



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

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## Abstract

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

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

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

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

**Keywords** Endometriosis · Ovarian cancer · Immune imbalance · Neoangiogenesis · Apoptosis

## Introduction

Endometriosis is a chronic, estrogen-dependent, progressive disease characterized by the presence of endometrium-like tissue, glands, and stroma, outside the uterine cavity [1]. It most commonly involves ovaries, fallopian tubes, and the pelvic peritoneum. This disease is due to the ectopic implantation of endometrium-like cells, accompanied with their elevated proliferation and migration. It is the leading cause of morbidity among premenopausal women, and the complex pathogenesis of this enigmatic disorder remains controversial despite extensive research [2], which started almost 160 years ago [3]. This complex disease, affecting

approximately 10% of women of reproductive age, has strong effects on the life of many women. It can cause spontaneous pregnancy loss and infertility in up to 50% of the women [4]. The main diagnostic tool for endometriosis is laparoscopy and histological confirmation on the surgical specimen, although ultrasound is able to identify both ovarian endometriomas (cysts) and deep infiltrating endometriosis [5]. The most commonly suggested causes of endometriosis are retrograde menstruation, genetic predisposition, lymphatic spread, immune dysfunction, metaplasia, or environmental causes [6, 7]. Besides significant negative effects on women's health and wellbeing [8], the risk of development of ovarian cancer cannot be overlooked [9]. Initially considered a benign disease, endometriosis, and particularly ovarian endometriosis, may increase the risk of developing malignancy.

This assumption started in 1925, when Sampson described endometrial carcinoma of the ovary arising in endometrial tissue [10], and was subsequently supported in 1953, when Scott wrote about malignant changes in endometriosis and pointed out that benign endometriosis might be observed in proximity to the endometriosis-related cancer [11]. Numerous studies suggested that atypical endometriosis might be a middle step in progression from benign disease to cancerous disease. Subsequent research revealed numerous anatomical and physiological features shared by endometriosis and oral cancer including the ability to evade

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apoptosis, dysregulation of stem cells, formation of new vascular system, development of metastases, and appearance of a microenvironment helping the whole process. Endometriosis patients bear stronger risk of developing cancer, particularly hematopoietic and ovarian, [12–15].

Two main mechanisms have been suggested to describe the association between ovarian cancer and endometriosis: (1) both diseases coexist and are a result of shared risk factors and their effects; and (2) endometriotic cells gradually transform to cancer cells.

Considering the worldwide increasing attention on this problem [16], in this article we aimed to summarize the most recent knowledge about the topic.

## Risk of ovarian cancer in women affected by endometriosis

The hypothesis that atypical endometriosis might represent a transitional step between normal endometriosis and cancer originated from histopathological studies [17]. From this hypothesis it was only small step to assumption that endometriosis is really a premalignant condition. This was further supported by the fact that over two thirds of endometriosis-associated ovarian tumors develop when atypical ovarian endometriosis is present [18]. Figure 1 summarizes the association between individual types of ovarian cancer and endometriosis.

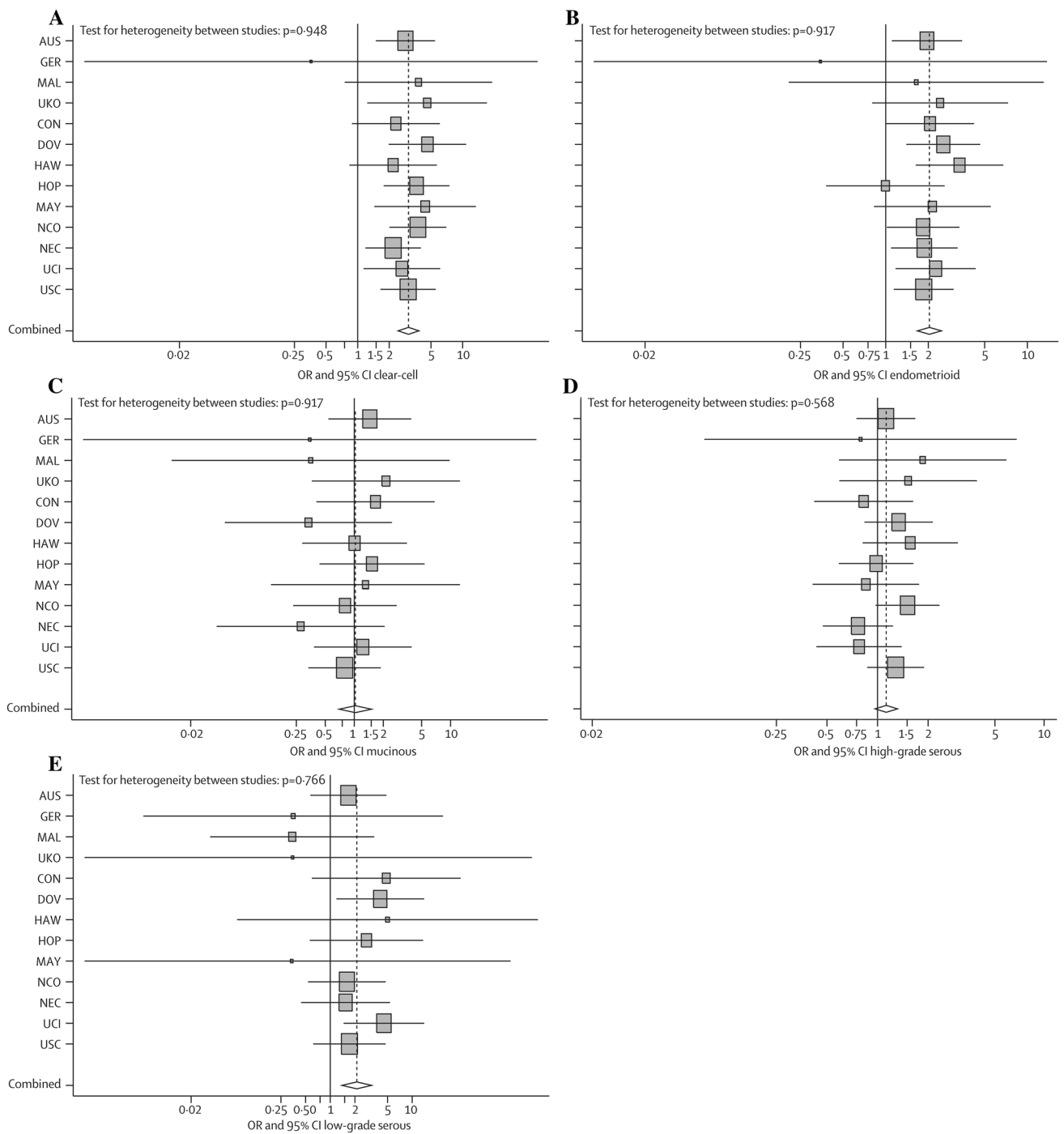
Subsequently, many retrospective studies have documented higher rates of endometriosis in patients with ovarian cancer and vice versa (see below). There are numerous similarities between ovarian cancer and endometriosis, some of which can influence the incidence rate. Infertility or late menopause are examples of factors related to an increased risk [19]. Hysterectomy, use of oral contraceptives, and tubal ligation can lower the risk [20].

Accumulated evidence suggests that ovarian endometriosis can give rise to various ovarian malignancies, generally termed endometriosis-associated ovarian carcinoma (EAOC), which include ovarian clear cell carcinoma (OCCC), endometrioid carcinoma, and rare seromucinous tumors. In general, EAOC refers to ovarian cancer with both cancer cells and endometriosis in the same ovary, cancer in one ovary and endometriosis in the other, or the presence of ovarian cancer and pelvic endometriosis [21]. Some suggest EAOC is classified separately from classical ovarian cancer based on findings of younger age of patients, lower levels of CA-125 marker, and higher number of clear cells [22]. However, recent classification of EAOC by histotype suggested the high variability of both prognostic and clinical factors which does not allow to clearly distinguishing between ovarian and EAOC [23].

The capability of endometriosis to undergo malignant transformation is already well established. However, it is still not possible to identify definite intermediate precursors. The closest example might be an atypical endometriosis with features that are neither benign nor fully malignant [17]. Later studies showed that these lesions are present in 50% of endometrioid and clear cells carcinomas [24]. Molecular pathways associated with ARID1A mutations have recently been reported and suggest progression from endometriosis to atypical endometriosis and subsequent EAOC [25]. Clear cell adenocarcinoma of the ovary is type of chemoresistant cancer frequently associated with endometriosis [26]. The cause of this malignant disease is hypothesized to be the existence of abundant free iron in endometriotic cysts leading to persistent oxidative stress and subsequent carcinogenesis. Recent mechanisms involved in the malignant transformations are summarized in Fig. 2. Some studies proposed that Met signaling pathway plays an important role in clear cell adenocarcinoma development [27].

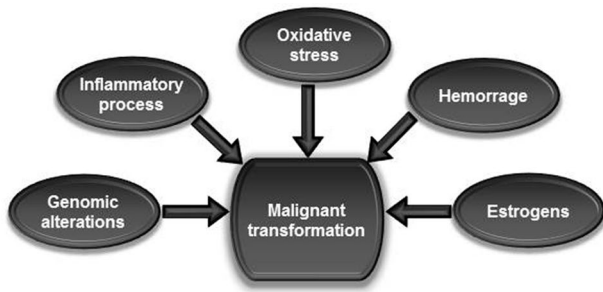
The first large epidemiology study used over 20,000 women with endometriosis and found significant increase in ovarian cancer occurrence [28]. Subsequent large studies have demonstrated presence of ovarian cancer in 5–10% of patients with endometriosis, but the numbers sometimes vary and some studies found that endometriosis is associated with 1.2–1.8 times increased risk of ovarian cancer [29]. Other studies found the risk to be from 0.2–2.5% [30] or even threefold [31]. The same data were found in an analysis of Taiwanese women [32]. A Swedish study of over 64,000 women found that patients with endometriosis have an increased risk of certain malignancies (ovarian, endocrine, non-Hodgkin lymphoma, and brain tumors), and this risk increases with early diagnosed or longstanding disease [33]. A study of 45,000 Danish women confirmed not only the increased risk of ovarian cancer, but also the increased risks of endometrial and breast cancers [34]. In addition, the risk of colorectal cancer was increased 13-fold in women with internal endometriosis [35]. Relative risk to develop ovarian cancer might be up to 1.42 [29, 36], but the more relevant absolute risk data suggested 1.3% in general female populations and 1.8% in women with endometriosis.

A meta-analysis of almost 500,000 women confirmed the increased risk of cancer development, but found that these cases were mostly slow-growing, less invasive, low-grade tumors [29]. Review of literature published in the last 5 years confirmed these data and suggested that the high risk of cancer development might result from high estrogen concentration resulting in malignant proliferation of cysts, and/or from mutation in the ARID1A gene (a member of the SWI/SNF family) and consequent loss of BAF250a expression [37]. A retrospective analysis of 140 patients found that those with endometriosis-associated tumors had a better chance for survival [38]. However, the limited number



**Fig. 1** Association between endometriosis and subtypes of invasive ovarian. **a** Clear cell. **b** Endometrioid. **c** Mucinous. **d** High-grade serous. **e** Low-grade serous. Data are site-specific stratified and adjusted ORs (squares) and 95% CI (horizontal lines). AUS Australian Cancer Study, Australian Ovarian Cancer Study, GER German Ovarian Cancer Study, MAL Malignant Ovarian Cancer Study, UKO United Kingdom Ovarian Cancer Population Study, CON Connecticut Ovary Study, DOV Diseases of the Ovary and their Evaluation Study,

HAW Hawaii Ovarian Cancer Study, HOP Hormones and Ovarian Cancer Prediction Study, MAY Mayo Clinic Ovarian Cancer Study, NCO North Carolina Ovarian Cancer Study, NEC New England Case–Control Study of Ovarian Cancer, UCI University of California, Irvine Ovarian Cancer Study, USC University of Southern California, Study of Lifestyle and Women’s Health, OR odds ratio. From Pearce et al. [88]



**Fig. 2** Different mechanisms suggested for the malignant transformation of an endometriosis. Based on Grandi et al. [21]

of patients in this analysis does not allow us to make any conclusions.

Several studies to determine if the presence of endometriosis can influence the prognostic factor for better cancer survival have found a sort of compromise—patients with endometriosis alone had no prognostic significance; but patients with both were younger, with lower stage and grade, having cancer confined to the pelvis, and had improved progression-free and overall survival [39]. Conversely, other studies found no clear-cut correlations between endometriosis and ovarian cancer, and solicited future and more robust data analysis to draw a firm conclusion [40]. Similarly, a retrospective study of ovarian cancer patients suggested that due to the rarity of the OCCC subtype, a cause-and-effect relationship between OCCC and endometriosis needs statistical studies of the entire population [41].

The question of the possible protective effects of endometriosis on survival from cancer is still open, as the research data are not conclusive. On one hand, no association between the presence of endometriosis and survival was found [42]; on the other hand, other studies revealed better survival endometriosis patients [43]. The latter findings were even more pronounced in breast and ovarian cancer [44], regardless one-sided oophorectomy or radical excision of endometriosis [45]. Recent meta-analysis of risks and prognosis did not answer the question of potential protection, but clearly documented that endometriosis is directly associated with the increased risk of development of ovarian cancer [29].

As most of the studies used patient data from only one country, it is possible that the endometriosis-ovarian cancer connection differs based on socioeconomics, nutrition, or health care conditions.

Two potential scenarios leading to endometriosis-related ovarian cancer have been proposed [46]. One scenario involves extracellular hemoglobin, iron, and heme (from the repeated hemorrhages occurring in endometriosis) causing cellular oxidative damage via increased reactive oxygen species with subsequent DNA damage and resulting mutations. The second involves persistent production of antioxidants,

which would favor tumor-potentiating environment. Both possibilities support the notion of the double-edged sword of redox imbalance; for review, see Fontana et al. [47].

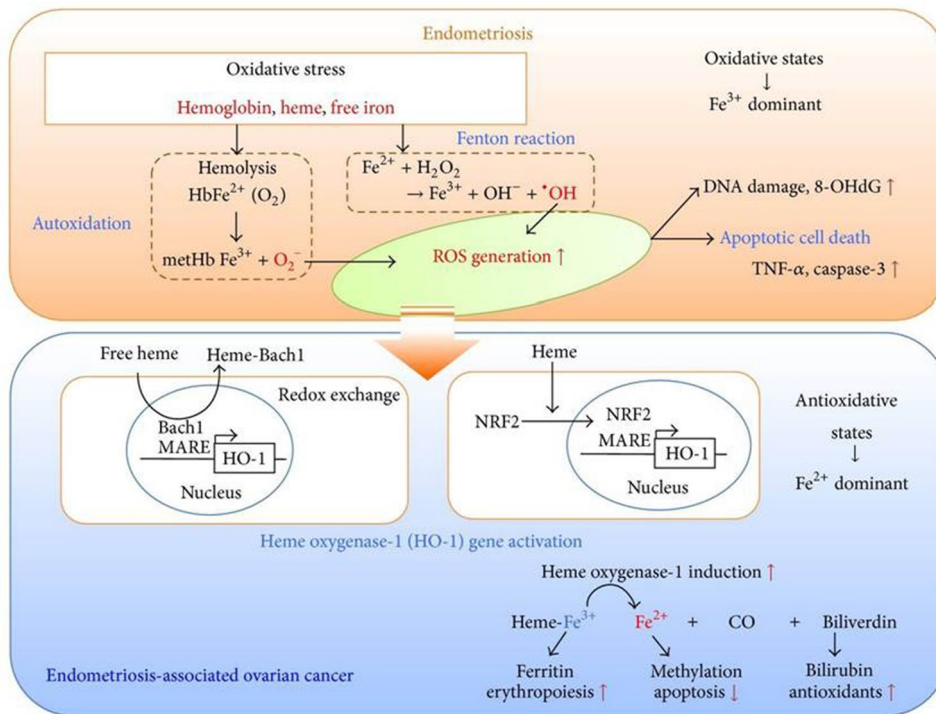
Several pathways linking endometriosis and ovarian cancer have been suggested including oxidative stress, prevalence of certain cytokines, genetic mutations, and hyperestrogenic milieu. Balance of oxidants and endogenous antioxidants might play an important role in malignant transformation (individual steps are summarized in Fig. 3). Atypical endometriosis is particularly dangerous and considered by some to be an intermediate precursor linking classical endometriosis and clear cell adenocarcinoma [48]. In patients who underwent a procedure for ovarian cancer, approximately 10% had coexisting ovarian endometriosis. This number increased to 37% in patients with clear cell ovarian cancer [49]. In addition, there is substantial evidence of aberrant function of almost all types of immune cells in women with endometriosis: decreased T cell reactivity and NK cytotoxicity [50]; polyclonal activation of B cells and increased antibody production [51]; increased number and activation of peritoneal macrophages [52]; alteration of apoptotic pathways [53–55]; and changes in inflammatory mediators [56] (Fig. 4). A potential process of the development of ovarian cancer from endometriosis is shown in Fig. 5.

From the clinical point of view, ovarian cancer can develop after endometriosis excision and is more likely to develop from recurrent endometrioma [57]. Despite current efforts, we definitely need more research before we can draw a firm conclusion.

### Biomarkers and genetic approaches

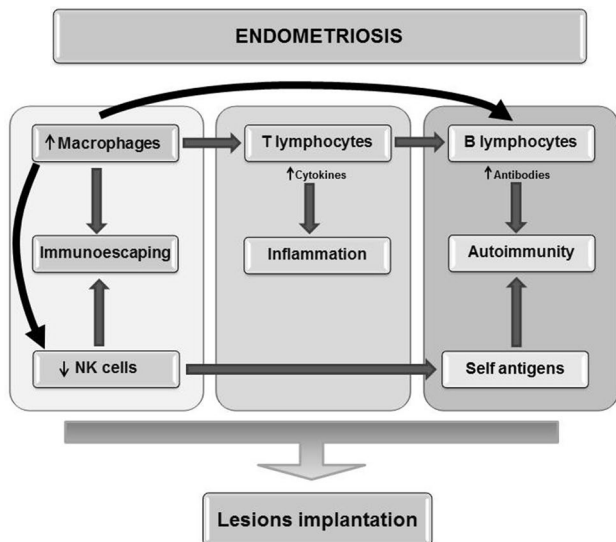
Development of reliable biomarkers might provide a positive outcome for early detection of endometriosis-related cancers. A recent study focused on the possible clinical relevance of the combined detection of serum Smac, HE4, and CA125 in endometriosis-associated ovarian cancer; although serum Smac levels were significantly lower in the cancer group, the expressions of the other two used markers were significantly higher [58]. As the differences also reflected the situation before and after surgery, these combinations might provide an early diagnosis of endometriosis-associated ovarian cancer. From the clinical point of view, new development or an increase of symptoms, such as dyspareunia or dysmenorrhoea, should call for attention for the possibility of development of ovarian cancer, particularly in presence of solid mass and elevated serum HE4 [59].

Emerging data have suggested that dysregulation of microRNA (miRNA) expression might play a role in the development of endometriosis [60]. In addition, comprehensive miRNA profiling from ovarian cancer and its associated endometriosis showed that the expressions of miRNAs were significantly different [61]. These authors suggested

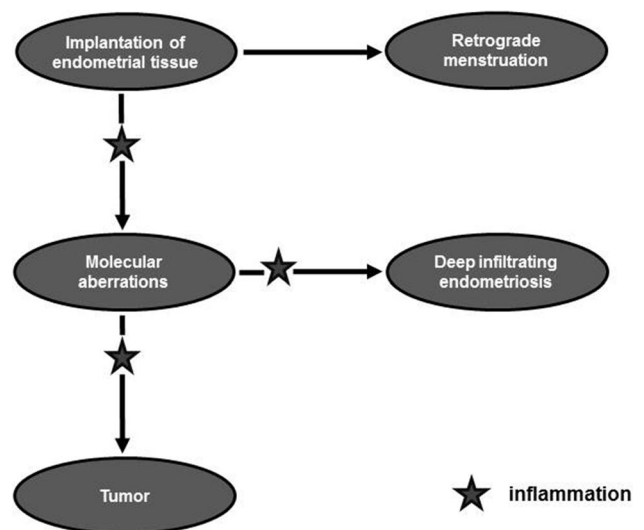


**Fig. 3** Malignant transformation of endometriosis: a fine-tuned balance between the formation of oxidants and the availability of endogenous antioxidants. Cell-free hemoglobin, heme, and iron massively released into the endometriotic cyst fluid space during menstruation are prone to autoxidation and may spontaneously convert oxyHb to metHb. ROS ( $O_2^-$ ) are continuously generated by the autoxidation of hemoglobin. Iron derivatives also stimulate Fenton reaction, contributing to the generation of ROS ( $\cdot OH$ ) in endometriotic cyst. Fur-

thermore, hemoglobin and heme activate expression of a variety of antioxidant genes. Heme stimulates antioxidant HO1 gene expression through direct binding to Bach1 or induction of NRF2 gene. Antioxidant is considered to be a double-edged sword. Excess ROS causes cell death. Antioxidants alleviate cell death by scavenging ROS ( $O_2^-$  and  $\cdot OH$ ), allowing for increased cell survival and then carcinogenesis. From Iwabuchi et al. [89]



**Fig. 4** Immune cells involved in endometriosis-cancer transformation. Based on Riccio et al. [90]



**Fig. 5** Potential process of the establishment and evolution of endometriosis lesions to ovarian cancer. Based on Dawson et al. [91]

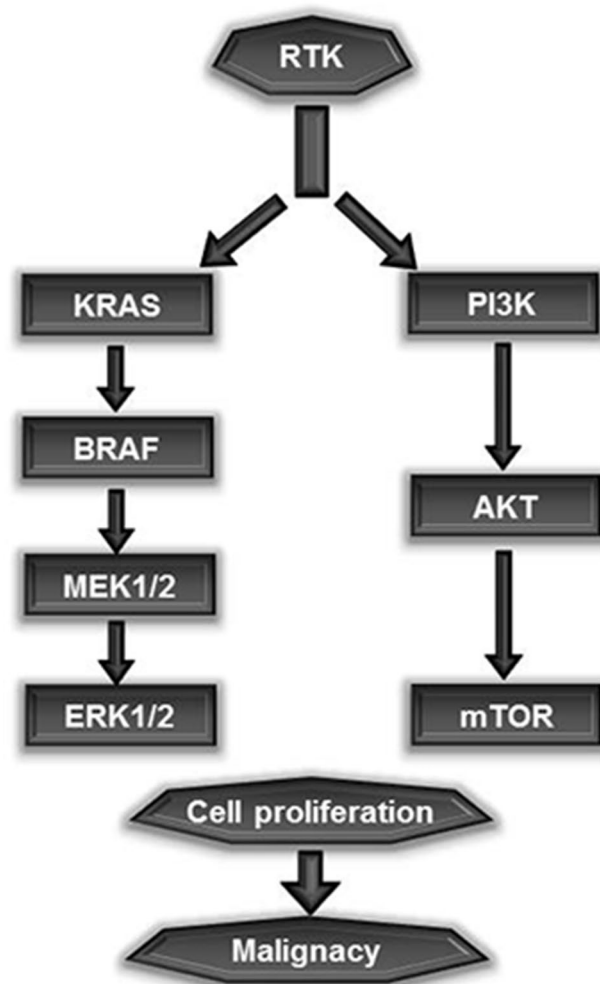
the possible use of these miRNAs as either a diagnostic or a prognostic tool, but not enough information about their targets is currently available, making their use in diagnosis or therapy of endometriosis infeasible at this time. In addition, the abovementioned study did not determine why this expression differs, why it is relevant, or whether the changes in miRNA expressions in endometriosis led to ovarian cancer development.

Some studies suggested that miRNAs might be considered plasma biomarkers. A reverse-transcriptase quantitative PCR experiment identified 23 individual miRNAs with a different expression in patients suffering from EAO or endometriosis [62]. Subsequent studies confirmed changes in expression patterns of these mRNAs can serve as specific biomarkers useful in diagnostic practice. Another study, unfortunately suffering from low number of study subjects, found differences in expression of mRNAs for progesterone receptors (decrease) and TGF- $\beta$ 1, COX-2, VEGF, ER-1 $\alpha$ , and androgen receptors (increase) [63].

Mutations are often connected with cancer development. Genetic mutations, together with a rather permissive micro-environment, are often hypothesized to result in malignant changes of endometriosis [64]. Whole-genome sequencing resulted in the discovery of new mutations, but multiple somatic mutations were also detected by examining single genes. Genes and signaling pathways associated with EAOs include PTEN, CTNNB1, PIK3CA, Src, KRAS, microsatellite instability, and ARID1A [23, 65], which are known to play key roles in the recurrence of epithelial ovarian cancer [66]. TP53 is one of the best-known tumor-suppressor genes, and mutations in TP53 are present in up to 50% of ovarian cancer [67]. Similarly, mutations in catenin beta 1 (CTNNB1) were found in 60% of ovarian endometrioid carcinomas [68]. The loss of ARID1A expression usually coexists with the activation of PI3K-Akt pathway or with XNF217 amplification, suggesting an early event in the malignant transformation of endometriotic tissue to clear cell carcinoma [69]. Molecular pathways involved in pathogenetic processes of endometriosis-associated ovarian cancer are summarized in Fig. 6.

A recent epigenetic study focused on the possible relationship between methylation status of RASSF2A gene promoter and EAO [70]. This study comprised 40 women, and showed lower expression in OCC and ovarian-endometrial carcinoma groups with the methylation status related to clinical grading and staging, meaning that it might develop into solid indicator for early detection.

Another study employed immunohistochemistry and compared various molecular changes in endometriosis-associated OCC [71]. The authors found that PTEN was significantly lowered in both endometriosis and invasive tumor tissue, while estrogen receptor was lost in OCC. ZRCC5, PTCH2, EF1A2, and PPIR14B were strongly overexpressed



**Fig. 6** Molecular pathways involved in endometriosis-associated ovarian cancer pathogenesis

in OCC. Knockdown experiments in clear cell cancer cell line demonstrated significant growth inhibition. In cancer cells, there was loss of expression of serous ovarian cancer lineage marker WT1. The authors concluded that the loss of PTEN expression represents an important early event in endometriosis development whereas the loss of endocrine receptors and polycomb-mediated transcriptional programming might play a role in malignant transformation.

Numerous studies compared somatic cancer-associated mutations in endometriotic lesions and found PTEN mutations in up to 53% of lesions [72, 73]. PTEN is a tumor suppressor gene with clear association with ovarian cancer, where it is required for appropriate regulation of the PI3K enzyme pathway [74]. This pathway is crucial for progression from endometriosis to ovarian cancer [75].

Other studies showed no changes in TP53 or PIK3CA mutations, and KRAS mutation was found in deep infiltrating endometriotic lesions which only very rarely undergo

malignant transformation [76], making correlation between cancer mutations and endometriosis-based cancer development unclear.

A hospital-based case–control analysis used 12 single-nucleotide polymorphisms genotyped using TaqMan Open Array analysis and showed that rs11651755 in HNF1B modified the risk of both endometriosis and ovarian cancer [77]. These results suggest common etiology and that HNF1B may be somehow involved in the pathogenetic pathway from endometriosis to cancer.

## Stem cells

The existence of lesions is still not fully answered and none of the current theories dealing with the causes of endometriosis clearly explained them. When individual hypothesis failed, a possibility of combined mechanisms occurred. Some of the most recent suggestions propose that endometriotic lesions originate from ectopic endometrial stem cell progenitors [78–80]. The fact that monthly regeneration of the endometrium occurring after menstrual shedding supports this hypothesis [80]. It is possible that the stem cells are responsible for unusual translocation of both layers of endometriosis [81]. Contrary to the traditional theories, development of endometriosis might be caused or at least heavily influenced by these stem cells [81]. If this hypothesis is right, endometriotic lesions might be at least partly clonal in origin [82]. Readers interested in more information about the connection between stem cells and endometriosis could read a review [83]. This possibility is further supported by that fact that some HOX genes involved both in eutopic endometrium and ovarian cancer [84] are manifested in primitive hematopoietic cells [85]. In addition, we should not overlook the possibility that the transformation of stem cells can play an important role in ovarian cancer development [86]. However, research in this area is far from offering any direct evidence, therefore we can only hypothesize about the possible role of stem cells and the calls of direct targeting as a therapeutical tool [87] are clearly premature.

## Conclusions

The evidence showing that patients with endometriosis have a higher risk of developing ovarian cancer is compelling. Endometriosis in younger women, which persists into an older age, creates a long window for malignant transformation. However, the question of how much higher the absolute risk is not fully clear. What remains inconclusive is how much this association is causative. Somatic mutations of PIK3CA, PTEN, and ARID1A probably play a role in the disease progression and malignant

transformation. To identify which patients are most at risk, further studies are clearly needed.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interests.

**Informed consent** Not relevant for this study.

**Ethical approval** Not relevant for this study.

## References

- de Ziegler D, Borghese B, Chapron C (2010) Endometriosis and infertility: pathophysiology and management. *Lancet* 376(9742):730–738. [https://doi.org/10.1016/S0140-6736\(10\)60490-4](https://doi.org/10.1016/S0140-6736(10)60490-4)
- Baldi A, Campioni M, Signorile PG (2008) Endometriosis: pathogenesis, diagnosis, therapy and association with cancer (review). *Oncol Rep* 19(4):843–846
- von Rokytansky C (1860) Über Uterusdrüsen-Neubildung in Uterus- und Ovarial-Sarcomen. *Z Ges Artze Wein* 37:577–593
- Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D’Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W, European Society of Human Reproduction Embryology (2014) ESHRE guideline: management of women with endometriosis. *Hum Reprod* 29(3):400–412. <https://doi.org/10.1093/humrep/det457>
- Guerriero S, Condous G, van den Bosch T, Valentin L, Leone FP, Van Schoubroeck D, Exacoustos C, Installé AJ, Martins WP, Abrao MS, Hudelist G, Bazot M, Alcazar JL, Goncalves MO, Pascual MA, Ajossa S, Savelli L, Dunham R, Reid S, Menakaya U, Bourne T, Ferrero S, Leon M, Bignardi T, Holland T, Jurkovic D, Benacerraf B, Osuga Y, Somigliana E, Timmerman D (2016) Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. *Ultrasound Obstet Gynecol* 48(3):318–332. <https://doi.org/10.1002/uog.15955>
- Sofo V, Gotte M, Lagana AS, Salmeri FM, Triolo O, Sturlese E, Retto G, Alfa M, Granese R, Abrao MS (2015) Correlation between dioxin and endometriosis: an epigenetic route to unravel the pathogenesis of the disease. *Arch Gynecol Obstet* 292(5):973–986. <https://doi.org/10.1007/s00404-015-3739-5>
- Vetvicka V, Kralickova M (2015) Current theories on endometriosis pathogenesis. *Edorium J Mol Pathol* 1:1–4
- Vitale SG, La Rosa VL, Rapisarda AMC, Lagana AS (2017) Impact of endometriosis on quality of life and psychological well-being. *J Psychosom Obstet Gynaecol* 38(4):317–319. <https://doi.org/10.1080/0167482X.2016.1244185>
- Kralickova M, Losan P, Vetvicka V (2014) Endometriosis and cancer. *Women’s Health* 10(6):591–597. <https://doi.org/10.2217/whe.14.43>

10. Sampson JA (1925) Endometrial carcinoma of the ovary, arising in endometrial tissue in that organ. *Arch Surg* 10(1):1–72. <https://doi.org/10.1001/archsurg.1925.01120100007001>
11. Scott RB (1953) Malignant changes in endometriosis. *Obstet Gynecol* 2(3):283–289
12. Hunn J, Rodriguez GC (2012) Ovarian cancer: etiology, risk factors, and epidemiology. *Clin Obstet Gynecol* 55(1):3–23. <https://doi.org/10.1097/GRF.0b013e31824b4611>
13. Olovsson M (2011) Immunological aspects of endometriosis: an update. *Am J Reprod Immunol* 66(Suppl 1):101–104. <https://doi.org/10.1111/j.1600-0897.2011.01045.x>
14. Sayasneh A, Tsivos D, Crawford R (2011) Endometriosis and ovarian cancer: a systematic review. *ISRN Obstet Gynecol* 2011:140310. <https://doi.org/10.5402/2011/140310>
15. Vlahos NF, Kalampokas T, Fotiou S (2010) Endometriosis and ovarian cancer: a review. *Gynecol Endocrinol* 26(3):213–219. <https://doi.org/10.1080/09513590903184050>
16. Kvaskoff M, Horne AW, Missmer SA (2017) Informing women with endometriosis about ovarian cancer risk. *Lancet* 390(10111):2433–2434. [https://doi.org/10.1016/S0140-6736\(17\)33049-0](https://doi.org/10.1016/S0140-6736(17)33049-0)
17. LaGrenade A, Silverberg SG (1988) Ovarian tumors associated with atypical endometriosis. *Hum Pathol* 19(9):1080–1084
18. Maiorana A, Cicerone C, Niceta M, Alio L (2007) Evaluation of serum CA 125 levels in patients with pelvic pain related to endometriosis. *Int J Biol Markers* 22(3):200–202
19. Ness RB, Cottreau C (1999) Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst* 91(17):1459–1467
20. Wang C, Liang Z, Liu X, Zhang Q, Li S (2016) The association between endometriosis, tubal ligation, hysterectomy and epithelial ovarian cancer: meta-analyses. *Int J Environ Res Public Health* 13:11. <https://doi.org/10.3390/ijerph13111138>
21. Grandi G, Toss A, Cortesi L, Botticelli L, Volpe A, Cagnacci A (2015) The association between endometriomas and ovarian cancer: Preventive effect of inhibiting ovulation and menstruation during reproductive life. *Biomed Res Int* 2015:751571. <https://doi.org/10.1155/2015/751571>
22. Zorn KK, Tian C, McGuire WP, Hoskins WJ, Markman M, Muggia FM, Rose PG, Ozols RF, Spriggs D, Armstrong DK (2009) The prognostic value of pretreatment CA 125 in patients with advanced ovarian carcinoma: a Gynecologic Oncology Group study. *Cancer* 115(5):1028–1035. <https://doi.org/10.1002/cncr.24084>
23. Ruderman R, Pavone ME (2017) Ovarian cancer in endometriosis: an update on the clinical and molecular aspects. *Minerva Ginecol* 69(3):286–294. <https://doi.org/10.23736/S0026-4784.17.04042-4>
24. Ogawa S, Kaku T, Amada S, Kobayashi H, Hirakawa T, Ariyoshi K, Kamura T, Nakano H (2000) Ovarian endometriosis associated with ovarian carcinoma: a clinicopathological and immunohistochemical study. *Gynecol Oncol* 77(2):298–304. <https://doi.org/10.1006/gyno.2000.5765>
25. Wilbur MA, Shih IM, Segars JH, Fader AN (2017) Cancer implications for patients with endometriosis. *Semin Reprod Med* 35(1):110–116. <https://doi.org/10.1055/s-0036-1597120>
26. Mandai M, Yamaguchi K, Matsumura N, Baba T, Konishi I (2009) Ovarian cancer in endometriosis: molecular biology, pathology, and clinical management. *Int J Clin Oncol* 14(5):383–391. <https://doi.org/10.1007/s10147-009-0935-y>
27. Yamashita Y, Akatsuka S, Shinjo K, Yatabe Y, Kobayashi H, Seko H, Kajiyama H, Kikkawa F, Takahashi T, Toyokuni S (2013) Met is the most frequently amplified gene in endometriosis-associated ovarian clear cell adenocarcinoma and correlates with worsened prognosis. *PLoS ONE* 8(3):e57724. <https://doi.org/10.1371/journal.pone.0057724>
28. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A (1997) Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 176(3):572–579
29. Kim HS, Kim TH, Chung HH, Song YS (2014) Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis. *Br J Cancer* 110(7):1878–1890. <https://doi.org/10.1038/bjc.2014.29>
30. Gadducci A, Lanfredini N, Tana R (2014) Novel insights on the malignant transformation of endometriosis into ovarian carcinoma. *Gynecol Endocrinol* 30(9):612–617. <https://doi.org/10.3109/09513590.2014.926325>
31. Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS (2008) Risk of epithelial ovarian cancer in relation to benign ovarian conditions and ovarian surgery. *Cancer Causes Control* 19(10):1357–1364. <https://doi.org/10.1007/s10552-008-9207-9>
32. Chang WH, Wang KC, Lee WL, Huang N, Chou YJ, Feng RC, Yen MS, Huang BS, Guo CY, Wang PH (2014) Endometriosis and the subsequent risk of epithelial ovarian cancer. *Taiwan J Obstet Gynecol* 53(4):530–535. <https://doi.org/10.1016/j.tjog.2014.04.025>
33. Melin A, Sparen P, Persson I, Bergqvist A (2006) Endometriosis and the risk of cancer with special emphasis on ovarian cancer. *Hum Reprod* 21(5):1237–1242. <https://doi.org/10.1093/humrep/dei462>
34. Mogensen JB, Kjaer SK, Mellemkjaer L, Jensen A (2016) Endometriosis and risks for ovarian, endometrial and breast cancers: a nationwide cohort study. *Gynecol Oncol* 143(1):87–92. <https://doi.org/10.1016/j.ygyno.2016.07.095>
35. Kok VC, Tsai HJ, Su CF, Lee CK (2015) The risks for ovarian, endometrial, breast, colorectal, and other cancers in women with newly diagnosed endometriosis or adenomyosis: a population-based study. *Int J Gynecol Cancer* 25(6):968–976. <https://doi.org/10.1097/IGC.0000000000000454>
36. Wang Q, Wang L, Ding X, Liu A (2017) Expression and significance of ARID1A mRNA in endometriosis-associated ovarian cancer. *J BUON* 22(5):1314–1321
37. Brilhante AV, Augusto KL, Portela MC, Sucupira LC, Oliveira LA, Pouchaim AJ, Nobrega LR, Magalhaes TF, Sobreira LR (2017) Endometriosis and ovarian cancer: an integrative review (endometriosis and ovarian cancer). *Asian Pac J Cancer Prev* 18(1):11–16. <https://doi.org/10.22034/APJCP.2017.18.1.11>
38. Garrett LA, Growdon WB, Goodman A, Boruta DM, Schorge JO, del Carmen MG (2013) Endometriosis-associated ovarian malignancy: a retrospective analysis of presentation, treatment, and outcome. *J Reprod Med* 58(11–12):469–476
39. Dinkelspiel HE, Matrai C, Pauk S, Pierre-Louis A, Chiu YL, Gupta D, Caputo T, Ellenson LH, Holcomb K (2016) Does the presence of endometriosis affect prognosis of ovarian cancer? *Cancer Invest* 34(3):148–154. <https://doi.org/10.3109/07357907.2016.1139716>
40. Taniguchi F (2017) New knowledge and insights about the malignant transformation of endometriosis. *J Obstet Gynaecol Res* 43(7):1093–1100. <https://doi.org/10.1111/jog.13372>
41. Szubert M, Suzin J, Obirek K, Sochacka A, Loszakiewicz M (2016) Clear cell ovarian cancer and endometriosis: is there a relationship? *Prz Menopauzalny* 15(2):85–89. <https://doi.org/10.5114/pm.2016.61190>
42. Noli S, Cipriani S, Scarfone G, Villa A, Grossi E, Monti E, Vercellini P, Parazzini F (2013) Long term survival of ovarian endometriosis associated clear cell and endometrioid ovarian cancers. *Int J Gynecol Cancer* 23(2):244–248. <https://doi.org/10.1097/IGC.0b013e31827aa0bb>
43. Bounous VE, Ferrero A, Fuso L, Ravarino N, Ceccaroni M, Menato G, Biglia N (2016) Endometriosis-associated ovarian cancer: a distinct clinical entity? *Anticancer Res* 36(7):3445–3449



44. Melin A, Lundholm C, Malki N, Swahn ML, Sparen P, Bergqvist A (2011) Endometriosis as a prognostic factor for cancer survival. *Int J Cancer* 129(4):948–955. <https://doi.org/10.1002/ijc.25718>
45. Melin AS, Lundholm C, Malki N, Swahn ML, Sparen P, Bergqvist A (2013) Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer. *Acta Obstet Gynecol Scand* 92(5):546–554. <https://doi.org/10.1111/aogs.12123>
46. Kobayashi H (2016) Potential scenarios leading to ovarian cancer arising from endometriosis. *Redox Rep* 21(3):119–126. <https://doi.org/10.1179/1351000215Y.0000000038>
47. Fontana J, Zima M, Vetvicka V (2018) Biological markers of oxidative stress in cardiovascular diseases: after so many studies, what do we know? *Immunol Invest*. <https://doi.org/10.1080/08820139.2018.1523925>
48. Vercellini P, Vigano P, Buggio L, Makieva S, Scarfone G, Cribiu FM, Parazzini F, Somigliana E (2018) Perimenopausal management of ovarian endometriosis and associated cancer risk: when is medical or surgical treatment indicated? *Best Pract Res Clin Obstet Gynaecol* 51:151–168. <https://doi.org/10.1016/j.bpobgyn.2018.01.017>
49. Dzatic-Smiljkovic O, Vasiljevic M, Djukic M, Vugdalic R, Vugdalic J (2011) Frequency of ovarian endometriosis in epithelial ovarian cancer patients. *Clin Exp Obstet Gynecol* 38(4):394–398
50. Lagana AS, Triolo O, Salmeri FM, Granese R, Palmara VI, Ban Frangez H, Vrtcnik Bokal E, Sofo V (2016) Natural killer T cell subsets in eutopic and ectopic endometrium: a fresh look to a busy corner. *Arch Gynecol Obstet* 293(5):941–949. <https://doi.org/10.1007/s00404-015-4004-7>
51. Riccio LGC, Baracat EC, Chapron C, Batteux F, Abrao MS (2017) The role of the B lymphocytes in endometriosis: a systematic review. *J Reprod Immunol* 123:29–34. <https://doi.org/10.1016/j.jri.2017.09.001>
52. Hanada T, Tsuji S, Nakayama M, Wakinoue S, Kasahara K, Kimura F, Mori T, Ogasawara K, Murakami T (2018) Suppressive regulatory T cells and latent transforming growth factor-beta-expressing macrophages are altered in the peritoneal fluid of patients with endometriosis. *Reprod Biol Endocrinol* 16(1):9. <https://doi.org/10.1186/s12958-018-0325-2>
53. Salmeri FM, Lagana AS, Sofo V, Triolo O, Sturlese E, Retto G, Pizzo A, D'Ascola A, Campo S (2015) Behavior of tumor necrosis factor-alpha and tumor necrosis factor receptor 1/tumor necrosis factor receptor 2 system in mononuclear cells recovered from peritoneal fluid of women with endometriosis at different stages. *Reprod Sci* 22(2):165–172. <https://doi.org/10.1177/1933719114536472>
54. Sturlese E, Salmeri FM, Retto G, Pizzo A, De Dominicis R, Ardita FV, Borrielli I, Licata N, Lagana AS, Sofo V (2011) Dysregulation of the Fas/FasL system in mononuclear cells recovered from peritoneal fluid of women with endometriosis. *J Reprod Immunol* 92(1–2):74–81. <https://doi.org/10.1016/j.jri.2011.08.005>
55. Vetvicka V, Lagana AS, Salmeri FM, Triolo O, Palmara VI, Vitale SG, Sofo V, Kralickova M (2016) Regulation of apoptotic pathways during endometriosis: from the molecular basis to the future perspectives. *Arch Gynecol Obstet* 294(5):897–904. <https://doi.org/10.1007/s00404-016-4195-6>
56. Jorgensen H, Hill AS, Beste MT, Kumar MP, Chiswick E, Fedorcsak P, Isaacson KB, Lauffenburger DA, Griffith LG, Qvigstad E (2017) Peritoneal fluid cytokines related to endometriosis in patients evaluated for infertility. *Fertil Steril* 107(5):1191–1199. <https://doi.org/10.1016/j.fertnstert.2017.03.013>
57. Haraguchi H, Koga K, Takamura M, Makabe T, Sue F, Miyashita M, Urata Y, Izumi G, Harada M, Hirata T, Hirota Y, Wada-Hiraike O, Oda K, Kawana K, Fujii T, Osuga Y (2016) Development of ovarian cancer after excision of endometrioma. *Fertil Steril* 106(6):1432–1437. <https://doi.org/10.1016/j.fertnstert.2016.07.1077>
58. Xu XR, Wang X, Zhang H, Liu MY, Chen Q (2018) The clinical significance of the combined detection of serum Smac, HE4 and CA125 in endometriosis-associated ovarian cancer. *Cancer Biomark* 21(2):471–477. <https://doi.org/10.3233/CBM-170720>
59. Capriglione S, Luvero D, Plotti F, Terranova C, Montera R, Scalletta G, Schiro T, Rossini G, Benedetti Panici P, Angioli R (2017) Ovarian cancer recurrence and early detection: may HE4 play a key role in this open challenge? A systematic review of literature. *Med Oncol* 34(9):164. <https://doi.org/10.1007/s12032-017-1026-y>
60. Pan Q, Luo X, Toloubeydokhti T, Chegini N (2007) The expression profile of micro-RNA in endometrium and endometriosis and the influence of ovarian steroids on their expression. *Mol Hum Reprod* 13(11):797–806. <https://doi.org/10.1093/molehr/gam063>
61. Wu RL, Ali S, Bandyopadhyay S, Alesh B, Hayek K, Daaboul MF, Winer I, Sarkar FH, Ali-Fehmi R (2015) Comparative analysis of differentially expressed miRNAs and their downstream mRNAs in ovarian cancer and its associated endometriosis. *J Cancer Sci Ther* 7(7):258–265. <https://doi.org/10.4172/1948-5956.1000359>
62. Suryawanshi S, Vlad AM, Lin HM, Mantia-Smaldone G, Laskey R, Lee M, Lin Y, Donnellan N, Klein-Patel M, Lee T, Mansuria S, Elishaev E, Budi R, Edwards RP, Huang X (2013) Plasma microRNAs as novel biomarkers for endometriosis and endometriosis-associated ovarian cancer. *Clin Cancer Res* 19(5):1213–1224. <https://doi.org/10.1158/1078-0432.CCR-12-2726>
63. Meng Q, Sun W, Jiang J, Fletcher NM, Diamond MP, Saed GM (2011) Identification of common mechanisms between endometriosis and ovarian cancer. *J Assist Reprod Genet* 28(10):917–923. <https://doi.org/10.1007/s10815-011-9573-1>
64. Wei JJ, William J, Bulun S (2011) Endometriosis and ovarian cancer: a review of clinical, pathologic, and molecular aspects. *Int J Gynecol Pathol* 30(6):553–568. <https://doi.org/10.1097/PGP.0b013e31821f4b85>
65. Pavone ME, Lyttle BM (2015) Endometriosis and ovarian cancer: links, risks, and challenges faced. *Int J Womens Health* 7:663–672. <https://doi.org/10.2147/IJWH.S66824>
66. Lagana AS, Colonese F, Colonese E, Sofo V, Salmeri FM, Granese R, Chiofalo B, Ciancimino L, Triolo O (2015) Cytogenetic analysis of epithelial ovarian cancer's stem cells: an overview on new diagnostic and therapeutic perspectives. *Eur J Gynaecol Oncol* 36(5):495–505
67. Schuijter M, Berns EM (2003) TP53 and ovarian cancer. *Hum Mutat* 21(3):285–291. <https://doi.org/10.1002/humu.10181>
68. Matsumoto T, Yamazaki M, Takahashi H, Kajita S, Suzuki E, Tsuruta T, Saegusa M (2015) Distinct beta-catenin and PIK3CA mutation profiles in endometriosis-associated ovarian endometrioid and clear cell carcinomas. *Am J Clin Pathol* 144(3):452–463. <https://doi.org/10.1309/AJCPZ5T2POOFMQVN>
69. Ayhan A, Mao TL, Seckin T, Wu CH, Guan B, Ogawa H, Futagami M, Mizukami H, Yokoyama Y, Kurban RJ, Shih Ie M (2012) Loss of ARID1A expression is an early molecular event in tumor progression from ovarian endometriotic cyst to clear cell and endometrioid carcinoma. *Int J Gynecol Cancer* 22(8):1310–1315. <https://doi.org/10.1097/IGC.0b013e31826b5dcc>
70. Xia Y, Xiong N, Huang Y (2018) Relationship between methylation status of RASSF2A gene promoter and endometriosis-associated ovarian cancer. *J Biol Regul Homeost Agents* 32(1):21–28
71. Worley MJ Jr, Liu S, Hua Y, Kwok JS, Samuel A, Hou L, Shoni M, Lu S, Sandberg EM, Keryan A, Wu D, Ng SK, Kuo WP, Parral-Herran CE, Tsui SK, Welch W, Crum C, Berkowitz RS, Ng SW (2015) Molecular changes in endometriosis-associated ovarian clear cell carcinoma. *Eur J Cancer* 51(13):1831–1842. <https://doi.org/10.1016/j.ejca.2015.05.011>
72. Govatati S, Kodati VL, Deenadayal M, Chakravarty B, Shivaji S, Bhanoori M (2014) Mutations in the PTEN tumor gene and risk of

- endometriosis: a case-control study. *Hum Reprod* 29(2):324–336. <https://doi.org/10.1093/humrep/det387>
73. Sato N, Tsunoda H, Nishida M, Morishita Y, Takimoto Y, Kubo T, Noguchi M (2000) Loss of heterozygosity on 10q2.33 and mutation of the tumor suppressor gene PTEN in benign endometrial cyst of the ovary: possible sequence progression from benign endometrial cyst to endometrioid carcinoma and clear cell carcinoma of the ovary. *Cancer Res* 60(24):7052–7056
  74. Ramaswamy S, Nakamura N, Vazquez F, Batt DB, Perera S, Roberts TM, Sellers WR (1999) Regulation of G1 progression by the PTEN tumor suppressor protein is linked to inhibition of the phosphatidylinositol 3-kinase/Akt pathway. *Proc Natl Acad Sci USA* 96(5):2110–2115
  75. Anglesio MS, Bashashati A, Wang YK, Senz J, Ha G, Yang W, Aniba MR, Prentice LM, Farahani H, Li Chang H, Karnezis AN, Marra MA, Yong PJ, Hirst M, Gilks B, Shah SP, Huntsman DG (2015) Multifocal endometriotic lesions associated with cancer are clonal and carry a high mutation burden. *J Pathol* 236(2):201–209. <https://doi.org/10.1002/path.4516>
  76. Anglesio MS, Papadopoulos N, Ayhan A, Nazeran TM, Noe M, Horlings HM, Lum A, Jones S, Senz J, Seckin T, Ho J, Wu RC, Lac V, Ogawa H, Tessier-Cloutier B, Alhassan R, Wang A, Wang Y, Cohen JD, Wong F, Hasanovic A, Orr N, Zhang M, Popoli M, McMahon W, Wood LD, Mattox A, Allaire C, Segars J, Williams C, Tomasetti C, Boyd N, Kinzler KW, Gilks CB, Diaz L, Wang TL, Vogelstein B, Yong PJ, Huntsman DG, Shih IM (2017) Cancer-associated mutations in endometriosis without cancer. *N Engl J Med* 376(19):1835–1848. <https://doi.org/10.1056/NEJMOa1614814>
  77. Burghaus S, Fasching PA, Haberle L, Rubner M, Buchner K, Blum S, Engel A, Ekici AB, Hartmann A, Hein A, Beckmann MW, Renner SP (2017) Genetic risk factors for ovarian cancer and their role for endometriosis risk. *Gynecol Oncol* 145(1):142–147. <https://doi.org/10.1016/j.ygyno.2017.02.022>
  78. Maruyama T, Yoshimura Y (2012) Stem cell theory for the pathogenesis of endometriosis. *Front Biosci (Elite Ed)* 4:2754–2763
  79. Lagana AS, Vitale SG, Salmeri FM, Triolo O, Ban Frangez H, Vrtacnik-Bokal E, Stojanovska L, Apostolopoulos V, Granese R, Sofo V (2017) Unus pro omnibus, omnes pro uno: a novel, evidence-based, unifying theory for the pathogenesis of endometriosis. *Med Hypotheses* 103:10–20. <https://doi.org/10.1016/j.mehy.2017.03.032>
  80. Lagana AS, Salmeri FM, Vitale SG, Triolo O, Gotte M (2018) Stem cell trafficking during endometriosis: may epigenetics play a pivotal role? *Reprod Sci* 25(7):978–979. <https://doi.org/10.1177/1933719116687661>
  81. Masuda H, Matsuzaki Y, Hiratsu E, Ono M, Nagashima T, Kajitani T, Arase T, Oda H, Uchida H, Asada H, Ito M, Yoshimura Y, Maruyama T, Okano H (2010) Stem cell-like properties of the endometrial side population: implication in endometrial regeneration. *PLoS ONE* 5(4):e10387. <https://doi.org/10.1371/journal.pone.0010387>
  82. Deane JA, Gualano RC, Gargett CE (2013) Regenerating endometrium from stem/progenitor cells: is it abnormal in endometriosis, Asherman's syndrome and infertility? *Curr Opin Obstet Gynecol* 25(3):193–200. <https://doi.org/10.1097/GCO.0b013e32836024e7>
  83. Kralickova M, Vetvicka V (2015) Endometriosis: are stem cells involved? *Int J Clin Exp Med Sci* 1:65–69
  84. Cheng W, Liu J, Yoshida H, Rosen D, Naora H (2005) Lineage infidelity of epithelial ovarian cancers is controlled by HOX genes that specify regional identity in the reproductive tract. *Nat Med* 11(5):531–537. <https://doi.org/10.1038/nm1230>
  85. Taylor HS, Vanden Heuvel GB, Igarashi P (1997) A conserved Hox axis in the mouse and human female reproductive system: late establishment and persistent adult expression of the Hoxa cluster genes. *Biol Reprod* 57(6):1338–1345
  86. Bapat SA, Mali AM, Koppikar CB, Kurrey NK (2005) Stem and progenitor-like cells contribute to the aggressive behavior of human epithelial ovarian cancer. *Cancer Res* 65(8):3025–3029. <https://doi.org/10.1158/0008-5472.CAN-04-3931>
  87. Taylor HS, Osteen KG, Bruner-Tran KL, Lockwood CJ, Krikun G, Sokalska A, Duleba AJ (2011) Novel therapies targeting endometriosis. *Reprod Sci* 18(9):814–823. <https://doi.org/10.1177/1933719111410713>
  88. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, Nagle CM, Doherty JA, Cushing-Haugen KL, Wicklund KG, Chang-Claude J, Hein R, Lurie G, Wilkens LR, Carney ME, Goodman MT, Moysich K, Kjaer SK, Hogdall E, Jensen A, Goode EL, Fridley BL, Larson MC, Schildkraut JM, Palmieri RT, Cramer DW, Terry KL, Vitonis AF, Titus LJ, Ziogas A, Brewster W, Anton-Culver H, Gentry-Maharaj A, Ramus SJ, Anderson AR, Brueggmann D, Fasching PA, Gayther SA, Huntsman DG, Menon U, Ness RB, Pike MC, Risch H, Wu AH, Berchuck A (2012) Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol* 13(4):385–394. [https://doi.org/10.1016/S1470-2045\(11\)70404-1](https://doi.org/10.1016/S1470-2045(11)70404-1)
  89. Iwabuchi T, Yoshimoto C, Shigetomi H, Kobayashi H (2015) Oxidative stress and antioxidant defense in endometriosis and its malignant transformation. *Oxid Med Cell Longev* 2015:848595. <https://doi.org/10.1155/2015/848595>
  90. Riccio LGC, Santulli P, Marcellin L, Abrao MS, Batteux F, Chapron C (2018) Immunology of endometriosis. *Best Pract Res Clin Obstet Gynaecol* 50:39–49. <https://doi.org/10.1016/j.bpobgyn.2018.01.010>
  91. Dawson A, Fernandez ML, Anglesio M, Yong PJ, Carey MS (2018) Endometriosis and endometriosis-associated cancers: new insights into the molecular mechanisms of ovarian cancer development. *Ecancermedscience* 12:803. <https://doi.org/10.3332/ecancer.2018.803>
  92. Maniglio P, Ricciardi E, Lagana AS, Triolo O, Caserta D (2016) Epigenetic modifications of primordial reproductive tract: a common etiologic pathway for Mayer-Rokitansky-Kuster-Hauser Syndrome and endometriosis? *Med Hypotheses* 90:4–5. <https://doi.org/10.1016/j.mehy.2016.02.015>

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