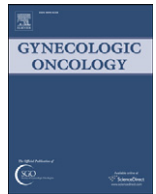




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## Review

## The association between endometriosis and ovarian cancer: A review of histological, genetic and molecular alterations

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## ABSTRACT

**Objective.** This article represents a review of histologic and genetic findings in endometriosis and describes the mechanisms whereby genetic and non-genetic factors potentially contribute to the neoplastic progression of endometriosis.

**Methods.** Literature review of the English language literature based on searching in the MEDLINE (PubMed) database and additional collection of reports by systematically reviewing all references from retrieved papers.

**Results.** Atypical endometriosis seems to represent a transition from benign endometriosis to carcinoma. Endometriosis is characterized by genetic instability: like neoplasms endometriosis seems to be monoclonal in origin, several studies have documented loss of heterozygosity (LOH) in endometriosis, data suggest that mutation of the tumor suppressor gene PTEN play a part in the malignant transformation of endometriosis, some studies have revealed TP53 mutations in endometriotic lesions, and mutation of ARID1A seems to be an important early event in the malignant transformation of endometriosis to endometrioid and clear cell carcinomas. Heme and iron induced oxidative stress, inflammation, and hyperestrogenism are possible links between endometriosis and cancer.

**Conclusions.** The histological and genetic alterations in endometriosis seem to explain why endometriosis can be a precursor of some ovarian cancers, especially clear cell and endometrioid carcinomas. However, the exact molecular mechanisms that may lead to this malignant transformation of endometriosis are not completely understood. More and larger studies are needed to clarify how exactly endometriotic tissue undergoes malignant transformation.

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## Introduction

Endometriosis is an estrogen-dependent, chronic gynecological disorder and is classically defined as the presence of endometrial glands and stroma outside the uterine cavity and musculature [1,2]. The precise etiology of endometriosis is not known but one widely

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accepted mechanism for the development of endometriotic lesions is the adhesion and growth of endometrial fragments deposited into the peritoneal cavity via retrograde menstruation [3–5]. Although endometriosis is considered to be a benign condition, it does share common characteristics with malignant cells. Endometriosis, like cancer, can be both locally and distantly metastatic and it can attach to other tissues, invade, and damage them [6]. In 1925, Sampson [7] was the first to document the case of suspected malignant transformation in endometriosis. Since then, several studies have focused on the relationship between endometriosis and gynecological cancer, especially ovarian cancer. Data from large cohort and case–control studies [8–15] indicate that endometriosis patients have an increased risk of ovarian cancer. Further, endometriosis-associated ovarian cancers are predominantly clear cell and endometrioid histologic subtypes. That is, studies [8,12,15–29] have documented that endometriosis is associated with an approximately 3-fold statistically significant risk of endometrioid and clear cell ovarian cancer. In addition, endometriosis-associated ovarian cancer seems to be a distinct clinical entity; patients are younger, diagnosed in earlier stages, have lower grade lesions and a better survival [13,19,28–30].

In a recent paper we reviewed the epidemiological data concerning endometriosis and ovarian cancer [31]. The aim of this article is to represent a review of histologic and genetic findings in endometriosis and to describe the mechanisms whereby genetic and non-genetic factors potentially contribute to the neoplastic progression of endometriosis.

## Methods

This article reviews the English language literature for studies on the histologic, genetic and molecular mechanisms that could potentially explain the increased risk of ovarian cancer among endometriosis patients. We searched in the MEDLINE (PubMed) database for a 20-year period (January 1990–June 2011), combining the keywords “endometriosis” with “neoplasms” or “ovarian neoplasms”. Additional reports were collected by systematically reviewing all references from retrieved papers.

## Results

### *Atypical endometriosis: a precursor of malignancy*

Similarly to the eutopic endometrium studies have documented the presence of hyperplasia and cytological atypia in endometriosis. Cytologic atypia denotes the presence of cytologic atypia within the lining of endometriotic cysts, whereas hyperplasia refers to the same spectrum of hyperplasia (simple or complex, with or without cytologic atypia) encountered in the endometrium. These two conditions are often referred to collectively as atypical endometriosis, but they should be separately recognized as their clinical significance likely differs [32]. Hence, the term “atypical” has been used with different meanings among pathologists. In general, several studies have suggested that atypical endometriosis may represent a transition from benign endometriosis to carcinoma [21,33–36].

LaGrenada and Silverberg [35] were the first to publish a case series of five ovarian tumors (three clear-cell and two endometrioid carcinomas) associated with atypical endometriosis. In four of these tumors a direct continuous transition was seen from clearly benign epithelium through atypical endometriosis to carcinoma. A case report by Moll et al. [36] demonstrated a chronological association; a woman who on a biopsy specimen first showed atypia within ovarian endometriosis, and then 3 years later had a clear cell carcinoma arising in the same ovary. In a review of 339 patients with cystic ovarian endometriosis Prefumo et al. [34] found that atypia was significantly more present in patients with endometriosis-associated ovarian cancer (endometrioid adenocarcinoma) compared to patients with

endometriosis alone (100% of 14 cases compared to 2% of 325 controls,  $P < 0.00001$ ). Further, the authors documented that complex hyperplasia, but not simple hyperplasia, was significantly more common in cases with associated ovarian carcinoma than in those without malignancy (50% of 14 compared to 1% of 325,  $P < 0.00001$ ). This is supported by Fukunaga et al. [33], who reported that atypical endometriotic foci were observed in 61% of 54 endometriosis-associated ovarian cancers, while such foci were seen in only 1.7% of 255 endometriosis cases without cancers. Finally, Ogawa et al. [21] observed atypical endometriosis in 29 out of 37 (78%) cases with endometriosis-associated ovarian cancer. Interestingly, the transition from typical endometriosis to atypical endometriosis was observed in 22 cases, and the transition from atypical endometriosis to carcinoma, in 23 cases.

Given this evidence atypical endometriosis (both cytological atypia and hyperplasia) is likely a lesion that represents a transition from benign endometriosis to carcinoma.

### *Genetic alterations in endometriotic tissue*

Genomic instability is a known characteristic of cancer cells [37]. In addition, it is well known that most neoplasms are monoclonal in origin, and clonal outgrowth is thought to be a fundamental feature of human neoplasms [38,39]. Several studies have demonstrated evidence for monoclonality of endometriosis. In seven studies [40–46] identified from 1995 to 2003 endometriotic tissue was monoclonal in 60–100% of the samples investigated (100% in five of the studies). However, these findings have been challenged by Mayr et al. [47], who only found monoclonality in 2 of 32 (6%) samples of endometriotic lesions.

Other studies have documented loss of heterozygosity (LOH) in endometriosis [41,48–52]. LOH commonly indicates regions of tumor suppressor gene inactivation, which is central to the development of malignant tumors as well as their precursors. Jiang et al. [41] revealed LOH at candidate ovarian tumor suppressor gene loci in 11 of 40 (27.5%) endometriosis samples. In another study [48], the same authors detected common LOH events in 9 of 11 cases of ovarian endometriosis adjacent or contiguous to ovarian carcinoma. Based on statistical analysis, these common genetic alterations were very unlikely to have occurred as independent events, indicating a possible malignant genetic transition spectrum between endometriosis and cancer. This has been further supported by Prowse et al. [49], who analyzed four endometrioid and six clear cell carcinomas with coexisting endometriosis and found 22 common LOH events. Again, statistical analyses suggested that it was very unlikely that these common genetic alterations had occurred independently. In addition, Obata et al. [50] observed frequent LOH in ovarian atypical endometriosis, and Goumenou et al. [51] found LOH at loci harboring candidate genes implicated in limiting malignant transformation in 8 of 22 (36.4%) endometriosis samples. Interestingly, occurrence of these genetic alterations increased 3-fold from stage II ovarian endometriosis to more severe stages of the disease, suggesting that LOH events accumulate as the disease progresses.

LOH at locus 10q23.3 and mutation of the tumor suppressor gene PTEN (located on 10q23.3) occur frequently in both endometrial and ovarian carcinoma. Sato et al. [52] identified LOH at 10q23.3 in 13 of 23 of endometrial cysts of the ovary (56.5%), 8 of 19 ovarian endometrioid carcinomas (42.1%), and 6 of 22 clear cell carcinomas (27.3%). Further, somatic mutations in the PTEN gene were identified in 20.6% of endometrial cysts of the ovary, 20% of endometrioid carcinomas and 8.3% of clear cell carcinomas. This suggests that inactivation of the PTEN is an early event in the malignant transformation of endometriosis. These findings are supported by Martini et al. [53], who detected reduced PTEN protein expression in 7 of 46 (15%) cases of endometriosis. In addition, a mouse model by Dinulescu et al. [54] provided a support for a role of PTEN in the malignant transformation

of endometriosis; forced expression of oncogenic K-ras or conditional PTEN deletion in ovarian surface epithelium resulted in preneoplastic ovarian lesions with an endometrial glandular morphology, while the combination of both gave rise to invasive and widely metastatic endometrioid ovarian adenocarcinomas. In conclusion, the described LOH events represent a convincing piece of evidence that there might be a continuum between endometriosis and ovarian cancer, the last-mentioned events being the most important. The results from the LOH studies are summarized in Table 1.

Mutation or loss of function of the tumor suppressor gene TP53 (on chromosome 17p13.1), which encodes for the nuclear protein p53, is a frequent and important genetic event in the development of ovarian cancer. Mutations of the TP53 gene are related to overexpression of non-functional p53 protein, which accumulates within the nuclei [55,56]. Therefore, several studies have investigated whether endometriosis harbor mutations in this gene [41,57–62]. Bischoff et al. [57] reported that chromosomal loss of TP53 frequently occurred in severe/late stage endometriosis. Nezhat et al. [58] detected p53 accumulation in 9% and 25% of benign endometriotic lesions next to clear cell carcinoma and endometrioid carcinoma, respectively, while p53 staining was negative in endometriosis without carcinoma. Further, Sainz de la Cuesta et al. [59] found a statistically significant prevalence of p53 overexpression in the transition from typical to atypical endometriosis and to ovarian cancer associated with endometriosis. Finally, Akahane et al. [60] observed TP53 mutation in 4 of 13 (30.8%) specimens of endometriosis coexisting with ovarian clear cell carcinoma, whereas this study did not detect mutations in seven cases of solitary ovarian endometriosis and nine cases of endometriosis coexisting with ovarian endometrioid carcinoma. Moreover, other studies [41,61,62] have also failed to detect mutations in the TP53 gene and/or p53 overexpression in solitary endometriotic lesions not associated with carcinomas. In addition, several published studies show no or very low percentage of TP53 mutation in clear cell ovarian cancer [63,64].

Most recently, a very interesting study by Wiegand et al. [65] has identified ARID1A mutations in endometriosis-associated ovarian carcinomas (clear-cell and endometrioid carcinomas). ARID1A is thought to be a tumor-suppressor gene, and the protein encoded by the ARID1A, BAF250a, is a key component of the multi-protein SWI/SNF chromatin remodeling complex present in all eukaryotes. This complex is involved in the regulation of many cellular processes, including development, differentiation, proliferation, DNA-repair, and tumor suppression. Based on genome-wide mutational analysis, ARID1A mutations were seen in 55 of 119 ovarian clear-cell carcinomas (46%), 10 of 33 endometrioid carcinomas (30%), and none of the 76 high-grade serous ovarian carcinomas. Immunohistochemical analyses confirmed the loss of expression of the BAF250a protein and its correlation with ARID1A mutation status. More important, in two patients, ARID1A mutations and loss of BAF250a expression were evident in the tumor and contiguous atypical endometriosis but not in distant endometriotic lesions. These results provide convincing evidence for the inactivation of ARID1A in the development of clear-cell and endometrioid ovarian cancers. Further, the data suggest that ARID1A inactivation occurs early in the development of these tumors, during transformation of endometriosis. In addition, the presence of ARID1A mutations in ovarian clear cell and uterine

endometrioid carcinomas have also been documented by Jones et al. [66] and Guan et al. [67], respectively.

#### Heme and free iron induced oxidative stress

Heme and free iron are pro-oxidant and can induce oxidative stress and DNA damage, possibly increasing the risk of some cancer [68,69]. Retrograde menstruation, a widely accepted etiology of endometriosis, and the repetition of hemorrhage in the endometriotic (chocolate) cysts during the reproductive period result in excess accumulation of heme and free iron in endometriotic lesions, which may play a role in carcinogenesis [69,70]. Yamaguchi et al. [70] found that the free iron concentration in endometriotic cysts was significantly higher than that in nonendometriotic cysts ( $P < 0.01$ ). In addition, the concentrations of stress-related factors such as lactose dehydrogenase (a marker of tissue damage), lipid peroxidase (a marker of oxidative stress), and 8-hydroxy-2-deoxyguanosine (a marker of DNA damage) were also significantly higher in endometriotic cysts. Moreover, in vitro analyses showed that the contents of endometriotic cysts could produce more reactive oxygen species and induce gene mutations more frequently than the contents in the other cysts.

#### Inflammation

As noted for centuries, inflammation may be central to carcinogenesis. As described by Balkwill and Mantovani [71] “If genetic damage is ‘the match that lights the fire’ of cancer, some types of inflammation may provide the ‘fuel that feeds the flames’”. Inflammatory cells and cytokines may promote angiogenesis, cell proliferation, inhibition of apoptosis, invasion, metastasis, and production of reactive oxygen species that may in turn induce DNA damage and mutations. Thus, inflammation may contribute to tumor growth and progression [71,72].

Endometriosis is associated with a local inflammatory reaction; inflammatory cells surround sites of endometriosis, and increased levels of cytokines and growth factors have been observed in the peritoneal fluid of women with endometriosis [73,74]. It has been proposed that this inflammation may serve to promote the growth and invasion of ectopic endometrium and constitute a link between endometriosis and ovarian cancer [75]. As an example, a study by Daraï et al. [76] reported that endometriosis was associated with serum tumor necrosis factor- $\alpha$  levels similar to those found in women with ovarian cancer, while serum interleukin-6 levels and cyst fluid interleukin-8 levels were intermediate between those observed in benign and malignant ovarian tumors. Slater et al. [77] observed that levels of growth hormone and interleukin-6 were increased in endometriosis and endometrioid adenocarcinomas, compared to normal uterine epithelial cells, suggesting that these proteins appear to be involved in the progression of both conditions. High concentrations of interleukin-1 have been detected in the peritoneal fluid of women with endometriosis [74]. In addition, Wu et al. [78] found that ectopic endometrium was at least 100 times more sensitive to interleukin-1 $\beta$  (IL-1 $\beta$ ), compared with eutopic endometrium. IL-1 $\beta$  can upregulate cyclooxygenase-2 (COX-2) expression, leading to subsequent increased synthesis of prostaglandin  $E_2$  (PGE $_2$ ). Interestingly, PGE $_2$  regulates key-processes, which are characteristic for

**Table 1**

LOH events in endometriosis, ovarian clear cell carcinomas (CCC), ovarian endometrioid carcinomas (EC) and common events in coexisting endometriosis and ovarian cancer.

Author	Endometriosis (%)	CCC (%)	EC (%)	Common LOH events in coexisting endometriosis and ovarian cancer (%)
Jiang et al. 1996 [41]	27.5			
Jiang et al. 1998 [48]				81.8
Prowse et al. 2006 [49]				22 common LOH events in 4 EC and 6 CCC with coexisting endometriosis
Goumenou et al. 2001 [51]	36.4			
Sato et al. 2000 [52]	56.5	27.3	42.1	

tumor growth, e.g. angiogenesis, proliferation, and inhibition of apoptosis [79,80]. Moreover, Rask et al. [81] have demonstrated an increase of COX-2 in epithelial ovarian cancer, correlating to stage with significant elevations in stages II and III.

#### *Steroid hormones*

Estrogens have been linked to the pathogenesis of the gynecological cancers; breast-, endometrium-, and ovary-cancer [82–84]. Moreover, hyperestrogenism stimulates the growth of endometriosis and seems to be associated with the malignant transformation of endometriotic cysts [85,86]. Some studies [87,88] have demonstrated a local increase in estradiol concentration in endometriotic lesions. The enzyme aromatase catalyzes the conversion of androstenedione and testosterone, derived from ovarian and adrenal sources, to estrone and estradiol, respectively. This enzyme is normally absent in eutopic endometrium, but studies by Zeitoun and Bulun [87] have shown high levels of aromatase activity in endometriotic lesions, resulting in increased conversion of androgens to estrogens. Further, another study by Zeitoun et al. [88] found that the enzyme (17 $\beta$ -hydroxysteroid dehydrogenase type 2), which catalyzes the inactivation of estradiol to the less potent estrone, was absent in endometriotic lesions but was normally expressed in eutopic endometrium. In addition, the enzyme (17 $\beta$ -hydroxysteroid dehydrogenase type 1) converting estrone to estradiol was present in endometriosis. In sum, synthesis of the potent estradiol is increased while inactivation is decreased resulting in higher local concentrations of this hormone. Estradiol stimulates cyclooxygenase-2 (COX-2), giving rise to increased PGE<sub>2</sub> formation. PGE<sub>2</sub> is as mentioned above implicated in tumor progression but also stimulates further aromatase activity creating a positive feedback loop in favor of continuous estrogen formation in endometriosis [87]. A study by O'Donnell et al. [89] has shown that the potential carcinogenic action of estrogens in ovarian cancer cells was mediated through estrogen receptor alpha (ER- $\alpha$ ), whereas estrogen receptor beta (ER- $\beta$ ) did not seem to be involved. Interestingly, Matsuzagi et al. [90] have demonstrated higher ER- $\alpha$  than ER- $\beta$  levels in active endometriosis compared to inactive endometriosis, suggesting that ER- $\alpha$  may be essential for the pathogenesis of endometriosis.

Progesterones generally repress estrogen receptors, inhibiting the effects of estrogens at the cellular level. However, there is evidence of a relative progesterone resistance within endometriotic lesions; the presence of the inhibitory progesterone receptor isoform A, the absence of the stimulatory progesterone receptor isoform B, and progesterone receptor gene polymorphism have been observed in endometriosis [2,91,92]. This could lead to further escalation of estrogen actions on endometriotic lesions.

#### **Discussion**

Generally speaking, support to the idea of endometriosis as a precursor of some ovarian cancers comes from the cases of atypical endometriosis with evidence of a histologically-proven transition from benign disease to malignancy. However, conclusive evidence is lacking on this subject, and it cannot be ruled out that the occurrence of atypical endometriosis in ovarian carcinomas is purely coincidental. Further, if ovarian carcinomas do arise from endometriosis, one would expect to find genetic alterations common to both diseases. Conversely, if endometriosis represents a distinct entity then one would expect to find alterations unique to this disease. The genetic studies tend to suggest that endometriotic lesions may harbor mutations in genes critical to cancer development. Moreover, the frequency of genetic aberrations seems to increase for cases of endometriosis adjacent or contiguous to ovarian cancer, and these cases tend to share the same genetic mutations, which supports the model of endometriosis as a malignant precursor. However, it is not clear whether

these genetic alterations support causality as poor consistency exists among the DNA analyses of endometriosis, and the real frequency of these genetic alterations is presently unknown [93]. The recent study by Wiegand et al. [65] may have found a definitive link suggesting that clear cell and endometrioid carcinomas arise from endometriosis and that mutation of ARID1A is important in this process. However, this conclusion is based on only two observations, necessitating extensive validation involving endometriotic lesions from patients with ovarian cancer and patients without cancer. As mentioned above ARID1A mutations in uterine carcinomas have also been documented [67,94]. This is not surprising and further supports the hypothesis of endometriosis as a malignant precursor, since clear cell and endometrioid carcinomas of the ovary seem to be derived from ectopic uterine epithelium, that is, endometriosis. It also raises the possibility that treatments that are effective for uterine clear cell and endometrioid carcinomas could be effective for their ovarian counterparts. Furthermore, if the loss of ARID1A is an early event in the malignant transformation of endometriosis, then perhaps this intervention could serve as a prevention strategy. Should endometriotic lesions be analyzed for expression of BAF250a, the protein encoded by ARID1A? Should patients with endometriotic lesions that show loss of expression be viewed as being at high risk for the development of clear-cell or endometrioid ovarian cancers? Much work remains to be done to define the role of ARID1A in the origin of ovarian cancer. Nonetheless, the discovery by Wiegand et al. has provided an important step forward and the origin of ovarian cancer is becoming clearer.

Recently, our knowledge of epithelial ovarian cancer has evolved decisively. Molecular genetic studies [63,64,95] have led to the development of a new paradigm for the pathogenesis and origin of epithelial ovarian cancer based on a dualistic model of carcinogenesis that divides epithelial ovarian cancer into two broad categories designated types 1 and 2. Type 1 tumors are composed of low-grade serous, low grade endometrioid, clear cell, mucinous, and transitional (Brenner) carcinomas. They are genetically indolent, present in stage 1 and the majority is characterized by specific mutations, including PTEN and ARID1A. Though belonging to type 1 low grade tumor clear cell and mucinous tumors are generally chemoresistant and they are quite aggressive particularly at late stages. Type 2 tumors comprise high grade serous, high-grade endometrioid, malignant mixed mesodermal tumors, and undifferentiated carcinomas. They are aggressive, present in advanced stage, and have a very high frequency of TP53 mutations but rarely harbor the mutations detected in type 1 tumors. In addition, it has been proposed that serous tumors arise from the implantation of epithelium (benign or malignant) from the fallopian tube. Similarly, it seems that endometriosis is the precursor of endometrioid and clear cell carcinomas. As endometriosis is thought to develop from endometrial tissue by retrograde menstruation, these tumors can also be regarded as involving the ovary secondarily. Thus, it appears that both type 1 and 2 ovarian tumors develop independently along different molecular pathways and that both types develop outside the ovary and involve it secondarily. This new dualistic model can explain why some studies [41,60–62] have failed to detect mutations in the TP53 gene and/or p53 overexpression in endometriotic lesions because this mutation is only associated with high grade endometrioid carcinomas and not the other endometriosis-associated ovarian cancers, low-grade endometrioid and clear cell carcinomas. Overall, these findings represent a major shift in our understanding of the origins of ovarian carcinomas and will allow for a more rational approach to screening, treatment, and prevention that potentially can have a significant impact on reducing the mortality of this devastating disease. For example, the heterogeneity of ovarian carcinoma clearly indicates that one screening test will not be effective in detecting all the different types of ovarian carcinomas. In addition, the genes in types 1 and 2 could provide potential targets for therapeutic intervention and moreover, future analysis



of overexpressed genes in ovarian cancer should take into account the histologic type of the tumors being studied and the data should be compared with appropriate normal tissue.

In conclusion, the exact molecular mechanisms that may lead to malignant transformation of endometriosis are not completely understood. As regards heme and iron induced oxidative stress, inflammation, and hyperestrogenism, these theories are possible links between endometriosis and cancer, but definitive data are lacking. More and larger studies are needed to address this problem. Yet, the studies imply interesting knowledge and hormonal modulation, antioxidant, and anti-inflammatory agents could provide future prevention and treatment of endometriosis-mediated lesions. Today, progestin therapy is a standard treatment for endometriosis but as mentioned above studies [2,91,92] have demonstrated a relative progesterone resistance within endometriotic lesions. This finding could explain why endometriosis in some patients fails to regress in response to treatment with progestins. The potential etiology regarding the association between endometriosis and ovarian cancer seems to be multifactorial. For example, clear cell and endometrioid ovarian carcinomas develop from endometriosis that frequently involves multiple sites in the pelvis, but still these neoplasms are almost always confined to the ovaries. It is likely that the propensity for growth in the ovary is multifactorial, but the precise reasons for this are unknown [63]. Given the high prevalence of endometriosis and the high mortality of ovarian cancer the potential association has important public health implications. Identification and characterization of somatic mutations and possible carcinogenic factors such as heme and iron induced oxidative stress, inflammation, and hyperestrogenism are not only fundamental in understanding the molecular pathogenesis of cancer but also can provide the rationale for the development of personalized diagnostic tests and therapy, and that is why it is essential to further investigate the histologic, genetic and molecular alterations in endometriotic tissue.

#### Conflict of interest statement

The authors declare that there are no conflicts of interest.

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