Commentary

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Endometriosis and endometriosis-associated ovarian cancer, possible connection and early diagnosis by evaluation of plasma microRNAs

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Abstract: Endometriosis and endometriosis-associated ovarian cancer (EAOC) are related yet different gynecological conditions, often with EAOC developing upon endometriosis. This latter significantly increases the risk for ovarian cancer, especially endometrioid and clear cell types. Detecting EAOC poses a notable challenge due to its frequently asymptomatic initial phases and the absence of reliable screening methods, emphasizing the necessity for better diagnostic techniques. MicroRNAs (miRNAs) have been recognized as potential biomarkers for both endometriosis and EAOC. The research identified specific miRNAs including miR-21, miR-200, and miR-145, as exhibiting dysregulation in both conditions, indicating the early onset of these alterations and suggesting their potential involvement in the process of malignant transformation to EAOC. Furthermore, diagnostics using miRNAs hold great promise for non-invasive personalized assessments, leading to earlier detection and more effective individualized treatment plans. In this short perspective paper, we aim to highlight the potential link between endometriosis and EAOC discussing the possibility of early diagnosis through the evaluation of miRNAs in the blood of patients affected by these conditions.

Keywords: endometriosis; endometriosis-associated ovarian cancer; microRNA; differential diagnosis

Introduction

Endometriosis is a chronic condition in which endometrial-like tissue grows outside the uterus. Commonly found on the ovaries, fallopian tubes, or other pelvic structures, this ectopic tissue can lead to symptoms such as chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility [1]. Although endometriosis is considered a benign disorder, several studies have shown a link between this condition and an increased risk of developing certain types of endometriosis-associated ovarian cancer (EAOC), in particular, two histological types: endometrioid- and clear cell-ovarian carcinoma [2].

The ovarian form of endometriosis is more likely to progress into cancer and this evolution can take only 60–120 months in some cases [3]. A significant percentage of endometrioid ovarian carcinomas (10–50 %) arise from endometriosis, with strict anatomopathological criteria defined for this malignant transformation. Similarly, clear-cell ovarian carcinomas are linked to endometriosis in 25–58 % of cases [4, 5].

The exact mechanism by which endometriosis leads to tumor lesions remains still unclear. However, evidence suggests that endometriosis and certain types of ovarian cancer share some genetic alterations that drive malignant transformation. Key driver events in EAOC include the loss-of-function mutations in ARID1A (involved in chromatin remodeling) and PTEN (a tumor suppressor gene), as well as activating mutations in the PIK3CA and KRAS genes. Epigenetic modifications and microRNA (miRNA) alterations further contribute to this process [6]. Moreover, the chronic inflammation, characteristic of endometriosis, and prolonged exposure to estrogen may foster the development of cancerous cells and promote the progression of specific types of ovarian cancer [7].

The diagnosis and management of epithelial ovarian cancer (EOC) are increasingly influenced by the identification of key tumor biomarker mutations, particularly in endometrioid and clear cell subtypes. Recent studies highlight the complex relationship between these biomarkers

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and chemotherapy response, paving the way for personalized treatment strategies. Given the molecular heterogeneity of EOC, identifying specific biomarkers is crucial for driving targeted therapies, such as PARP inhibitors for BRCA-mutated ovarian cancer [8].

BRCA1/2 mutations and homologous recombination repair deficiency (HRD) play a central role in EOC treatment decisions, while other genetic alterations, including mismatch repair (MMR) deficiencies, also contribute to therapeutic stratification. HRD status is particularly relevant due to its correlation with platinum sensitivity and response to PARP inhibitors; however, the lack of standardized, validated HRD testing remains a significant limitation. Currently, no universal treatment algorithm exists for advanced EOC, underscoring the need for further research to refine biomarker-driven approaches and develop more effective targeted therapies [9]. Integrating comprehensive genomic profiling into clinical practice enables a more precise selection of chemotherapy and targeted treatments, ultimately aiming to improve patient outcomes in EOC.

As regards the therapeutic options, recent advancements in immuno-oncology have led to the development of immune checkpoint inhibitors (ICIs), which hold promise for treating various cancers, including ovarian cancer. While numerous mutations have been identified, and several ICIs are under clinical evaluation, meaningful survival benefits in EOC remain limited, particularly outside of biomarker-selected therapies. The effectiveness of ICI monotherapy in EOC has been modest, in contrast to the significant advantages observed in other solid tumors. A meta-analysis of seven randomized phase III trials [10] found that single-agent PD-L1 inhibitors did not provide substantial benefit in newly diagnosed ovarian cancer. However, in patients without tumor BRCA mutations, maintenance therapy with a combination of bevacizumab, olaparib, and durvalumab improved progression-free survival compared to bevacizumab alone.

In both platinum-sensitive and platinum-resistant EOC, ICIs have shown no significant impact. Ongoing trials are exploring whether integrating ICIs with standard PARP inhibitors and bevacizumab may enhance treatment outcomes. Additionally, combinations of CTLA-4 and PD-1 inhibitors, as well as ICIs combined with other novel therapeutic approaches, are being investigated as potential strategies to boost immunotherapy effectiveness in EOC [10]. However, further research is essential to better define the role of ICIs in ovarian cancer and to identify predictive biomarkers for optimal patient selection.

In light of all the above premises, this perspective paper explores the potential connection between endometriosis and EAOC, emphasizing the role of circulating miRNAs as potential biomarkers for early detection and timely identification of malignant transformation in endometriosis.

Problem to address

Women with endometriosis are at increased risk of developing ovarian cancer, particularly if the endometriosis is long-lasting and involves the ovaries. The key to managing this condition is early and accurate differential diagnosis, which allows for the prompt administration of effective therapies, improving quality of life for patients and slowing disease progression. However, the variability of symptoms and lack of specific diagnostic tests often make early diagnosis of endometriosis challenging. Differential diagnosis, on the other hand, would enable the identification of patients at risk of malignant transformation, allowing for more accurate monitoring and timely surgical intervention if necessary. Nevertheless, distinguishing between benign and malignant endometriosis still represents a difficult diagnostic challenge for clinicians.

Understanding microRNA role in disease pathogenesis

The timely diagnosis of both diseases remains a challenge, largely due to the lack of non-invasive methods and the often-subtle symptoms in early stages. This is where miRNAs have emerged as powerful diagnostic tools. MiRNAs are short, single-stranded RNA molecules that regulate gene expression at the post-transcriptional level by binding to complementary sequences in messenger RNA. They are involved in diverse cellular processes including growth, differentiation, apoptosis, and immune responses [11], and also play a role in modulating key processes dysregulated in both endometriosis and EAOC: inflammation, fibrosis, cell proliferation, angiogenesis, and epithelial-mesenchymal transition (EMT). Their molecular stability and differential expression in diseases like endometriosis and EAOC make them promising diagnostic biomarkers. The abnormal expression of specific miRNAs has been also linked to disease progression, making them valuable markers for prognosis too.

Can assessing microRNAs aid in differentiating endometriosis that progresses to malignancy?

Over the years it has become evident that endometriosis exhibits a distinct miRNA expression signature, as several

miRNAs have been found differentially expressed in endometriosis patients compared to healthy individuals including miR-21, miR-29, miR-145, and miR-200 [12–15]. It has also been reported that there are differences in the plasma miRNA expression between endometriosis, epithelial ovarian cancer, and high-grade serous ovarian cancer [16].

Although several studies support the use of miRNAs as endometriosis biomarkers, others have observed altered miRNA expression profiles shared by both endometriosis and EAOC, raising the possibility of using these miRNAs to identify endometrioid lesions likely to progress to EAOC [13, 15]. The work of Szubert et al. has demonstrated convergent trends in miRNA expression between endometriosis and EAOC [6]. Furthermore, the aberrant expression of miR-21 and miR-200 in both conditions provides additional support for a molecular link [13]. Within this context, miR-21 assumes a critical role, promoting tumorigenesis through the suppression of PTEN and the subsequent activation of the PI3K/AKT signaling pathway [17]. This mechanism also encompasses miR-221, the overexpression of which is frequently observed in EAOC and generally associated with the malignant progression of carcinomas in various organs. MiR-221 further contributes to PTEN suppression by binding to its 3′-untranslated region (3′-UTR) [13]. Furthermore, the loss of miR-200 expression has been associated with increased invasiveness and metastatic potential via the aberrant modulation of the EMT pathway [18]. In EAOC, the loss of miR-145 has been linked to increased cell proliferation, invasion, and migration, thereby contributing to the aggressive phenotype and chemoresistance observed in this malignancy [14]. Similarly, miR-143 overexpression in EAOC has been reported and its deregulation may promote cell migration and invasion by suppressing FNDC3B [19]. Finally, dysregulation of miR-125a in EAOC suggests its potential involvement in the modulation of cell migration, invasion, and ErbB signaling [20].

Consequently, miRNAs offer a potential tool for identifying at-risk patients and preventing complications. Early detection of malignancy in women with endometriosis is critical for distinguishing between those likely to develop EAOC and those with benign disease. This distinction is essential to optimize preventive and diagnostic strategies, as treatment after cancer progression is significantly less effective. In this scenario, some authors have recently underlined the role of miRNAs in monitoring minimal residual disease (MRD)–the presence of minimal or undetectable tumor cells persisting after treatment, particularly neoadjuvant chemotherapy and interval debulking surgery [21]. MRD constitutes a critical determinant of prognosis, recurrence and overall survival. Therefore, the integration of miRNA profiling with MRD assessment may facilitate improvements in personalized treatment strategies and enable real-time monitoring of tumor evolution and recurrence.

The potential for non-invasive and personalized diagnosis

A significant advantage of utilizing miRNAs for the diagnosis of both endometriosis and EAOC lies in the potential for developing non-invasive diagnostic modalities. Current diagnostic approaches, such as laparoscopy or imaging, are characterized by invasiveness, high cost, or limited sensitivity. A miRNA-based assay utilizing blood or urine samples would represent a less invasive and more accessible alternative, potentially facilitating earlier and more accurate disease detection. Furthermore, miRNA-based diagnostics offer considerable promise for the realization of personalized medicine. Given the variability in individual miRNA expression profiles as a function of disease phenotype, genetic constitution and environmental exposures, the profiling of these patterns enables clinicians to tailor therapeutic strategies to specific disease subtypes, thereby optimizing patient outcomes.

Conclusions

The observed dysregulation of miRNAs in endometriosis and EAOC underscores their critical involvement in disease pathogenesis. MiRNAs participate in a range of cellular processes that contribute to both the initiation and progression of these diseases. While further investigation is required to fully elucidate the specific mechanisms through which miRNAs exert their influence, their potential as biomarkers offers significant promise for future research endeavors and clinical applications.

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References

1. Pejovic T, Cathcart AM, Alwaqfi R, Brooks MN, Kelsall R, Nezhat FR. Genetic links between endometriosis and endometriosis-associated ovarian cancer – a narrative review (Endometriosis-Associated cancer). Life 2024;14:704.
2. Steinbuch SC, Lüß AM, Eltrop S, Götte M, Kiesel L. Endometriosis-associated ovarian cancer: from molecular pathologies to clinical relevance. Int J Mol Sci 2024;25:4306.
3. Murakami K, Kotani Y, Shiro R, Takaya H, Nakai H, Matsumura N. Endometriosis-associated ovarian cancer occurs early during follow-up of endometrial cysts. Int J Clin Oncol 2020;25:51–8.
4. Kvaskoff M, Mu F, Terry KL, Harris HR, Poole EM, Farland L, et al. Endometriosis: a high-risk population for major chronic diseases? Hum Reprod Update 2014;21:500–16.
5. Gadducci A, Multinu F, Cosio S, Carinelli S, Ghioni M, Aletti GD. Clear cell carcinoma of the ovary: epidemiology, pathological and biological features, treatment options and clinical outcomes. Gynecol Oncol 2021; 162:741–50.
6. Szubert M, Nowak-Glück A, Domańska-Senderowska D, Szymańska B, Sowa P, Rycerz A, et al. miRNA expression profiles in ovarian endometriosis and two types of ovarian cancer – endometriosis-associated ovarian cancer and high-grade ovarian cancer. Int J Mol Sci 2023;24:17470.
7. Adilbayeva A, Kunz J. Pathogenesis of endometriosis and endometriosis-associated cancers. Int J Mol Sci 2024;25:7624.
8. Aravantinou-Fatorou A, Georgakopoulou VE, Dimopoulos MA, Liontos M. Precision medicine in gynecological cancer (review). Biomed Rep 2025;22:43.
9. Tonti N, Golia D'Augè T, Cuccu I, De Angelis E, D'Oria O, Perniola G, et al. The role of tumor biomarkers in tailoring the approach to advanced ovarian cancer. Int J Mol Sci 2024;25:11239.
10. Bogani G, Moore KN, Ray-Coquard I, Lorusso D, Matulonis UA, Ledermann JA, et al. Incorporating immune checkpoint inhibitors in epithelial ovarian cancer. Gynecol Oncol 2025;193:30–40.
11. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281–97.
12. Ochoa Bernal MA, Song Y, Joshi N, Burns GW, Paul EN, Vegter E, et al. The regulation of MicroRNA-21 by Interleukin-6 and its role in the development of fibrosis in endometriotic lesions. Int J Mol Sci 2024;25: 8994.
13. Gaia-Oltean AI, Braicu C, Gulei D, Ciortea R, Mihu D, Roman H, et al. Ovarian endometriosis, a precursor of ovarian cancer: histological aspects, gene expression and microRNA alterations (review). Exp Ther Med 2021;21:243.
14. Hua M, Qin Y, Sheng M, Cui X, Chen W, Zhong J, et al. MiR-145 suppresses ovarian cancer progression via modulation of cell growth and invasion by targeting CCND2 and E2F3. Mol Med Rep 2019;49: 3575–83.
15. Kluz N, Kowalczyk E, Wasilewska M, Gil-Kulik P. Diagnostic value and molecular function of MicroRNAs in endometrial diseases: a systematic review. Cancers (Basel) 2024;16:2416.
16. Suryawanshi S, Vlad AM, Lin HM, Mantia-Smaldone G, Laskey R, Lee M, et al. Plasma MicroRNAs as novel biomarkers for endometriosis and endometriosis-associated ovarian cancer. Clin Cancer Res 2013;19: 1213–24.
17. Liu HY, Zhang YY, Zhu BL, Feng FZ, Yan H, Zhang HY, et al. MiR-21 regulates the proliferation and apoptosis of ovarian cancer cells through PTEN/PI3K/AKT. Eur Rev Med Pharmacol Sci 2019;23: 4149–55.
18. Koutsaki M, Libra M, Spandidos DA, Zaravinos A. The miR-200 family in ovarian cancer. Oncotarget 2017;8:66629–40.
19. Kumari P, Sharma I, Saha SC, Srinivasan R, Minhas P. Diagnostic potential of differentially regulated microRNAs among endometriosis, endometrioid ovarian cancer, and endometrial cancer. J Cancer Res Therapeut 2021;17:1003–11.
20. Kumari P, Sharma I, Saha SC, Srinivasan R, Bhardwaj P. Role of serum microRNAs as biomarkers for endometriosis, endometrioid carcinoma of ovary & endometrioid endometrial cancer. Indian J Med Res 2022; 156:516–23.
21. Della Corte L, Russo G, Pepe F, Pisapia P, Dell'Aquila M, Malapelle U, et al. The role of liquid biopsy in epithelial ovarian cancer: state of the art. Crit Rev Oncol Hematol 2024;194:104263.