

Endometriosis and ovarian cancer

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Abstract

Endometriosis is the leading cause of morbidity among premenopausal women and the complex pathogenesis of this disease remains controversial despite extensive research. This disease represents one of the most common gynecological problems. It is generally believed that this disease is due primarily to retrograde menstruation or transplanted shed endometrium. Based on overwhelming data, ovarian endometrioma is considered a neoplastic process, since most endometriosis-associated ovarian carcinoma occur in the presence of atypical ovarian endometriosis. A study comparing patients with typical epithelial ovarian cancer with endometriosis-associated ovarian cancer demonstrated that the patients with the latter disease strongly differ in both biological and histological characteristics. The prevalence of this disease is not completely established, but approximately 15 percent of women suffer from this disease. In addition, we know about the possible links between endometriosis and cancer for almost 100 years. Despite clear evidence revealing that endometriosis increases ovarian

cancer risks, it is possible that it may not affect disease progression after the appearance of ovarian cancer. However, despite clear evidence revealing that endometriosis increases ovarian cancer risk, our knowledge of the risk factors is far from established. In our review, we focused on the most recent approaches including possible biomarkers and genetic approaches.

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Key words: Endometriosis; Ovarian cancer; Biomarkers; Cancer; Histology

Core tip: Endometriosis is a multifactorial disease, which, despite intensive research in the last decades, is still not fully explained. In addition, many questions remain to be answered as to the exact events leading from cysts to endometriosis-associated ovarian cancer. Surprisingly, having endometriosis might be less risky than undergoing *in vitro* fertilization, which can increase the risk of ovarian cancer. Our review summarizes current hypothesis on probable mechanisms and attributing factors such as longstanding estrogen stimulation, repeated heavy menstruation and early events on the molecular level. Thus far, however, no single one can be used for diagnosis or treatment.

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INTRODUCTION

Endometriosis is a common gynecologic disorder usually defined as presence and/or growth of endometrial tissue outside the uterine cavity. Although the prevalence of this disease is not clear, approximately 7%-15% of women of reproductive age^[1] have endometriosis, but significantly increases in cases of infertility^[2]. Despite the fact that this

disorder was first described in 1860^[3], the definite cause of endometriosis is still unclear and this disease remains to be one of the most enigmatic female diseases. Probably the most accepted mechanism is the adhesion and subsequent growth of endometrial fragments occurring in the peritoneum by retrograde menstruation. Another possibility is the occurrence of anatomical abnormalities. The repeated events of hemorrhage can also contribute to carcinogenesis and further cancer progression^[4]. Lately, the hereditary aspect gained traction, with *CYP11A1* m1 polymorphism (particularly *CYP10* variable number of tandem repeats allele) and *GSTM1* null deletion playing an important role^[5]. A detailed summary of possible theories is reviewed by Baldi *et al*^[6] and Yuan *et al*^[7]. In addition, at least three theories supporting the concept of *in situ* development exist, including a Mullerian and Wolffian rest theory, coelomic metaplasia theory and metaplasia following endometrial stimulation theory (for review see Thomas *et al*^[8]). However, none of these theories explain all the different types of endometriosis^[9]. Based on overwhelming data, ovarian endometrioma can be viewed as a neoplastic process.

RELATION BETWEEN ENDOMETRIOSIS AND OVARIAN CANCER

The possibility of transformation of endometriotic tissue into malignant ovarian cancer has been recognized for almost 100 years^[10]. In 1925, Sampson^[10] first described malignant changes in endometriosis and proposed the following criteria for diagnosing the carcinomatous development in endometriosis: (1) coexistence of carcinoma and endometriosis within the same ovary, (2) a similar histological pattern and (3) exclusion of a second malignant tumor elsewhere. Later, in 1953, Scott^[11] postulated that in addition to the criteria by Sampson, morphological changes demonstrated by benign endometriosis that are contiguous with malignant tissue is a prerequisite for adjudication of a malignancy originating from endometriosis. Histopathological studies have assumed atypical endometriosis to be a transition between benign endometriosis and cancer^[12] suggesting the possibility that endometriosis is in fact a premalignant condition. This is supported by the fact that between 60% to 80% of endometriosis-associated ovarian carcinoma occur in the presence of atypical ovarian endometriosis^[13].

A summary of more recent cohort studies showed a standardized incidence ratio around 2^[14]. Tumors arising from the transformed endometriomas are predominantly of the clear cell and endometrioid types^[15]. A study of operated ovarian cancer patients showed that full 10% of patients had coexisting ovarian endometriosis. This number increased to 36.8% in patients with clear cell ovarian cancer^[16]. These types of studies led to the definition of “endometriosis-associated ovarian carcinoma” (EAOC), which describes ovarian cancer having both cancer cells and endometriosis in the same ovary, presence of cancer in one ovary and endometriosis in second ovary or the

presence of ovarian cancer and pelvic endometriosis. Histological evaluations showed significant clinical differences between patients with EAOC and non-endometriosis-associated ovarian cancer^[17]. Some studies found that the risk is increased up to 8-fold^[18], but the actual increases fluctuate widely among individual studies^[19]. For a review of ovarian cancer etiology and risk factors see Hunn *et al*^[20].

However, despite clear evidence revealing that endometriosis increases ovarian cancer risk, the results from meta-analysis suggested that it may not affect disease progression after the appearance of ovarian cancer^[21]. In addition, some studies even suggested that the association with endometriosis might have a survival benefit^[22]. No associations were observed for common benign gynecologic disorders such as uterine myoma, adenomyosis or endometrial polyps^[23]. On the other hand, Brinton *et al*^[24] showed an increased risk of extra-pelvic carcinomas (including breast cancer) in patients with endometriosis. The newest results are less clear since the outcome of studies examining the association between endometriosis and breast cancer are often contradictory^[14] and the newest population-based cohort studies show no overall association^[25]. A study evaluating possible risk factors revealed only one-ovarian endometriomas of 9 cm or more in diameter was a strong predictor of development of ovarian cancer^[26].

An interesting observation was the measurement of the incidence of ovarian cancer confined to endometrial polyps, which can reach between 0.5% to almost 5% depending on the diagnostic methods^[27]. These polyps can be found with increased frequency in women with endometriosis, but the retrospective analysis did not reach clear conclusions^[28].

Despite the extensive research, the exact mechanisms leading to malignant transformation of endometrial tissue are not established. In endometriosis-associated cancer, the benign-appearing ovarian masses can be detected several years before cancer diagnosis^[29].

Ovarian cancer resulting from endometriosis has some special characteristics such as having endometrioid or clear cell histology, being diagnosed earlier than other types of ovarian cancer and have a better prognosis^[30]. However, the question of endometriosis being a prognostic factor for cancer survival is not clear. On one hand, some studies found no definitive association between the presence of endometriosis and survival^[31]. On the other hand, a large Swedish study found significantly better survival in women with endometriosis than for all malignancies combined. In the cases of breast and ovarian cancer, this survival was even more pronounced^[32]. The protective effect for both one-sided oophorectomy and radical excision of all visible endometriosis was described^[33]. The most recent meta-analysis of risks and prognosis of ovarian cancer confirmed that endometriosis is strongly associated with the increased risk of ovarian cancer and these cancers show favorable characteristics including low grades and specific histology^[21].

Both diseases are progressive and estrogen dependent, often associated with late menopause and infertility. In addition, tubal ligation, hysterectomy and progesterone treatment can decrease the incidence of both diseases^[34].

HORMONE THERAPY

Despite the fact that postmenopausal endometriosis is rare, there is a risk in patients taking hormone therapy^[35]. Hormone therapy, particularly estrogen therapy, is often supposed to stimulate the growth of endometriosis, with additional increase in the risk of ovarian cancer development, which is particularly dangerous in postmenopausal endometriosis, where estrogen therapy should be used only in combination with progesterone^[35]. Estrogen-induced triggering is the same in endometriosis and estrogen-dependent cancer. The quantification of estrogen derivatives was even suggested to be a prognostic factor in ovarian cancer development^[36]. *In vitro* experiments using ovarian cancer cell lines showed similarly increased expression of ER- α receptors as in active endometriosis^[37] which was connected with the pathogenesis of endometriosis. Implants of endometriosis contain estrogen, progesterone and androgen receptors, but the effects of these hormones are opposite-estrogen stimulates proliferation and androgens cause atrophy and regression. The findings show that the basalis has approximately five times as many lymphatic vessels as the functionalis, but it cannot be currently explained^[38].

STEM CELLS

Since several theories about the causes of endometriosis failed to explain all types of lesions and suggest the possibility of combined mechanisms, recent hypothesis include the likelihood that endometriotic lesions arise from ectopic endometrial stem cell progenitors (for review see Maruyama *et al.*^[39]). The origin of oocytes in adult ovaries has been disputed for a long time. Some of the recent studies suggested the possibility that newly implantation of persistent fetal stem cells might play role in tissue regeneration and/or growth. A finding that several *HOX* genes controlling lineage infidelity in ovarian cancer^[40] are expressed in primitive hematopoietic cells suggested a role in early hematopoietic differentiation. Some studies even suggested that *HOX* genes expressed in ovarian epithelial cells might regulate cancer stem cells. At the same time, stem cell transformation can be underlying cause of ovarian cancer^[41,42].

BIOMARKERS

The main risk factor is clearly the age at endometrioma diagnosis. As independent prognostic factors, endometrioma of a diameter above 9 cm and postmenopausal status were established^[26]. There is some evidence that drugs employed in *in vitro* fertilization might increase the risk of ovarian cancer^[43]. However, some studies found

opposite results, so at present, no clear conclusion can be reached.

An effort to determine the potential association between endometriosis and ovarian cancer led to the study evaluating the expression of possible biomarkers which have been previously shown to participate in the pathogenesis of these diseases. The results revealed that endometriosis and epithelial ovarian cancer cells manifested significantly higher levels of mRNAs of transforming growth factor- β 1, cyclooxygenase-2, vascular endothelial growth factor, ER-1 α , aromatase and androgen receptors, whereas the mRNA levels of progesterone receptors were much lower^[44]. The clinical importance of this report is somewhat limited due to the low number of patients; however, its conclusion deserves further investigation.

An additional possible biochemical marker might be cancer antigen CA125^[13], which is commonly used for the monitoring of epithelial ovarian cancer. Since endometriosis is also often associated with a high level of this antigen, it cannot be used for differential diagnosis. A detailed study suggested that a CA72-4 antigen can serve in this role as a biomarker useful to confirm the benign nature of endometriomas in patients with high CA125 levels^[45].

An immunohistochemistry study of ovarian cancers arising from endometriosis confirmed that the estrogen-dependent cancers are substantially more associated with endometrioid adenocarcinoma than clear cell carcinomas. The positive hepatocyte nuclear factor-1 beta was common in clear cell carcinomas, but rare in endometrioid adenocarcinoma, which correlated with *p53* staining, but reversely correlated with estrogen receptor presence^[46].

Suryawanshi *et al.*^[47] focused on plasma microRNAs as a novel biomarker. Using a reverse transcriptase quantitative polymerase chain reaction, the authors identified 23 microRNAs which are differentially expressed in healthy people and patients with either endometriosis or EAO. These microRNAs were subsequently further evaluated in a larger cohort. The results showed that plasma microRNA expressing patterns might serve as specific and reliable diagnostic biomarkers^[47] resulting in some authors suggesting that microRNA studies will lead to changes in current treatment of both endometriosis and ovarian cancer^[48].

GENETIC APPROACHES

A wide variety of molecular alterations have been reported to be involved in the malignant transformation of endometriosis, some of which are common in both endometriosis and ovarian cancer, whereas the others are universal among various tumors. Only a very few were suggested to specifically refer to the malignancies of endometriosis.

Many hypothesize that changes in the expression of tumor suppressor genes and oncogenes occurring in the eutopic endometrium might lead to overgrowth of endometrial foci outside the uterus^[49,50].

Microsatellite analysis showed that loss of heterozygosity on p16 (Ink4), gut-associated lymphatic tissue (GALT), and *p53* occurs in endometriosis. Similarly, activation of mutated *K-ras* gene is an important step in both genesis and progression of ovarian cancer. Alternation of *p53* gene caused aberrant regulation of the H-ras protooncogene^[51]. Using a murine model of mutationally activated *K-ras* gene, it was demonstrated that these animals develop both endometrial lesions and the ovarian tissue. The following mutation blocking the expression of *PTEN* caused ovarian cancer^[52]. *K-ras* mutation may promote carcinogenesis of endometriosis leading to ovarian clear cell carcinoma^[53].

Mutations in *ARID1A* and *PIK3CA* were first described in numerous cases of ovarian clear cell carcinoma, but later also in precursor endometriosis tissues. In addition, *PTEN-PIK3CA-mTOR* pathway was strongly implicated by finding *PIK3CA* mutation in up to 46% clear cell ovarian cancer^[54]. *PIK3CA* mutation is considered to be an early event in the development of endometriosis-associated ovarian clear cell adenocarcinoma. For a better understanding of the effects of these two mutations, functional studies evaluating effects of individual mutations separately and in both normal endometrium and endometriotic epithelium are necessary. The sequence of events leading from normal eutopic endometrium to endometriosis and subsequent ovarian cancer is still hypothetical^[55].

Some studies suggested that a histologically normal endometrium may bear genetic damage caused by iron-dependent oxidative stress^[56]. Some authors suggested that suppression of pre-apoptotic gene Bax and/or up-regulation of anti-apoptotic gene Bcl-2 can be involved in endometriosis and malignancies^[57].

Genetic instability might lead to both endometriosis and ovarian cancer. It can include deactivation of some tumor-suppressing genes, changes in activity of enzymes involved in DNA repairs or mutations in genes such as GALT and GSTM. Similarly, mutations in tumor suppressive gene *PTEN* was often found both in endometrial and cancer tissues^[58]. In addition, *c-erbB-2* and *p53* genes have been found to associate with endometriosis-related ovarian cancer^[59]. The recent study showed that endometriotic lesions have mutations in cancer-related genes such as *PTEN*, *KRAS*, *p53*, and *ARID1A*^[48,60].

In addition, both endometriosis and EAOCs share some of the mediators implicated in inflammatory angiogenesis. They exhibit genetic polymorphisms of several genes including intercellular cell adhesion molecule-1, interleukin (IL)-6 and IL-10 promoters, tumor necrosis factor- α , and nuclear transcription factor- κ B^[61]. Further genetic factors such as loss of heterozygosity, *K-ras*, *P53*, and *PTEN* mutations or hepatocyte nuclear factor-1 β were suggested and tested (for review see Kobayashi *et al.*^[4]). Genome-wide association studies and as well as transcriptome sequencing have shown that genes from the 1p36 region might be important in both endometriosis and endometriosis-associated cancer development^[62].

In a recent study, the endometriosis-associated ovarian carcinogenesis has been linked to oxidative stress-induced increased genomic instability, aberrant methylation, and aberrant chromatin remodeling, as well as mutations of tumor suppressor genes^[63]. For a summary of the molecular biology aspects of ovarian cancer in endometriosis, see Mandai *et al.*^[64].

CONCLUSION

Endometriosis is a multifactorial disease and despite intensive research in the last several decades, many questions remain to be answered as to the exact events leading from endometriotic cysts to endometriosis-associated ovarian cancer. The probable mechanisms and attributing factors include longstanding estrogen stimulation, repeated heavy menstruation resulting in tissue damage and early events on the molecular level were repeatedly shown. Numerous markers have been proven to correspond with this type of cancer. Thus far, however, no single one can be used for diagnosis, not to mention treatment. Despite the fact that the links between endometriosis and ovarian cancer appear to be clear, we have to keep in mind that having endometriosis might be less risky than undergoing *in vitro* fertilization, which can increase the risk of ovarian cancer three times^[65]. The exact mechanisms of the endometriosis-ovarian cancer conversion are still not fully established and the need for new approaches in the understanding and treatment of endometriosis is urgent.

REFERENCES

- 1 **Sayasneh A**, Tsivos D, Crawford R. Endometriosis and ovarian cancer: a systematic review. *ISRN Obstet Gynecol* 2011; **2011**: 140310 [PMID: 21789283]
- 2 **Lapp T**. ACOG issues recommendations for the management of endometriosis. American College of Obstetricians and Gynecologists. *Am Fam Physician* 2000; **62**: 1431, 1434 [PMID: 11011865]
- 3 **von Rokytansky C**. Uber uterusdrusen-neubildung in uterus inder ovarilsarcomen. *Z Ges Artze Wein* 1860; **37**: 577-593
- 4 **Kobayashi H**, Kajihara H, Yamada Y, Tanase Y, Kanayama S, Furukawa N, Noguchi T, Haruta S, Yoshida S, Naruse K, Sado T, Oi H. Risk of carcinoma in women with ovarian endometrioma. *Front Biosci (Elite Ed)* 2011; **3**: 529-539 [PMID: 21196332 DOI: 10.2741/e267]
- 5 **Arvanitis DA**, Koumantakis GE, Goumenou AG, Mataliotakis IM, Koumantakis EE, Spandidos DA. CYP11A1, CYP19, and GSTM1 polymorphisms increase the risk of endometriosis. *Fertil Steril* 2003; **79** Suppl 1: 702-709 [PMID: 12620480 DOI: 10.1016/S0015-0282(02)04817-3]
- 6 **Baldi A**, Campioni M, Signorile PG. Endometriosis: pathogenesis, diagnosis, therapy and association with cancer (review). *Oncol Rep* 2008; **19**: 843-846 [PMID: 18357365]
- 7 **Yuan Z**, Wang Y, Cragun JM, Chambers SK, Zheng W. Cell origin of endometriosis: contribution by the fallopian tube epithelium. *Am J Clin Obstet Gynecol* 2013; **1**: 37-42
- 8 **Thomas EJ**, Prentice A. The aetiology and pathogenesis of endometriosis. *Reprod Med Rev* 1992; **1**: 21-36 [DOI: 10.1017/S0962279900000429]
- 9 **Vercellini P**, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. *Nat Rev Endocrinol* 2014; **10**: 261-275 [PMID: 24366116 DOI: 10.1038/nrendo.2013.255]

- 10 **Sampson J.** Endometrial carcinoma of the ovary arising in endometrial tissue of that organ. *Arch Surg* 1925; **10**: 1-72 [DOI: 10.1001/archsurg.1925.01120100007001]
- 11 **Scott RB.** Malignant changes in endometriosis. *Obstet Gynecol* 1953; **2**: 283-289 [PMID: 13087921]
- 12 **LaGrenade A,** Silverberg SG. Ovarian tumors associated with atypical endometriosis. *Hum Pathol* 1988; **19**: 1080-1084 [PMID: 3417292 DOI: 10.1016/S0046-8177(88)80090-X]
- 13 **Maiorana A,** Cicerone C, Niceta M, Alio L. Evaluation of serum CA 125 levels in patients with pelvic pain related to endometriosis. *Int J Biol Markers* 2007; **22**: 200-202 [PMID: 17922463]
- 14 **Vlahos NF,** Kalampokas T, Fotiou S. Endometriosis and ovarian cancer: a review. *Gynecol Endocrinol* 2010; **26**: 213-219 [PMID: 19718562 DOI: 10.1080/09513590903184050]
- 15 **Modesitt SC,** Tortolero-Luna G, Robinson JB, Gershenson DM, Wolf JK. Ovarian and extraovarian endometriosis-associated cancer. *Obstet Gynecol* 2002; **100**: 788-795 [PMID: 12383550 DOI: 10.1016/S0029-7844(02)02149-X]
- 16 **Dzatic-Smiljkovic O,** Vasiljevic M, Djukic M, Vugdelic R, Vugdelic J. Frequency of ovarian endometriosis in epithelial ovarian cancer patients. *Clin Exp Obstet Gynecol* 2011; **38**: 394-398 [PMID: 22268283]
- 17 **Wang S,** Qiu L, Lang JH, Shen K, Yang JX, Huang HF, Pan LY, Wu M. Clinical analysis of ovarian epithelial carcinoma with coexisting pelvic endometriosis. *Am J Obstet Gynecol* 2013; **208**: 413.e1-413.e5 [PMID: 23220508 DOI: 10.1016/j.ajog.2012.12.004]
- 18 **Buis CC,** van Leeuwen FE, Mooij TM, Burger CW. Increased risk for ovarian cancer and borderline ovarian tumours in subfertile women with endometriosis. *Hum Reprod* 2013; **28**: 3358-3369 [PMID: 24014607 DOI: 10.1093/humrep/det340]
- 19 **Heidemann LN,** Hartwell D, Heidemann CH, Jochumsen KM. The relation between endometriosis and ovarian cancer - a review. *Acta Obstet Gynecol Scand* 2014; **93**: 20-31 [PMID: 24011403 DOI: 10.1111/aogs.12255]
- 20 **Hunn J,** Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. *Clin Obstet Gynecol* 2012; **55**: 3-23 [PMID: 22343225 DOI: 10.1097/GRF.0b013e31824b4611]
- 21 **Kim HS,** Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis. *Br J Cancer* 2014; **110**: 1878-1890 [PMID: 24518590 DOI: 10.1038/bjc.2014.29]
- 22 **Garrett LA,** Growdon WB, Goodman A, Boruta DM, Schorge JO, del Carmen MG. Endometriosis-associated ovarian malignancy: a retrospective analysis of presentation, treatment, and outcome. *J Reprod Med* 2013; **58**: 469-476 [PMID: 24568040]
- 23 **Qiu L,** Wang S, Lang JH, Shen K, Huang HF, Pan LY, Wu M, Yang JX. The occurrence of endometriosis with ovarian carcinomas is not purely coincidental. *Eur J Obstet Gynecol Reprod Biol* 2013; **170**: 225-228 [PMID: 23866908 DOI: 10.1016/j.ejogrb.2013.06.015]
- 24 **Brinton LA,** Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 1997; **176**: 572-579 [PMID: 9077609 DOI: 10.1016/S0002-9378(97)70550-7]
- 25 **Bertelsen L,** Mellemkjaer L, Frederiksen K, Kjaer SK, Brinton LA, Sakoda LC, van Valkengoed I, Olsen JH. Risk for breast cancer among women with endometriosis. *Int J Cancer* 2007; **120**: 1372-1375 [PMID: 17187365 DOI: 10.1002/ijc.22490]
- 26 **Kobayashi H,** Sumimoto K, Kitanaka T, Yamada Y, Sado T, Sakata M, Yoshida S, Kawaguchi R, Kanayama S, Shigetomi H, Haruta S, Tsuji Y, Ueda S, Terao T. Ovarian endometrioma--risks factors of ovarian cancer development. *Eur J Obstet Gynecol Reprod Biol* 2008; **138**: 187-193 [PMID: 18162283 DOI: 10.1016/j.ejogrb.2007.06.017]
- 27 **Shushan A,** Revel A, Rojansky N. How often are endometrial polyps malignant? *Gynecol Obstet Invest* 2004; **58**: 212-215 [PMID: 15316149 DOI: 10.1159/000080189]
- 28 **Kontoravdis A,** Augoulea A, Lambrinoudaki I, Christodoulakos G, Tzortziotis D, Grammatikakis I, Kontoravdis N, Creatsas G. Ovarian endometriosis associated with ovarian cancer and endometrial-endocervical polyps. *J Obstet Gynaecol Res* 2007; **33**: 294-298 [PMID: 17578358 DOI: 10.1111/j.1447-0756.2007.00527.x]
- 29 **Kobayashi H.** Ovarian cancer in endometriosis: epidemiology, natural history, and clinical diagnosis. *Int J Clin Oncol* 2009; **14**: 378-382 [PMID: 19856043 DOI: 10.1007/s10147-009-0931-2]
- 30 **Komiyama S,** Aoki D, Tominaga E, Susumu N, Udagawa Y, Nozawa S. Prognosis of Japanese patients with ovarian clear cell carcinoma associated with pelvic endometriosis: clinicopathologic evaluation. *Gynecol Oncol* 1999; **72**: 342-346 [PMID: 10053105 DOI: 10.1006/gyno.1998.5284]
- 31 **Noli S,** Cipriani S, Scarfone G, Villa A, Grossi E, Monti E, Vercellini P, Parazzini F. Long term survival of ovarian endometriosis associated clear cell and endometrioid ovarian cancers. *Int J Gynecol Cancer* 2013; **23**: 244-248 [PMID: 23314280 DOI: 10.1097/IGC.0b013e31827aa0bb]
- 32 **Melin A,** Lundholm C, Malki N, Swahn ML, Sparen P, Bergqvist A. Endometriosis as a prognostic factor for cancer survival. *Int J Cancer* 2011; **129**: 948-955 [PMID: 20949560 DOI: 10.1002/ijc.25718]
- 33 **Melin AS,** Lundholm C, Malki N, Swahn ML, Sparèn P, Bergqvist A. Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer. *Acta Obstet Gynecol Scand* 2013; **92**: 546-554 [PMID: 23560387 DOI: 10.1111/aogs.12123]
- 34 **Kashyap S,** Davis OK. Ovarian cancer and fertility medications: a critical appraisal. *Semin Reprod Med* 2003; **21**: 65-71 [PMID: 12806561 DOI: 10.1055/s-2003-39996]
- 35 **Oxholm D,** Knudsen UB, Kryger-Baggesen N, Ravn P. Postmenopausal endometriosis. *Acta Obstet Gynecol Scand* 2007; **86**: 1158-1164 [PMID: 17851817 DOI: 10.1080/00016340701619407]
- 36 **Seeger H,** Wallwiener D, Kraemer E, Mueck AO. Estradiol metabolites are potent mitogenic substances for human ovarian cancer cells. *Eur J Gynaecol Oncol* 2005; **26**: 383-385 [PMID: 16122183]
- 37 **Lenhard M,** Tereza L, Heublein S, Ditsch N, Himsl I, Mayr D, Friese K, Jeschke U. Steroid hormone receptor expression in ovarian cancer: progesterone receptor B as prognostic marker for patient survival. *BMC Cancer* 2012; **12**: 553 [PMID: 23176303 DOI: 10.1186/1471-2407-12-553]
- 38 **Rogers PA,** Donoghue JF, Walter LM, Girling JE. Endometrial angiogenesis, vascular maturation, and lymphangiogenesis. *Reprod Sci* 2009; **16**: 147-151 [PMID: 19001552 DOI: 10.1177/1933719108325509]
- 39 **Maruyama T,** Yoshimura Y. Stem cell theory for the pathogenesis of endometriosis. *Front Biosci (Elite Ed)* 2012; **4**: 2854-2863 [PMID: 22652684 DOI: 10.2741/E589]
- 40 **Cheng W,** Liu J, Yoshida H, Rosen D, Naora H. Lineage infidelity of epithelial ovarian cancers is controlled by HOX genes that specify regional identity in the reproductive tract. *Nat Med* 2005; **11**: 531-537 [PMID: 15821746 DOI: 10.1038/nm1230]
- 41 **Bapat SA,** Mali AM, Koppikar CB, Kurrey NK. Stem and progenitor-like cells contribute to the aggressive behavior of human epithelial ovarian cancer. *Cancer Res* 2005; **65**: 3025-3029 [PMID: 15833827]
- 42 **Duke CM,** Taylor HS. Stem cells and the reproductive system: historical perspective and future directions. *Maturitas* 2013; **76**: 284-289 [PMID: 24144960 DOI: 10.1016/j.maturitas.2013.08.012]
- 43 **Vlahos NF,** Economopoulos KP, Fotiou S. Endometriosis, in vitro fertilisation and the risk of gynaecological malignancies, including ovarian and breast cancer. *Best Pract Res Clin Obstet Gynaecol* 2010; **24**: 39-50 [PMID: 19733123 DOI:

- 10.1016/j.bpobgyn.2009.08.004]
- 44 **Meng Q**, Sun W, Jiang J, Fletcher NM, Diamond MP, Saed GM. Identification of common mechanisms between endometriosis and ovarian cancer. *J Assist Reprod Genet* 2011; **28**: 917-923 [PMID: 21614520 DOI: 10.1007/s10815-011-9573-1]
 - 45 **Anastasi E**, Manganaro L, Granato T, Benedetti Panici P, Frati L, Porpora MG. Is CA72-4 a useful biomarker in differential diagnosis between ovarian endometrioma and epithelial ovarian cancer? *Dis Markers* 2013; **35**: 331-335 [PMID: 24191126 DOI: 10.1155/2013/984641]
 - 46 **Lai CR**, Hsu CY, Chen YJ, Yen MS, Chao KC, Li AF. Ovarian cancers arising from endometriosis: a microenvironmental biomarker study including ER, HNF1 β , p53, PTEN, BAF250a, and COX-2. *J Chin Med Assoc* 2013; **76**: 629-634 [PMID: 23962610 DOI: 10.1016/j.jcma.2013.07.008]
 - 47 **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, Budiu R, Edwards RP, Huang X. Plasma microRNAs as novel biomarkers for endometriosis and endometriosis-associated ovarian cancer. *Clin Cancer Res* 2013; **19**: 1213-1224 [PMID: 23362326 DOI: 10.1158/1078-0432.CCR-12-2726]
 - 48 **Siufi Neto J**, Kho RM, Siufi DF, Baracat EC, Anderson KS, Abrão MS. Cellular, histologic, and molecular changes associated with endometriosis and ovarian cancer. *J Minim Invasive Gynecol* 2014; **21**: 55-63 [PMID: 23962574 DOI: 10.1016/j.jmig.2013.07.021]
 - 49 **Ness RB**. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. *Am J Obstet Gynecol* 2003; **189**: 280-294 [PMID: 12861175 DOI: 10.1067/mob.2003.408]
 - 50 **Viganó P**, Somigliana E, Chiodo I, Abbiati A, Vercellini P. Molecular mechanisms and biological plausibility underlying the malignant transformation of endometriosis: a critical analysis. *Hum Reprod Update* 2012; **12**: 77-89 [PMID: 16172112 DOI: 10.1093/humupd/dmi037]
 - 51 **Zachos G**, Spandidos DA. Transcriptional regulation of the c-H-ras1 gene by the P53 protein is implicated in the development of human endometrial and ovarian tumours. *Oncogene* 1998; **16**: 3013-3017 [PMID: 9662334 DOI: 10.1038/sj.onc.1201836]
 - 52 **Dinulescu DM**, Ince TA, Quade BJ, Shafer SA, Crowley D, Jacks T. Role of K-ras and Pten in the development of mouse models of endometriosis and endometrioid ovarian cancer. *Nat Med* 2005; **11**: 63-70 [PMID: 15619626]
 - 53 **Otsuka J**, Okuda T, Sekizawa A, Amemiya S, Saito H, Okai T, Kushima M, Tachikawa T. K-ras mutation may promote carcinogenesis of endometriosis leading to ovarian clear cell carcinoma. *Med Electron Microsc* 2004; **37**: 188-192 [PMID: 15449112 DOI: 10.1007/s00795-004-0252-5]
 - 54 **Yamamoto S**, Tsuda H, Takano M, Iwaya K, Tamai S, Matsubara O. PIK3CA mutation is an early event in the development of endometriosis-associated ovarian clear cell adenocarcinoma. *J Pathol* 2011; **225**: 189-194 [PMID: 21735444 DOI: 10.1002/path.2940]
 - 55 **Gounaris I**, Charnock-Jones DS, Brenton JD. Ovarian clear cell carcinoma--bad endometriosis or bad endometrium? *J Pathol* 2011; **225**: 157-160 [PMID: 21898874 DOI: 10.1002/path.2970]
 - 56 **Yamaguchi K**, Mandai M, Toyokuni S, Hamanishi J, Higuchi T, Takakura K, Fujii S. Contents of endometriotic cysts, especially the high concentration of free iron, are a possible cause of carcinogenesis in the cysts through the iron-induced persistent oxidative stress. *Clin Cancer Res* 2008; **14**: 32-40 [PMID: 18172249 DOI: 10.1158/1078-0432.CCR-07-1614]
 - 57 **Meresman GF**, Vighi S, Buquet RA, Contreras-Ortiz O, Tesone M, Rumi LS. Apoptosis and expression of Bcl-2 and Bax in eutopic endometrium from women with endometriosis. *Fertil Steril* 2000; **74**: 760-766 [PMID: 11020520 DOI: 10.1016/S0015-0282(00)01522-3]
 - 58 **Martini M**, Ciccarone M, Garganese G, Maggiore C, Evangelista A, Rahimi S, Zannoni G, Vittori G, Larocca LM. Possible involvement of hMLH1, p16(INK4a) and PTEN in the malignant transformation of endometriosis. *Int J Cancer* 2002; **102**: 398-406 [PMID: 12402310 DOI: 10.1002/ijc.10715]
 - 59 **Prefumo F**, Venturini PL, Fulcheri E. Analysis of p53 and c-erbB-2 expression in ovarian endometrioid carcinomas arising in endometriosis. *Int J Gynecol Pathol* 2003; **22**: 83-88 [PMID: 12496703 DOI: 10.1097/00004347-200301000-00016]
 - 60 **Romero I**, Bast RC. Minireview: human ovarian cancer: biology, current management, and paths to personalizing therapy. *Endocrinology* 2012; **153**: 1593-1602 [PMID: 22416079 DOI: 10.1210/en.2011-2123]
 - 61 **Tempfer CB**, Simoni M, Destenaves B, Fauser BC. Functional genetic polymorphisms and female reproductive disorders: part II--endometriosis. *Hum Reprod Update* 2009; **15**: 97-118 [PMID: 18805939 DOI: 10.1093/humupd/dmn040]
 - 62 **Falconer H**, Sundqvist J, Xu H, Vodolazkaia A, Fassbender A, Kyama C, Bokor A, D'Hooghe TM. Analysis of common variations in tumor-suppressor genes on chr1p36 among Caucasian women with endometriosis. *Gynecol Oncol* 2012; **127**: 398-402 [PMID: 22910690 DOI: 10.1016/j.ygyno.2012.08.013]
 - 63 **Shigetomi H**, Tsunemi T, Haruta S, Kajihara H, Yoshizawa Y, Tanase Y, Furukawa N, Yoshida S, Sado T, Kobayashi H. Molecular mechanisms linking endometriosis under oxidative stress with ovarian tumorigenesis and therapeutic modalities. *Cancer Invest* 2012; **30**: 473-480 [PMID: 22530740 DOI: 10.3109/07357907.2012.681821]
 - 64 **Mandai M**, Yamaguchi K, Matsumura N, Baba T, Konishi I. Ovarian cancer in endometriosis: molecular biology, pathology, and clinical management. *Int J Clin Oncol* 2009; **14**: 383-391 [PMID: 19856044 DOI: 10.1007/s10147-009-0935-y]
 - 65 **van Leeuwen FE**, Klip H, Mooij TM, van de Swaluw AM, Lambalk CB, Kortman M, Laven JS, Jansen CA, Helmerhorst FM, Cohlen BJ, Willemsen WN, Smeenk JM, Simons AH, van der Veen F, Evers JL, van Dop PA, Macklon NS, Burger CW. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Hum Reprod* 2011; **26**: 3456-3465 [PMID: 22031719 DOI: 10.1093/humrep/der322]

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