cancers are known as endometriosis-associated ovarian cancer (EAOC). In a clinical and histological correlation study of endometriosis and ovarian cancer [26], out of 76 with stage 1 invasive ovarian cancer, ovarian endometrioma was present in 40 cases. Fifty-four patients had non-serous carcinomas (40 endometrioid, 10 clear, and 4 mixed endometrioid and clear cell carcinoma), and all had ovarian endometriomas, peritoneal endometriosis, or both. Interestingly, one third had abnormal endometrial pathology such as endometrioid adenocarcinoma, hyperplasia, or polyp. No serous carcinoma patient presented with pelvic pain and abnormal vaginal bleeding with or without pelvic pain [26].

The type II serous carcinomas, which overall represents the bulk of ovarian malignancies, were not associated with pelvic endometriosis.

Recent molecular studies in type I ovarian carcinomas identified the presence of somatic mutations in *ARID1A*, *KRAS*, *PTEN*, *PIK3CA*, *MLH1*, and B catenin [27, 28]. In addition, *TP53*, *BCL2*, and *POLE* mutations have also been described [29, 30].

Similar gene mutations have been found both in EAOC and adjacent benign endometriosis suggesting that they share the common clonal origin [31]. PTEN mutation were found in benign endometriotic cysts as well as in endometrioid and clear cell ovarian carcinoma suggesting that PTEN may be involved early in malignant transformation of endometriosis. On the other hand, in EAOC, KRAS mutation is frequently seen in endometrioid and mucinous carcinomas, but it is not present in adjoining endometriosis or atypical endometriosis.

ARID1A is a tumor suppressor gene that encodes BAF250a protein, a member of SWI/SNF chromatin remodeling complex [32]. Mutations in *ARID1A* have been found in clear cell carcinoma (46–95%) and in endometrioid carcinoma of the ovary (30%) [33]. The high frequency of *ARID1A* mutation, leading to a functional loss of the protein, strongly suggests its role in EAOC.

TP53 mutation which is otherwise pathognomonic for high-grade serous ovarian carcinoma is found in 30% of endometriosis when it is associated with clear cell carcinoma. Benign endometriosis has not been associated with *TP53* mutation, and it has not been found in endometriosis coexisting with endometrioid carcinoma (reviewed in [4]).

4 Epigenetics

The role of epigenetic gene regulation in endometriosis and EAOC is currently under investigation. The exact mechanism and the interrelation of multiple epigenetic changes are not fully understood, yet it is known that EAOC despite sharing in general common genetic aberration does behave different biologically; this may be a consequence of epigenetic gene silencing or activation. The two main types of EAOC, clear cell carcinoma (CCC) and endometrioid cancer (EC), have different biomarkers. Transcription factor HNF1β (hepatocyte nuclear factor-1β) *is* a biomarker of ovarian CCC histology, but not of EC. HNF1β-positive cells have been found both in clear cell carcinoma and adjacent endometriosis. The main role of HNF1β is in glycogen synthesis, antioxidative defense, anti-apoptosis, and resistance to chemotherapy. HNF1β is overexpressed in clear cell carcinoma whereby it upregulated glycolysis and yielded increased amount of lactate. This allows cancer cells to avoid excess reactive oxygen species (ROS) production, thereby allowing survival advantage in endometrioma. On the other hand, HNF1β upregulates the synthesis of glutathione and antioxidant, and that gain also gives advantage to clear cell carcinoma survival.

EC has a high expression of estrogen receptors ERα and ERβ. This expression is significantly higher than in clear cell carcinoma (reviewed in [34]). Estrogen receptor expression may be modifiable by a number of facts such as epigenetic (methylation, acetylation) or heme binding. In endometriosis ERβ is hypomethylated, and therefore the protein is overexpressed, while ERα is lower in endometriosis [35]. Upregulation of ER and hyperestrogenic state may lead to malignant transformation into EC in endometriosis, not associated with clear cell carcinoma. Overexpression of ER is actually associated with better outcome of both EC and CCC, not having a role in cancer progression [36]. Further, hypomethylation of ER gene promoter is correlated with *HNF1β* gene promoter hypermethylation in EC [37]. The combination of low ER and high HNF1β is a potential marker of EC.

5 The Role of Microenvironment and Immune System

Endometriosis is a chronic inflammatory condition, and endometriotic cells are adaptable to microenvironment with high levels of cytokines and heme, initially. However, the interplay between these factors and endometriotic cells may start the cascade of cellular events eventually leading to remodeling of extracellular matrix and malignant transformation [38]. Several molecules have been reported as crucial in this process such as MMP-2 as well as CXCR4 which increases VEGF and stimulates the process of angiogenesis in endometriotic foci [39, 40].

The theory of the so-called redox imbalance has been out forward recently to unify different factors involved in the pathogenesis of endometriosis and associated cancers. In this hypothesis, repeated episodes of retrograde menstruation lead to

bleeding into endometriotic cysts and pelvic cavity and release of hemoglobin (Hob), free iron, and heme. Persistent exposure to high heme concentrations exposes tissues to high oxidative stress and formations of reactive oxidative species (ROS). ROS promote DNA damage and early carcinogenesis. It is important to know that most of the iron in endometriotic cyst is heme iron, and not free iron. Heme iron is oxidized to metHb with generation of superoxide anion 02—via antioxidation. The levels of nitric oxide which catabolizes the reaction from oxyHb to metHb is elevated in serum and peritoneal fluid of the patients with endometriosis. It is metHb that induces the production of free radicals, which damage DNA. However, seemingly paradoxically, metHb is downregulated in EAOC, which shows that disturbed balance between oxidative stress and antioxidants is in favor of antioxidants in EAOC (reviewed in [34]). Therefore, this concept of malignant transformation of endometriosis proposes that iron metabolism involvement in malignant transformation of endometriosis is a two-step process: first the by-products of heme metabolism induce ROS and oxidative stress, and then synthesis of antioxidants occurs with consequent resistance to apoptosis and tumor initiation (reviewed in [34]).

While scientists are on the tract to identify the molecular pathways involved in endometriosis and EAOC, the very critical clinical question remains as on how to identify women with endometriosis who are at risk of developing EAOC based on the current knowledge.

Although ovarian cancer will develop in only 0.3–1.6% of women with endometriosis, it is important to assess, document, and systematically follow up the risk factors that may predispose patients to developing ovarian cancer. These include the following: (1) long-standing endometriosis, (2) endometriosis diagnosed at an early age, (3) endometriosis associated with infertility, and (4) the presence of enlarging ovarian endometrioma or changing characteristics and mural nodule formation.

Women found to be at an increased risk of ovarian endometrioma have options of medical (hormonal) or surgical treatment. The treatment should be personalized based on patient's age, desire for childbearing, family history, and type and characteristics of endometriomas. Nezhat et al. have described two types of endometriomas: type I and type II [41].

Type I endometriomas are characterized by small lesions that spread across peritoneal and ovarian surfaces, whereas type II endometriomas originally start as functional hormone-secreting ovarian cysts that are invaded by cortical endometriosis and gradually develop into endometriomas. Hormonal treatment often results in incomplete regression of endometriotic lesions and recurrence of endometriomas. Additionally, in type II endometriomas, adjuvant hormonal suppressive therapy that prevents ovulation can decrease the risk of recurrent ovarian endometrioma formation [41]. Melin et al. showed that women who underwent unilateral oophorectomy for endometriosis had a significantly reduced risk of later development of ovarian cancer, with an OR of 0.19 (95% CI, 0.08–0.46) compared with controls. In addition, ovarian cancer was significantly less likely to develop in women who underwent radical surgical excision of all visible endometriosis, with an OR of 0.30 (95% CI, 0.12–0.74) [42].

In light of the accumulated data and observations regarding endometriosis and ovarian cancer, criteria may be established to stratify the risk of cancer by identifying and monitoring women with endometriosis for risk factors and pursuing risk-reducing medical and surgical treatment options in these women. At the time of surgical diagnosis and treatment, consideration for complete resection of pelvic endometriosis, salpingectomy, oophorectomy, or hysterectomy should be individualized based on a patient's age, desire for future fertility, and preoperative consultation with the patient [43]. These initiatives, if validated, should substantially reduce the risk of ovarian cancer as well as the total mortality risk. As new research becomes available, the recommendations may be refined in terms of both screening and prevention.

In addition to ovarian endometriosis, extraovarian endometriosis may also be associated with malignant transformation (i.e., bowel, bladder, cesarean section scars) [44, 45]. The review by Van Gorp et al. [10] shows ovarian cancer to be prevalent in 0.9% of all endometriosis cases. Furthermore, it shows 2.5% prevalence when present in the same ovary and 4.5% when coexistent with pelvic endometriosis. It is estimated that malignant extraovarian endometriosis accounts for 25% of all malignant endometriosis transformations, 80% of which are of the endometrioid cancer subtype [45]. This rate of incidence of non-ovarian endometriosis transformation suggests that a more in-depth focus on this issue is necessary. There are also reported cases of synchronous endometriosis-associated ovarian and endometrial cancers in certain patient populations.

6 Synchronous Endometrial Carcinoma with Endometrioid Ovarian Carcinoma

Although the association between endometriosis and some subtypes of ovarian cancer has been well established, there is less known about the association between endometriosis and endometrial cancer. More evidence is showing patients with a history of endometriosis that are presenting with synchronous endometrioid endometrial carcinomas (EEC) and endometrioid ovarian carcinomas (EOC). The rate of endometrial cancer diagnosis was significantly higher in women with endometriosis and EOC (33%) than in other ovarian malignancies (11%) ($p = 0.04$) [46, 47]. Deligdisch et al. (2007) retrospectively reviewed 76 patients with stage 1 ovarian carcinoma and histologic characteristics. Forty patients had a diagnosis of EOC with endometriosis, and 17/40 (22%) of patients had coinciding endometrial cancer or 11/40 (14%) with endometrial hyperplasia or polyps [48]. In an earlier study of endometrial cancer, Walsh et al. discovered that at time of surgery, 25% of patients with known endometrial carcinoma were found to have also ovarian carcinoma, >90% EOC [49]. Evidence from molecular studies by Schultheis et al. (2016) demonstrated that 17 patients who underwent genome sequencing had similarities in genetic mutations in EECs and EOCs. Interestingly, four patients had bilateral

EOCs and EEC which were found to be all clonally related [47]. Anglesio et al. showed that there is a clear genetic relationship between EOC and endometriosis [50]. There is no clear evidence of the pathogenesis for these findings; however there are several theories. It can be hypothesized that endometrial cells, migrating into the pelvis with the retrograde menstruation, can give rise to atypical endometriosis and to EAOC [51]. Another hypothesis is that synchronous endometrial and ovarian (SEO) carcinomas result from the dissemination of cells from one organ site to another. However, whether this can be considered a metastasis, dissemination, or the same mutation that occurs in both tissues remains unclear [51]. Most patients with simultaneous EOC and endometrial neoplasia display an analogous hyperestrogenic hormonal profile [26].

7 Treatment for EAOC

After primary staging and debulking surgery, there are no established guidelines for the management of a patient with endometriosis-associated ovarian carcinoma (EAOC). Depending on histologic type and disease stage, treatments are varied from expectant management, adjuvant chemotherapy, radiation therapy, or a combination approach due to the rarity of disease [52–57]. EAOC have mostly two main histologic subtypes: clear cell carcinoma (CCC) and endometrioid carcinoma (EC) [58]. Several population-based studies compared outcomes of patients with prior endometriosis with diagnosed CCC and EC versus patients without endometriosis. EAOC patients were diagnosed at a younger age, had earlier stage of disease, had decreased recurrence rates (26.9% vs. 41%), and had an improved overall 5-year survival (75% vs. 55%) [56, 58–60].

Early-stage disease CCC and EC treated with adjuvant chemotherapy was shown to decrease disease recurrence. Regimens mainly consisted of carboplatin/paciltaxel or irinotecan/cisplatin for 6 cycles in retrospective cohort studies [61–63]. This was beneficial for stage 1C yet controversial for stages 1A and 1B with lower recurrence rates and no significant difference in overall survival [64–66]. Later stages of CCC have shown resistance to chemotherapy, whereas chemotherapy for EC should remain with standard regimens [61, 62].

Later-stage CCC treated with radiotherapy has shown improved survival and decreased mortality in several studies likely due to its resistance to standard chemotherapy regimens. Nagai et al. (2007) treated patients with external beam radiotherapy versus platinum chemotherapy for stages 1–3. Results showed an increase in disease-free survival and overall survival (81.2% and 81.8%, respectively) in the radiation group versus 25.0% and 33.3% in the platinum group [67]. Swenerton et al. (2010) treated patients with adjuvant radiotherapy having a 40% reduction in disease-specific mortality [68]. Hoskins et al. (2012) treated patients with combination carboplatin/paclitaxel and radiation with an improved disease-free survival of 20% at 5 years [69].

Endocrine therapy for treatment of endometriosis has been previously studied to decrease symptoms and potential progression of disease after surgical treatment [70–73]. These hormonal treatments are also well documented in the treatment of endometrial carcinoma especially for premenopausal patients seeking future fertility [74, 75]. For both CCC and EC, there is evidence for the use of adjuvant treatment with aromatase inhibitors or progesterone [76, 77]. Several studies and phase II trials utilized aromatase inhibitors specifically with recurrent EC or chemotherapy-resistant EC with decreased rates of recurrence and increased survival [78–80]. Initial data for adjuvant aromatase inhibitors and progesterone treatments used as a long-term maintenance therapy have also been promising [43, 81, 82].

8 Conclusion

Although not yet fully delineated, there is a strong relationship between endometriosis, ovarian cancer, and some endometrial cancers. Gynecologists as well as general practitioners must be mindful of the apparently increased risk of ovarian cancer among endometriosis patients. Special attention should be paid to patients with early endometriosis diagnosis, a long-standing history of disease, associated infertility, and/or infertility treatment, as these patients seem to be at the highest risk. Advancements in more precise diagnostic analysis into the pathogenesis of endometriosis and the possibility of malignant transformation may help to provide new insights into diagnostic and treatment modalities. Specifically, further elucidation of the involved genetic and immune mechanisms of endometriosis is necessary. Overall, once the transition from benign endometriosis to atypical and malignant tissue is clearly elucidated, marker expression can be analyzed to guide clinical management and outcome. Genomics and proteomics may facilitate the development of these diagnostic and therapeutic tools. At this time, however, surgical resection followed by medical treatment remains the primary method of treatment of endometriosis. With the correlation of endometriosis and ovarian cancer continuing to strengthen over time, appropriate and timely resection and elimination of disease should be practiced.

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