

# Ovarian endometriosis, a precursor of ovarian cancer: Histological aspects, gene expression and microRNA alterations (Review)

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**Abstract.** Ovarian endometriosis is a frequent chronic gynecological disease with an uncertain evolution regarding its progression or association with ovarian malignant lesions. The present review summarized the histological aspects, gene expression and microRNA (miRNA/miR) alterations associated with ovarian endometriosis and cancer and their possible interaction. The endometriosis-ovarian cancer interaction has been proposed by certain researchers as a single entity. Histological results indicated that endometriosis has been in different circumstances coexisting with ovarian cancer, with reference to endometrioid and clear cell carcinoma. Endometriosis with moderate and severe atypia can influence cell proliferation and architecture, resulting in a possible malignant transformation. Gene expression analysis indicated that the pathologies of both endometriosis and ovarian cancer are characterized by genetic instability from a molecular point of view, as several important genetic mutations, including ARID1A, PI3KCA, PTEN, BRCA1, BRCA2, TP53 and KRAS genes, were identified. miRNA alterations have been implicated in the regulation of gene expression. Common dysregulated miRNAs, such as miR-331, miR-335, miR-891,

miR-548, miR-124, miR-148, miR-215, miR-192, miR-337, miR-153, miR-155, miR-144, miR-221 and miR-3688 were extensively investigated in understanding endometriosis and ovarian cancer evolution. From a combined viewpoint including histological aspects, gene expression and miRNA alterations, it is reasonable to speculate that endometriosis is associated with ovarian cancer. Ovarian endometriosis lesions may present a risk for ovarian malignant lesions, which supports a model of endometriosis as a malignant precursor. However, the endometriosis-ovarian cancer association is not widely accepted in the literature and additional studies are required to validate this association.

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*Abbreviations:* EAO, endometriosis-associated ovarian cancer; miRNAs, microRNAs

*Key words:* ovarian endometriosis, ovarian cancer, histology, gene expression, miRNAs

## 1. Introduction

Endometriosis is one of the most painful and frequent chronic gynecological diseases that is characterized by the presence and growth of endometrial ectopic tissue outside the uterus (1). The incidence and prevalence of endometriosis are difficult to quantify, considering that some patients with this pathology are asymptomatic. Hsiao *et al* (2) mentioned a prevalence rate of 10-15% among all women of reproductive age worldwide. In particular, ovarian endometriosis is one of the most frequent subtype that appears in 17-44% women diagnosed with endometriosis (3).

Sampson (4) in 1925, was the first to present with histological details the complex mechanism of the malignant transformation

of endometriosis and its association with epithelial ovarian cancer. Subsequently, Jiang *et al* (5) indicated that progression of endometriosis to ovarian cancer was corroborated by molecular data. At present, the two pathologies are frequently regarded as a single histological entity, which is known as endometriosis-associated ovarian cancer (EAOC) (6). The association between ovarian endometriosis and ovarian cancer is supported by epidemiological data debated in several studies (1,5-14).

Ovarian cancer represents a complex and heterogeneous malignant gynecological pathology (15) with a high mortality rate, with and a 5-year survival rate <45% (16), which is considered to be the second most common gynecologic malignancy in developed countries (17). The risk of ovarian cancer development is ~1% among patients during lifetime in developed countries (18).

In concordance with the histological modifications, the dynamics in coding and non-coding gene expression at cellular level is a decisive factor regarding the cellular phenotype (19). Among these transcripts, microRNAs (miRNAs/miRs), which are small sequences of 19-22 nucleotides in length without coding capacity, have been implicated in post-transcriptional regulation of protein expression (19). miRNAs are capable of regulating complex signaling networks due to their ability to target and influence the translation of coding genes (20). In the case of cancer, miRNAs are classified as tumor suppressors or oncogenes depending on their target genes and also their level of expression (21). The profile of differentially expressed miRNAs in patients with ovarian cancer and endometriosis was analyzed (22). The expression of miRNAs between ectopic and eutopic endometrium in patients with and without endometriosis offered information with diagnostic, prognostic or even therapeutic implications (23,24).

The present review focused on emphasizing the main histological aspects, gene expression and miRNAs alterations in ovarian endometriosis and cancer and their possible association, based on the latest published literature.

## 2. Histological aspects

Histology represents the study of the arrangement for various tissues, which requires a microscopic knowledge of the microanatomy (25). Histopathology is a branch of histology that involves the microscopic identification and study of diseased tissue that not only establish the diagnosis but is also crucial for providing prognostic in data clinical management (26).

*Ovarian endometriosis.* In a histopathological perspective, endometriosis is defined as the presence of endometrial-like glandular epithelium and stroma outside the uterus. At the immunohistochemical level, the phenotype of endometrial glands is similar to that of normal endometrial tissue (27). However, there are certain microscopic alterations specific of ovarian endometriosis, which are listed in Table I and illustrated in Fig. 1.

Regarding the presence of ectopic endometrial epithelium, several studies have documented the presence of hyperplasia and/or atypia in cytologic endometrial lesions (25-27). Atypical endometriosis has been indicated to confer a higher increase risk of malignant transformation to ovarian

cancer (28). A total of ~8% of ovarian endometriosis exhibits histopathological features of atypical endometriosis (4). The presence of hyperplastic lesions in the glandular epithelium is less frequent compared with that in atypia but may be present in some ovarian endometriosis cysts (28).

*Ovarian cancer.* Ovarian cancer is classified in two distinct subgroups, type I and II, taking into account the clinical features, histopathological characteristics and gene expression pattern (24,27). Type I subgroup is characterized by a low rate of proliferation, while type II subgroup exhibits a higher proliferation rate and is more aggressive (24,27). In addition, type I subgroup includes low-grade serous, borderline serous, mucinous, endometrioid and clear cell carcinoma, while type II subgroup is comprises high-grade serous carcinoma, mixed malignant mesodermal carcinosarcomas and undifferentiated carcinoma (28,29).

Two subcategories of type I epithelial ovarian cancer, endometrioid and clear cell carcinoma, appear to be more often derived from or coexist with ovarian endometriosis (9,10,18,30). These two subcategories are the most frequent types after serous carcinoma. Two previous population-based studies which reviewed the pathology using modern diagnostic criteria presented an estimated frequency of 12-13% for clear cell and 9-11% for endometrioid carcinoma, among 20% of all epithelial ovarian cancer (18,31).

The main histological characteristics of these two ovarian cancer subtypes are presented in Table II and Fig. 2.

*EAOC.* EAOC is defined as one of the following three conditions: i) Detection in the same ovary of endometriosis and ovarian cancer; ii) detection of endometriosis in one ovary and of ovarian cancer in the other; iii) coinciding identification of ovarian cancer in any of the ovaries and pelvic endometriosis (28). Considering the initial assumption of Sampson regarding the malignant transformation of endometriosis to ovarian cancer (2), when currently EAOC is considered as a single entity, it has been defined as cumulative histological features characteristic to benign endometriosis, endometriosis contiguous with or associated with an ovarian malignancy and malignant lesions intercalated with several intermediary lesions (Fig. 3) (32).

Several studies reporting histopathological characteristics of EAOC have been performed. Of these, Fukunaga *et al* (33) reported atypical endometriosis for 54% of clear cell and 42% of endometrioid carcinoma. Ballouk *et al* (34) indicated that half of the endometrial cysts demonstrated severe atypia and presented with an invasive capacity of malignancies.

## 3. Gene expression

Abnormal cell transformations, such as endometriosis and ovarian cancer, are sustained at molecular level via alterations in homeostatic gene expression profiles and signaling pathways (22). These changes often result in pathologically expressed proteins that finally lead to the alteration of cellular processes (5,32).

*Ovarian endometriosis.* From a molecular point of view, ovarian endometriosis is characterized by a broad and

Table I. Microscopic criteria for the diagnosis of endometriosis (27).

Type	Criteria
Endometrial type glandular epithelium and stroma with associated constellation of findings	Granulation tissue (macrophages) Hemosiderin deposit Fibrosis Pseudoxanthoma cells Island of residual glandular epithelium or endometrial stroma
Endometrioid cylindrical epithelium	Hyperchromatic nucleus Smudgy chromatin

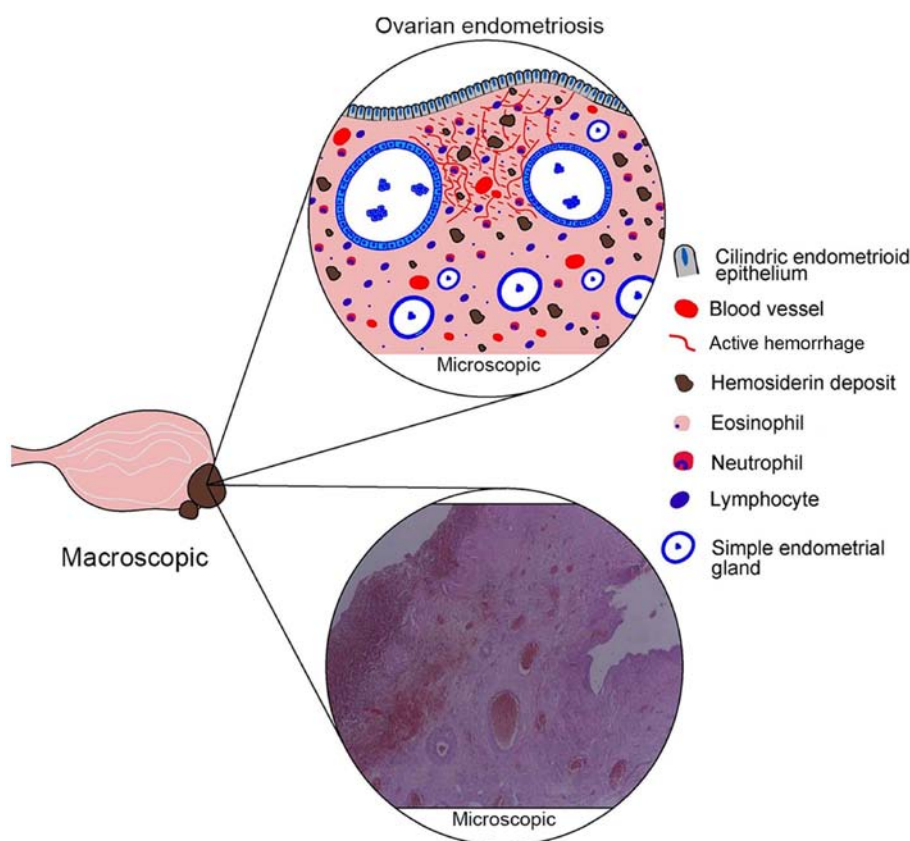


Figure 1. Histological aspects of ovarian endometriosis. In terms of macroscopic features, ovarian endometriosis usually takes the form of a cyst, well defined, unilocular or multilocular, varying in size, with chocolate cysts. In terms of microscopic features, schematic representation (upper image) with subsequent identification of important characteristics in the lower microscopic image outlines the defining endometriosis elements, which include cylindrical endometrial epithelium, endometrial-type glands (simple and/or sometimes atypical), endometrial stroma containing hemosiderin deposits, active bleeding, blood vessels and inflammatory infiltrates (eosinophils, neutrophils and lymphocytes).

important genetic variety which can result in a wide genetic instability (32). Histologically, molecular abnormalities can be concealed in benign endometriosis, which subsequently may lead to a malignant transformation (28).

In ovarian endometriosis, several studies have reported genetic mutations with important contributions in this pathology and its possible malignant transformation (Table III).

ARID1A is a gene identified to exhibit a tumor suppressor role, and the loss of ARID1A expression is considered to be responsible for the activation of early carcinogenic mechanisms (28). Mutations of ARID1A have been indicated

to be directly connected with atypical endometriosis (35). However, no alterations in the ARID1A expression level have been identified in paired samples of distal nonatypical endometriotic tissue (27).

PTEN, which is another tumor suppressor gene, has been reported to be present in endometriotic lesions, while it has been indicated that PTEN inactivation exhibits a significant role in the malignant evolution of endometriosis (36).

PIK3CA has been recognized for its oncogenic role. Mutations in this gene have been evaluated in nonatypical and atypical endometriosis, and are considered to be an early

Table II. Microscopic criteria for the diagnosis of endometrioid and clear cell ovarian cancer (27).

Endometrioid ovarian carcinoma	Clear cell ovarian carcinoma
Glandular, cribriform or solid architecture and morular or squamous differentiation	Tubulocystic, papillary or solid architecturea
Cuboid to columnar cells with grading similar to the uterine counterpart	Hobnail or polyhedral cells with abundant eosinophilic granular/clear cytoplasm, signet/ring-type cells
Nuclear grade determined by the variation in nuclear size, chromatin distribution and size of the nucleoli	Round/angular, hyperchromatic nuclei, marked nuclear pleomorphism
Mitoses present	Mitoses present
Endometriosis often present	Endometriosis often present

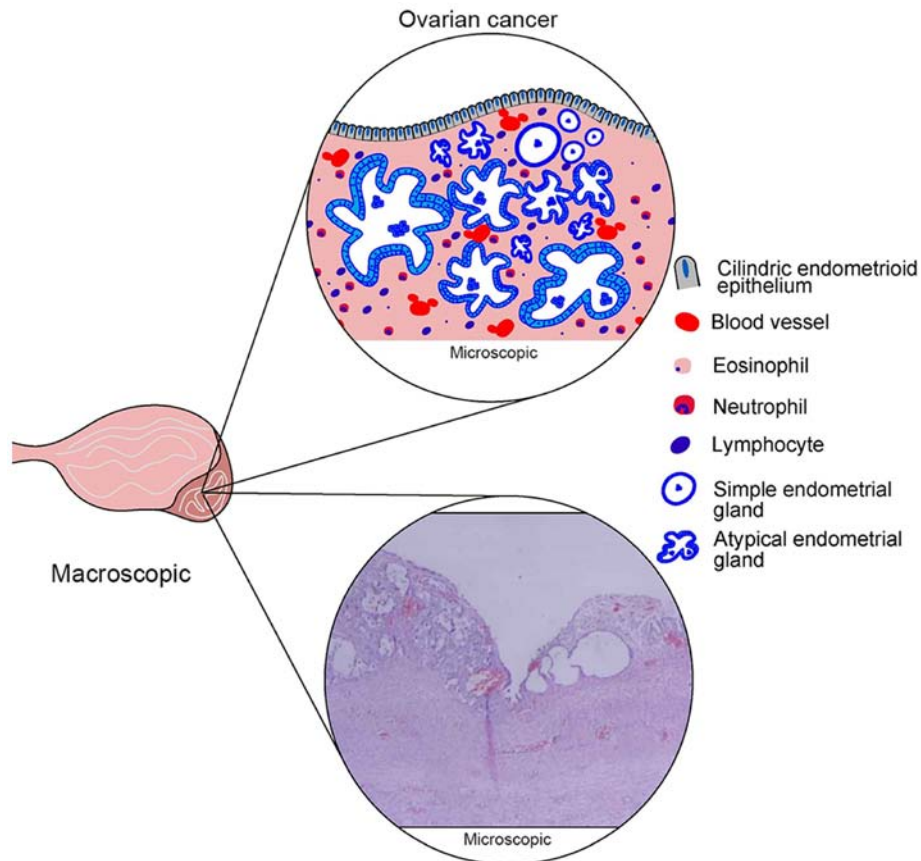


Figure 2. Histological aspects of ovarian cancer. In terms of macroscopic features, epithelial ovarian cancer (here referring to endometrioid and clear cell carcinoma) is a cumulative entity, presenting various forms with imprecise delimitation and variable dimensions. In terms of microscopic features, schematic representation (upper image) with subsequent identification of important characteristics in the lower microscopic image outlines the disordered architecture with numerous atypical glands and nuclear variations. These are associated with elements presented and described in the benign inflammatory endometriosis or the non-endometriotic process.

event in carcinogenesis, possibly at the beginning of malignant transformation of endometriosis (37).

CTNNB1 gene also exhibits an oncogenic function, which has been highlighted by its important role in the diagnosis of nonatypical and atypical endometriosis (38). CTNNB1 has been indicated to exhibit a prominent function in the early events of the transformation of endometriosis to ovarian cancer (38).

BRCA1 and BRCA2 are important early onset tumor suppressors genes. Mutations in the BRCA1 and BRCA2 genes have been reported in the evolution of various human cancers,

including ovarian tumors. However, regarding their role in endometriosis, there are fewer reports (18,39).

The presence of TP53 tumor suppressor gene mutations in atypical endometriosis is debated. Certain studies have indicated that alterations in the TP53 gene were present in atypical and low levels or absent in nonatypical endometriosis (37-39). It has been speculated, according to microarray results, that TP53 cancer-related pathways may participate in endometriosis progression (40).

KRAS is an oncogene, whose activation was detected in *de novo* endometriosis in mice. This suggested that activation

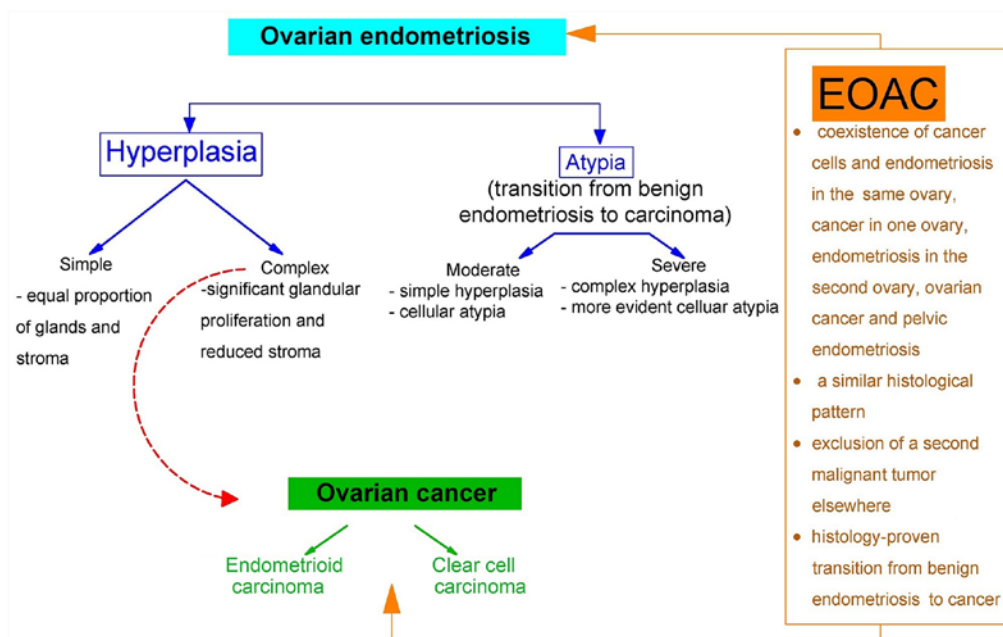


Figure 3. Overview of histological associations between ovarian endometriosis and the presence of malignant lesions. Ovarian endometriosis comprises different cellular alterations, such as simple/complex hyperplasia and moderate/severe atypia. These are present at certain moments of the evolution of endometrial lesions may be associated with ovarian cancer, such as endometrioid or clear cell carcinoma. The main histological characteristics of EOAC and their association with particular extrauterine sites are summarized. EOAC, endometriosis-associated ovarian cancer.

of KRAS is an important pathway in the initiation and progression of this disease (18). KRAS mutations have also been observed at an important level in the eutopic endometrium of patients with endometriosis (40).

**Ovarian cancer.** The classification of ovarian cancer based on histopathological and clinical features is accompanied by the gene expression pattern and mutational determination, which reflect the main factors responsible for the malignant transformation of ovarian cancer. These genes include KRAS, BRAF, PTEN, PIK3CA, CTNNB1 (the gene encoding  $\beta$ -catenin), ARID1A, PPP2R1A and rarely TP53 (18,28,29,41). Considering the differentiation of ovarian cancers in two subtypes (I and II) as artificial and limiting in managing the complex biology of the disease, another classification consisting of five different subcategories has been proposed, based on clinical, morphological and molecular abnormalities (28).

Among all subcategories of ovarian cancer introduced in routine classification, the two subcategories associated with endometriosis, endometrioid and clear cell carcinoma, are extensively studied at the molecular level (42). In these two subcategories, gene mutation patterns have been identified in a different frequency, which conferred heterogeneous reports on the progression of malignant ovarian lesions (Table IV). According to the experimental data, the inactivation of ARID1A and PTEN tumor suppressor gene pathways and the activation of the oncogenic pathways regulated by PI3KCA, KRAS and CTNNB1 are responsible for initiating complex processes, which have been suggested as potential mechanisms associated with the early carcinogenesis and transformation of ovarian cancer (28,38). Regarding the inactivating mutations in BRCA1/2 in endometrioid and clear cell carcinoma, there is no unanimously accepted opinion that BRCA gene mutations

contribute to the pathology of the two cancers (29,43). BRCA mutations or inactivation of gene expression have been indicated to occur more frequently in high grade serous carcinoma (29).

**EOAC.** The molecular pathways associated with the malignant transformation of EOAC remain to be fully elucidated. Endometriosis has been indicated to comprise mutations highlighted in coexisting tumors, which may designate a primary stage of evolution towards ovarian malignant transformation (44).

EOAC has been reported to exhibit a high percentage of PIK3CA and KRAS activating mutations and ARID1A and PTEN inactivating mutations (35,37,38), whilst a reduced percentage of cases has been indicated to comprise TP53 and BRCA1/2 mutations (45,46). A previous study has identified KRAS mutations in 29% of EOAC cases and only in 3% of tumors with no endometriosis (47). Lakhani *et al* (43) reported a smaller, but significant association between BRCA1/2 and endometrioid and clear cell carcinoma, namely for endometrioid: 33% of BRCA1, 29% of BRCA2 and for clear cell: 10% of BRCA1; 1.4% of BRCA2.

#### 4. miRNA alterations

Dysregulated miRNAs have been associated with a large number of human diseases, including cancer (48), cardiovascular disease (49), neurodegenerative disease (50,51) and diabetes mellitus (52). They comprise information identified as molecular signatures, which are represented by specific panels of upregulated and downregulated molecules. The altered molecules define different profiles of gene or protein expression in various diseases (53). The differential transcriptional profiles

Table III. Early abnormal molecular events in ovarian endometriosis.

Gene name	Function	(Refs.)
ARID1A	Tumor suppressor gene inactivation	(28)
PTEN	Tumor suppressor gene inactivation	(79)
PIK3CA	Oncogene activation	(80)
BRCA1/BRCA2	Tumor suppressor gene inactivation	(22,39)
CTNNB1	Oncogene activation	(38)

Table IV. Frequency of genetic alterations in endometrioid and clear cell ovarian carcinoma.

A, Endometrioid ovarian carcinoma		
Gene name	Frequency (%)	(Refs.)
ARID1A	30	(81)
PTEN	20	(29)
PIK3CA	31	(38)
TP53	30	(18)
BRCA1	33	(43)
BRCA2	29	(43)
KRAS	29	(47)
CTNNB1	40	(29)
B, Clear cell ovarian carcinoma		
Gene name	Frequency (%)	(Refs.)
ARID1A	46	(81)
PTEN	25	(44)
PIK3CA	35	(38)
TP53	10	(18)
BRCA1	10	(43)
BRCA2	4	(43)
KRAS	7	(82)
CTNNB1	3	(82)

of miRNAs between normal and pathological tissue samples may be used as diagnostic and prognostic tools (24). The interaction of miRNAs with different genes and their expression profiles is commonly specific for certain cell types and different stages of each disease (54). The present chapter presents the miRNAs that have been directly associated with the gene expression patterns previously reviewed in endometriosis and ovarian cancer and reported to be dysregulated in the two pathologies (Fig. 4).

*Ovarian endometriosis.* Endometriosis has been regarded as an ideal target for genomic sciences, since it lacks an

efficient diagnostic and therapeutic management, as it represents a heterogeneous disease with multiple phenotypes and a complex pathophysiology (55). Several studies have indicated that miRNAs were implicated in the progression of endometriosis (2,20,56). However, at present there is no specific clinical biomarker to be used in patients with endometriosis.

miR-200 family is one of the most widely studied miRNA families in endometriosis, and comprises miR-200a, miR-200b, miR-200c, miR-141 and miR-429 (57). miR-200b has been demonstrated to be the most downregulated transcript in previous studies on the molecular regulation of endometriosis (20). miRNAs of this family have been indicated to target PTEN and CTNNB1 genes (22).

miR-20a and miR-20b have been found to be dysregulated in ovarian endometriosis (55,58). miR-20b has been indicated to contribute to the process of neovascularization in endometriosis (55) and target PTEN and BRCA1 genes.

miR-17-5p was reported by Jia *et al* (59) to be upregulated in patients with endometriosis compared with those without the disease, and has been indicated to target the PIK3CA gene.

Other miRNAs associated with endometriosis include miR-34a/b/c, which were demonstrated by Burney *et al* (23) to be downregulated in ovarian endometriosis and target CTNNB1 and PTEN genes. miR-1-3p has been also reported to be upregulated in patients with endometriosis (20), and target the PIK3CA gene. The CTNNB1 gene has been indicated to be a target of miR-155-5p, which has been demonstrated to be dysregulated in endometriosis (60). miR-21-5p has been revealed to be involved in the pathogenesis of endometriosis exhibiting aberrant expression profiles (60) has been indicated to directly target BRCA1 and PTEN affecting their expression. PIK3CA, BRCA1 and BRCA2 have also been indicated to be targets of miR-335 (22).

*Ovarian cancer.* miRNAs present regulatory functions, certain of which exhibit important implications in carcinogenesis (61). Transcriptional microarray data have demonstrated that there is a different expression level of miRNAs between normal and tumor tissue (60). The up- and downregulation of miRNA expression have been associated with cancer development and progression (62). Alterations in miRNAs expression have been implicated in invasion and migration in ovarian carcinogenesis (63).

miR-200 family has been indicated to be involved in the metastasis of ovarian cancer (19). Notch signaling is considered to be a regulator of cell invasion in tumors (59). Notch signaling blockade via the miR-200 family has been indicated to represent a promising therapeutic approach for ovarian cancer (64).

miR-335 has been demonstrated to be downregulated in primary ovarian cancer tissue compared with normal tissue (65). Cao *et al* (65) also reported that patients with primary ovarian cancer who exhibited a low expression of miR-335 had a shorter survival period. In addition, miR-335 level has been revealed to be an important prediction factor of tumor recurrence (65). miR-335 has been indicated to target PIK3CA, BRCA1 and BRCA2 genes (22).

miR-17-5p has been reported to be overexpressed in ovarian cancer. Liu *et al* (66) demonstrated that miR-17 stimulated

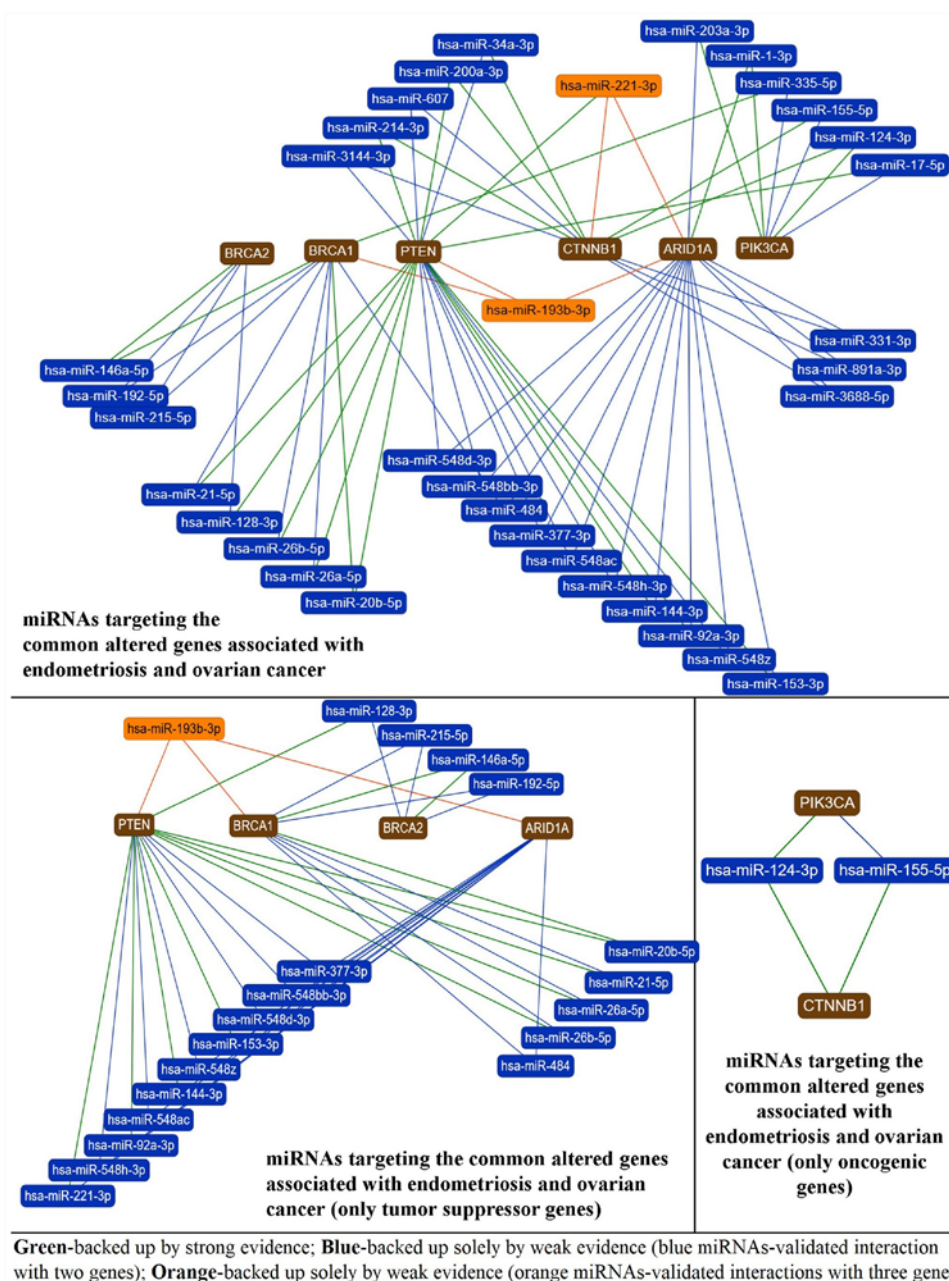


Figure 4. miRNAs targeting common altered genes in endometriosis and ovarian cancer. BRCA1, BRCA2, PTEN, CTNNB1, ARID1A and PIK3CA are altered in terms of mutation or expression in both endometriosis and ovarian cancer and are targeted by multiple miRNAs. The first graphical representation highlights miRNAs that have >1 of these genes in their target profile (miRNAs linked to the gene via green, blue or orange lines), with a special focus on miR-221-3p and miR-193b-3p that target simultaneously PTEN, CTNNB1, ARID1A (miR-221-3p) and BRCA1, PTEN and ARID1A (miR-193b-3p). The remaining miRNAs target simultaneously only two genes. The second graph illustrates the miRNAs that have >1 of these genes in their target profile, but only illustrates the tumor suppressor genes that are common between endometriosis and ovarian cancer (PTEN, BRCA1, BRCA2 and ARID1A). miR-193b-3p targets concomitantly three tumor suppressor genes and may become an important prognostic marker or therapeutic target in endometriosis and ovarian cancer or a marker of endometriosis transition toward ovarian malignancy, which requires validation. The third graph highlights the miRNAs that target simultaneously the two oncogenic genes (PIK3CA and CTNNB1) associated with endometriosis and ovarian cancer, miR-124-3p and miR-155-5p. The data were generated with miRTargetLink online software (22). miRNA/miR, microRNA.

the proliferation rate, accelerated cell cycle progression and affected the invasion capacity of the ovarian cancer cells *in vitro*. miR-17 has been also indicated to be involved in the transition from low to high degree ovarian cancer (66) and directly target the PIK3CA gene (22).

miR-34a-3p has been revealed to be frequently downregulated in ovarian cancer, being directly transactivated by the TP53 tumor suppressor gene, which is frequently dysregulated in ovarian epithelial cancer (67). miR-34 has been

indicated to affect the motility, proliferation and migration of ovarian cancer cells (67) and directly target the CTNNB1 gene (22).

miR-1 level has been demonstrated to be decreased in ovarian cancer compared with normal ovarian tissue, indicating the potential tumor suppressor role of this gene (68).

miR-155-5p was revealed by Gulei *et al* (69) to exhibit increased expression in endometriosis, which was further accentuated in ovarian cancer samples but without statistical

significance. miR-155 has been indicated to affect apoptosis and target the CTNNA1 gene (22).

miR-21-5p upregulation has been associated with ovarian cancer, where Liu *et al* (70) revealed that suppression of miR-21 reduced cell proliferation and promoted cell apoptosis by increasing PTEN expression. Apart from PTEN, miR-21 has been indicated to target the BRCA1 gene (22).

miR-148a is part of the miR-148/152 family. Downregulation of miR148/152 family members has been associated with unfavorable prognostic outcomes in ovarian cancer (71). miR-148a-5p targets the BRCA1 and BRCA2 genes (22).

Another miRNA associated with ovarian cancer is miR-20 which has been indicated to target the PIK3CA gene (22).

**EAOC.** Endometriosis presents a biological behavior with increased invasiveness similar to that of tumors. The invasion process is mediated by the downregulation of E-cadherin and alterations in the cell phenotype following epithelial-to-mesenchymal transition (72). This comprises a complex process converting the immotile epithelial cells into motile ones, as a response to injury (73). Therefore, endometriosis may be induced by epithelial-to-mesenchymal transition.

Fig. 4 presents the network of miRNAs-target genes in the context of ovarian endometriosis, EAOC and ovarian cancer. The three pathological states depicted in Fig. 4 have different common denominators of altered genes and miRNAs. However, large patient cohorts need to be employed before establishment of specific clinical signatures, such as a miRNA signature for the prediction of the evolution of endometriosis towards malignancy.

A synthesis of histological and molecular aspects encountered in ovarian endometriosis and ovarian cancer are highlighted in Fig. 5.

## 5. Impact of endometriosis on the prognosis of ovarian cancer

Endometriosis is considered by some specialists in the field as a pathology, although proof for its implications in ovarian cancer remain absent (18,74); however, there are studies that demonstrate the contrary.

Braicu *et al* (19) performed a meta-analysis demonstrating that patients with endometriosis presented an increased risk of developing ovarian cancer. The data indicated an increased ovarian cancer risk by 27% in case-control or two-cohort studies, which included 314,421 females with or without endometriosis, and by 80% in single-arm cohort studies, which included 79,388 females with endometriosis (30). The results are in accordance with those of previous studies (8,11) and they constitute epidemiological data that endometriosis may be associated with an increased risk of ovarian cancer (30).

Barreta *et al* (75) performed a database analysis between 1995 and 2016, aiming to clarify whether the clinicopathologies features and prognosis of patients with clear cell carcinoma and endometrioid carcinoma were associated with endometriosis. According to the original pathology report, 29 cases from a total of 55 cases, mentioned the presence of endometriosis. A second revision by an expert pathologist identified another 11 cases with endometrial foci. From the remaining 50 cases

after exclusion criteria, 40 cases (80%) were diagnosed as ovarian cancer associated with endometriosis (75).

Park *et al* (76) conducted a retrospective study between 1991 and 2012 that included 155 patients with clear cell carcinoma, 78 of which presented associated ovarian endometriosis.

Cases of EAOC in the aforementioned studies included young females with an early-stage disease, low-grade disease and specific histology of endometrioid and clear cell carcinoma. Ovarian endometriosis was strongly associated with an increased risk for ovarian cancer. In spite of favorable characteristics of EAOC, the findings indicated that endometriosis did not affect ovarian cancer prognosis after its onset, although a better overall survival was reported, primarily in clear cell carcinoma (30,75,76).

## 6. Conclusion

Endometriosis, which is one of the most frequent gynecological diseases, requires a more comprehensive understanding. In addition, considering the possibilities of evolution of the endometrial lesions, a need for accuracy in diagnosis and a therapy plan is required (54).

The presence and increased number of cases of atypical endometriosis, considered by several studies as an intermediate lesion between endometriosis and ovarian malignancy, may allow the identification of endometrial lesions at risk for malignant transformation (28,77,78). Since endometriosis is frequently observed in association with endometrioid and clear cell ovarian carcinoma, or in another perspective ovarian cancer arises from endometriosis, it can be hypothesized that endometriosis may be viewed as a preneoplastic or neoplastic process (36).

Moreover, the frequency of an aberrant mutation pattern seems to increase in cases of endometriosis adjacent or contiguous to ovarian cancer (28). Analyzing the presented aspects, it can be observed that all the gene mutations discussed (ARID1A, PI3KCA, PTEN, BRCA1/2, TP53 and KRAS) as being present in ovarian endometriosis (18,28,36,39,40,79,80) are also present in endometrioid and clear cell carcinoma (18,29,43,44,81,82), although certain among them (BRCA1/2, KRAS and TP53) are debated (39,40). Ovarian endometriosis and cancer tend to share the same genetic mutations, which also support the model of endometriosis as a malignant precursor. Development of genetic analyses to detect these mutations may represent a tool in the early detection of patients at risk to develop ovarian cancer (54).

miRNAs, which are involved in the regulation of gene expression, serve an important role in understanding endometriosis evolution and are currently extensively investigated (2). Increasing evidence suggests their role as biomarkers in endometriosis. miRNAs, such as miR-200, miR-17, miR-34, miR-1, miR-155 and miR-21, have been reported as being dysregulated in both endometriosis (23,57,59,60) and ovarian cancer (58,62,64-66,68), demonstrating the molecular association between these pathologies.

There are few studies that have indicated an association between ovarian endometriosis and ovarian cancer, but these data do exist (1). Ovarian endometriosis has been associated with an increased risk of ovarian cancer (36); however, no difference has been reported regarding prognosis in females with and without EAOC (18).



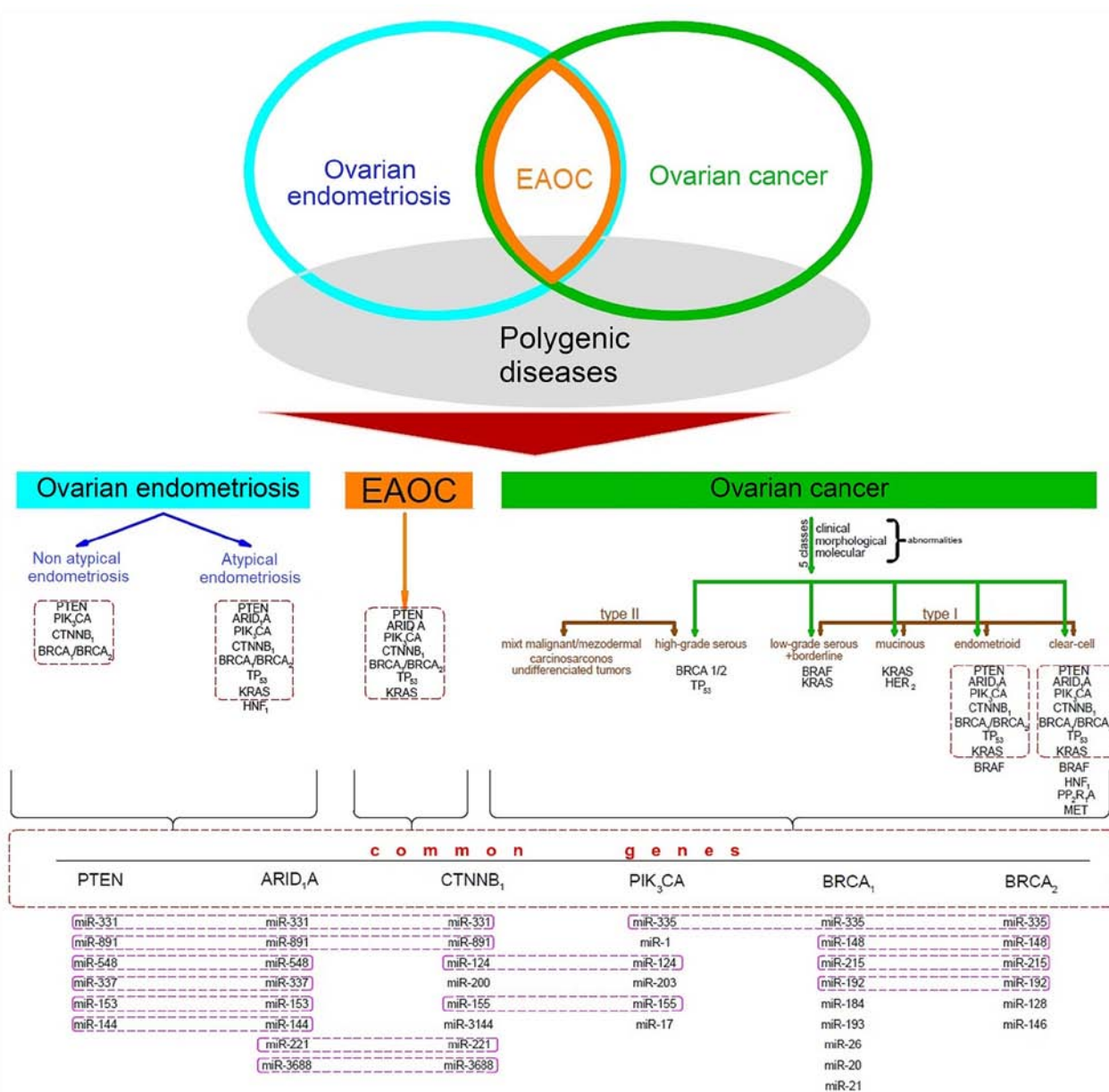


Figure 5. Overview of the histological and molecular association between ovarian endometriosis and ovarian malignant transformation. Molecular analysis of ovarian endometriosis focused on atypical and non-atypical endometriosis and ovarian cancer with focus on endometrioid ovarian carcinoma, clear cell ovarian carcinoma and EAO lesions has identified the presence of certain genetic mutations and dysregulated miRNAs. Their comparison has demonstrated the presence of certain mutated genes in all three pathologies (highlighted with a red frame), which include PTEN, ARID1A, PIK3CA, CTNNB1, BRCA1/BRCA2, TP53, KRAS. These genes are targeted by certain commonly dysregulated miRNAs, such as miR-331, miR-335, miR-891, miR-548, miR-124, miR-148, miR-215, miR-192, miR-337, miR-153, miR-155, miR-144, miR-221, miR-3688 and other miRNAs dysregulated in both endometriosis and ovarian cancer, such as miR-200, miR-17, miR-34, miR-1, miR-155 and miR-21. EAO, endometriosis-associated ovarian cancer; miRNA/miR, microRNA.

To elucidate the implications of the association of ovarian endometriosis and cancer, larger studies are required (1,18). As a perspective, every group managing endometriosis and ovarian cancer should publish their data regarding this association. Further research on this topic with extensive validation is needed. Novel molecular technologies investigating epigenetic, transcriptomic, proteomic and post-translational splicing alterations and complex chromosomal rearrangements may revolutionize the management of endometriosis (2). The goal of these innovative efforts is the development of more sensitive diagnostic and preventive tests. miRNAs may represent an important tool in the management of endometriosis (21). Their potential use in diagnosis and treatment implications

of endometriosis is a challenging and important step in its management. The early detection of the possible malignant lesions in females with endometriosis and the differentiation between women at risk of EAO and those who will continue to present a benign disease is important in order to improve the preventive and diagnostic methods, as managing the situation after cancer has developed is not as efficient (36,56). Until the materialization of these ideas, the caregivers in the clinics should pay attention in handling these cases.

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Not applicable.

## Authors' contributions

AIGO conceived the study, performed the histological, molecular and miRNA literature search and edited the manuscript. CB and DG performed the molecular and miRNA literature search and edited the manuscript. RC, DM and HR performed the clinical and histological literature search for endometriosis. AI performed the clinical and histological literature search for ovarian cancer. IBN supervised and critically revised the study. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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