
بسم الله الرحمن الرحيم

Endometriosis And Cancer

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Endometriosis is a disease with an estimated prevalence of 176 million women worldwide.

- Endometriosis is an important medical and social problem .
- Third most common factor in the pathogenesis of gynecologic diseases after inflammatory processes and uterine leiomyoma.
- incidence in fertile women ranges from 10% to 50%.

An association between endometriosis and ovarian cancer was first described by sampson et al in 1925 , who noticed malignant changes in the endometrial tissue of the ovaries .

- known risk factor for ovarian cancer(Pearce . C…2005)
- transform to atypical form and even undergo malignant transformation in 0.7–2.5% of cases (Liadmila . M …2020)

- Ovarian cancer has the highest mortality of all gynecologic cancers in Europe .
- Estimated 44,600 cases of cancer-related deaths in 2018 .
- The overall 5-year survival for ovarian cancer is < 50% , ranging from nearly 90% in stage IA disease to <20% in stage IV disease .

- Endometriosis-associated ovarian cancer (EAOC) is thought to develop from ovarian endometrial cysts
- endometrioid
- clear cell carcinoma
- Ovarian endometrioid carcinoma (OEC) is the most common type of EAOC(75%)

(Vercellini . P….2014)

- (ESHRE) guidelines recommend that even if endometriosis increases the risk of developing ovarian cancer, there is no way to reduce it .
- management should not be changed with concern for the ovarian cancer .
- the concept of "prevention of malignant transformation.

Endometriosis and EAOC

- Reflux of menstrual blood into the abdominal cavity
- The main symptoms of endometriosis are dysmenorrhea and infertility
- Treatment : medication or surgery and is selected based on the type and severity of the symptoms (patient's age and wishes for pregnancy
- With the recent developments in therapies, surgery can often be avoided in many cases of Ecs
- Major problem is that ovarian cancer can develop during follow-up of tumors that are considered as ECs.

- oxidative stress in the microenvironment of endometriosis
- cause infertility and carcinogenesis
- Yamaguchi et al. reported that fluid in ECs contains abundant iron, which causes oxidative stress; 5-fold diluted fluid from ECs caused DNA damage in Chinese hamster lung fibroblast V79 cells . (Yamagach , K :2008)
- Excess iron generates reactive oxygen species (ROS) through the Fenton reaction . (Kehev , J : 2000)

- ROS causes not only gene mutations but also epigenetic alterations, such as DNA methylation
- (Jto , F :2017)

- Kobayashi et al: at least two steps are necessary for ECs to develop into EAOC . (Kobayashi , H : 2016)

- first step: DNA damage, mutations, and genomic instability
- second step :

cells with high antioxidant capacity arise, selection of these cells might occur, resulting in their proliferation to cause carcinogenesis.

- interaction between oxidative stress and non-coding microRNAs has an important role in the development of EAOC , but further study is required. (Mari , AK xinder : 2019)

Clinical Epidemiology

- How Long Does It Take for ECs to Become EAOC?
- Women with endometriosis are more likely to develop EAOC in their late 40s, but after menopause, the incidence of ovarian cancer is not increased. (Melin , A :2006)(Aris , A : 2010)

- The risk ratio of ovarian cancer after menopause is 0.8 in women with previously diagnosed endometriosis . (Olsong , J :2002)

- There is no evidence that EAOC is more likely to develop in older women or
- that carcinogenesis is increased if ECs are followed up after menopause.

- These data contradict the hypothesis that prolonged exposure to the contents of ECs leads to DNA damage and increases carcinogenesis. Therefore, this hypothesis is not supported by the epidemiological data.

- In Japan, a prospective cohort study of carcinogenesis during follow-up of Ecs (Kabayashi , H :2007)

- 6398 cases of EC at an average age of 38.4 from 1985 to 1995 and followed up for an average of 12.8 years.
- ovarian cancer 46 cases (0.7%)
- Woman with ECs were nine times more likely to have ovarian cancer than healthy women
- Clear cell carcinoma
- Endometrioid carcinoma
- These results must be interpreted with care.

- "The risk of women who had been diagnosed with ECs being subsequently diagnosed with ovarian cancer", rather than "malignant transformation of ECs". (Kabayashi , H :2007)

- case reports of ovarian cancer originating from Ecs (Murakam , K :2020)
- histological types :clear cell carcinoma and endometrioid carcinoma.
- all cases were diagnosed with cancer within 10 years

- all reported cases of
  - *"malignant transformation of ECs"*
- might be *"cancer from the beginning"*

Probability of Ovarian Cancer Being Diagnosed in Surgical Specimens of Endometrial Cysts

- A retrospective single-center study found that 7629 surgeries were performed following preoperative diagnosis of ECs and 0.14% (11 cases) were diagnosed with ovarian cancer postoperatively (Kuo , H . H ….2017)

In another study : underwent surgery from 2000 to 2010, ovarian cancer occurred in 39/5945 cases in the endometriosis group and 36/23,780 cases in the control group .

The hazard ratio (HR) of ovarian cancer with endometriosis was 5.6 and that of developing OCCC was 7.4

It was considered that the "endometriosis group" included 0.4% (24 cases) of "ovarian cancer " . (Wang , K . C….. 2014)

12 cases of ovarian cancer occurred after surgery for endometriosis, but the risk was approximately 2–3 times higher than that of the controls. (40 years)

Large – scale propulation – Base Studies

- 13 case-control studies : relationship between endometriosis and the risk of developing ovarian cancer was investigated in 7911 ovarian cancers and 13,226 controls (pearce , L :2012)
- History of endometriosis
- risk of ovarian cancer was 1.49 times greater,
- risk of OCCC(3.73) and OEC (2.32)significantly higher.

- In a meta-analysis of 22 large population-based cohorts of 1.3 million women, 5584 cases of ovarian cancer were diagnosed and were examined for risk factors

- Risk of ovarian cancer was shown to increase by 1.35 times if previously diagnosed with endometriosis.

- History of endometriosis was a risk factor, rather than "malignant transformation of ECs". In such population-based studies, "cancer from the beginning" is less likely to be included

(wentzensen , A . : 2016)
(Kim , HS :2016)

Surgery and Medication for Endometriosis and Risk of Ovarian Cancer

- To determine the origin of cancer
- identify precancerous lesions by histopathology. The histology of ECs often shows a simple monolayer of epithelium, with few abnormal mitotic cells or stratification . (Irving j : 2019)
- most EC cases do not have precancerous lesions. (Fukunuge , M :1997)
- Nuclear atypia with no proliferative features, which are often seen, is considered to be a reactive change. A proliferative lesion similar to a precancerous lesion of endometrioid carcinoma of the endometrium is considered to be a true precancerous lesion, but this is rarely observed . (Mccluggage . W ….:2020)

- The relationship between the type of surgery and the risk of developing ovarian cancer is also important. Fallopian tubal ligation reduces serous carcinoma by only about 20% but OCCC and OEC by about 50% . (Cibula , D : 2011, Sieh , W : 2013)

- If ECs are the origin of ovarian cancer, cystectomy should be able to prevent ovarian cancer.

- Ovarian cancer sometimes occurs in the ipsilateral ovary following cystectomy . (Tanigachi . F : 2014 Haraguchi , H : 2016)

- That is, in such surgery, the risk of developing ovarian cancer did not decrease .

- In a study reported in 2019 that followed 830,000 women for 27 years .

- Thus, the risk of developing EAOC was reduced with hysterectomy rather than cystectomy of Ecs . (Dixoo – suen , S.C :2019)

- A reduction in menstrual blood and suppression of ovulation by OCs might also contribute to the prevention of EAOC . (Modugno , F : 2004)

Genetic Analysis of Endometrium, Endometriosis, and EAOC

EAOC arises from endometriosis because EAOC exhibits mutations in ARID1A, PIK3CA, and PTEN as well as loss of heterozygosity at a high frequency, which is also common in coexisting endometriosis (Ayhan , A ....2012 , Matsumoto , J ….2015)

- Recently, however, more detailed genetic mutation analyses of endometriosis using next-generation sequencing (NGS) are changing the conventional concept. In reports examining deep endometriosis, which is not usually associated with carcinogenesis,

- 19 of 24 patients had gene mutations and 5 had oncogenic mutations. (Sato , N ….2000)

- Endometriotic lesions in these cases, such as in the Douglas pouch, rectal surface, and peritoneum of the vesicouterine pouch, carried the same gene mutation . In other words, it was presumed that the origin of these gene mutations was eutopic endometrium(Arglesion , S….2017)

- In a study of 107 cases of EC and 82 cases of normal endometrium, Suda et al. reported numerous KRAS and PIK3CA mutations in both endometriosis and normal endometrial glandular epithelium, and the same mutations were observed even at different sites of endometriosis . (Suda . K ….2018)

- Genetic mutations found in endometriosis can also be found in eutopic normal endometrium by exome sequencing. (Li , a ...2014)

- EAOC and nearby endometriosis were the same clone . (Anglesie . MS… 2015)

- Endometriosis of the Douglas pouch, probably caused by reflux from the uterus, also had the same clone as the EAOC.

- A relationship between EAOC and eutopic endometrium .

Epidemiologically

The risk of developing endometrioid carcinoma of the endometrium is as high as 2.1 . or 2.8 times .in endometriosis cases . (Mogensen , J …2016 .Yu , HC …2015)

double cancer of the endometrium and ovary, endometriosis significantly coexisted, with 13 out of 13 cases . and 21 out of 24 cases . (Yamaoi.K…2012 . Kobauashi.Y …2015)

- Genomic sequencing of double cancer of the endometrium and ovary revealed they had the same clone in 22 of 23 cases except Lynch syndrome . (Schuhheis , A.m …2016)

- In another report, 13 out of 14 cases had the same clone .Thus, endometrial cancer, endometriosis, and ovarian cancer may be strongly related to each other in double cancer. (Chao .A …2016)

Reconsideration of the Developmental Mechanism of EAOC Based on Molecular and Epidemiological Data

- Carcinogenesis requires an initiator and a promoter. First, gene mutations occur frequently in endometrial glandular epithelial cells

- Eutopic endometrial glandular epithelial cells with sufficient gene mutations, when engrafted in the ovaries by menstrual blood reflux, cause carcinogenesis through the effect of the cancer-promoting ovarian microenvironment .

- Thus, EAOC with endometriosis occurs. In addition, the defect in the ovarian surface caused by ovulation may be particularly rich in growth factors as promoters, and OC prevents EAOC ovulation.

- The wound after cystectomy of ECs also causes the microenvironment to become rich in growth factors.

- These recurrences may not be the result of hematogenous metastasis or intra-abdominal dissemination, but rather, the tumor cells may remain in the genital tract and be transported from the endometrium to the ovaries.

Endometrial glands are known to be monoclonal . therefore, to prove that endometriosis or EAOC is caused by the regurgitation of endometrial gland ducts with genetic mutations, it is necessary to analyze each gene mutation in the glands and to identify the glands that are the same clones as endometriosis and EAOC . (Anglesie , MS … 2015 .TanaKa . M … 2003)

- If precancerous lesions are detected by meticulous sectioning of the endometrium in EAOC, it is considered that the sequencing analysis can prove that EAOC is derived from the endometrium. However, it is considered difficult to select endometrial glands to be sequenced based on histopathology.

- further advance the sequencing technology in addition to meticulous sectioning of the endometrium. (Eckert , MA … 2016)

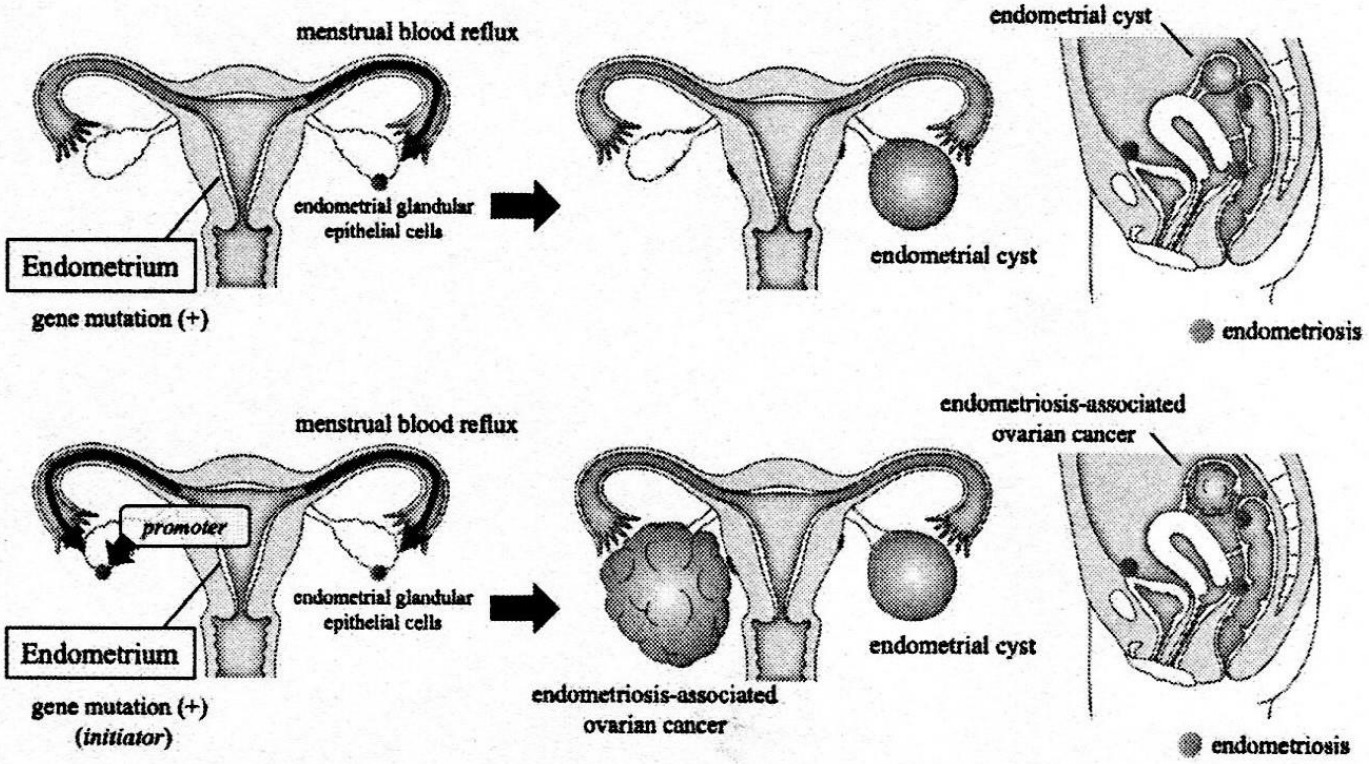


Figure 2. Mechanism of endometriosis-associated ovarian cancer carcinogenesis. Carcinogenesis requires an initiator and a promoter. Gene mutations occur frequently in endometrial glandular epithelial cells, but its mutations are often insufficient as initiators. Nonetheless, endometrial glandular epithelial cells with sufficient gene mutations cause carcinogenesis through the effect of the promoter. If they survive in the contralateral ovary or outside the ovary, they may not cause carcinogenesis, and such cells become endometriosis. This figure was made by modifying a figure from Clinical Gynecology and Obstetrics 2020 [69].

- Why clear cell carcinoma rarely occurs in the endometrium.
- Normal endometrial glandular epithelium includes estrogen receptor (ER)-positive secretory cells and ER-negative ciliated cells.
- Recently, it was proposed that each of them is highly likely to be the origin of OEC and OCCC . (Cochrane , DR … 2007)

- World Endometriosis Society stated that the relative and absolute risk of ovarian cancer in women with endometriosis is very low and routine screening for ovarian cancer was not recommended . (Johnson , NP … 2013)

The ESHRE guidelines :

Recommended not to manage endometriosis for carcinogenesis .

- If it is not necessary to consider fertility preservation
- The risk of ovarian cancer associated with endometriosis may be reduced by tubal ligation, salpingectomy, and hysterectomy. (Acoc comm,Hcc Opinim No 774).
- If the ECs were actually "cancer from the beginning", it is unlikely that OCs would prevent ovarian cancer.

- Asymptomatic ECs should be followed up .

- *Follow up several months or one year after diagnosing "ECs" to identify "cancer from the beginning" by monitoring the size or solid region.*

Screening of ovarian cancer has no effect on slow-growing type I ovarian cancer, including EAOC . (Temkin , SM …2017 . Grossman D,C …2018)

- *Many ovarian cancer cases have gene mutations and chromosome number abnormalities (copy number increases of chromosome 7q and 8q) in cervical Pap smear samples or endometrial Tao brush samples* *(Waney ,Y...2018)*

- proteomic analysis of endometrial fluid and circulating tumor DNA may be used to detect precursor lesions in EAOCs and to investigate the risk of developing EAOCs . (Dawson ,A …2018)

- There is still no standard use of therapies targeting EAOC genetic mutations.
- *However, the development of targeted therapy will play an important role in improving the prognosis of OCCC, especially in chemotherapy-resistant OCCC.*
- Immunotherapy has been shown to be effective as a treatment for EAOC.

- The expression of VEGF, an angiogenic factor, is significantly elevated in EAOC compared with endometriosis .(Barreta , A …2019)

- Expressed in more than 90% of OCCC cases .(Mabuchil , S … 2019)

Anti-VEGF antibodies, which are angiogenesis inhibitors, have already been used for ovarian cancer, including EAOC . (Burger , RO …2011. Coleman , N …2017)

- Several clinical trials of immunotherapy for ovarian cancer have also been conducted, mainly with immune checkpoint inhibitors.(Hamanishi , J …2015)

- ARID1A gene mutations are found in as many as 50% of OCCC cases .

- *The activity of histone deacetylase 6 (HDAC6) has been shown to be closely associated with ovarian cancer with ARID1A mutations , and the efficacy of HDAC6 inhibitors and combination therapy with anti-PD-L1 antibodies has been demonstrated in an OCCC mouse model lacking the ARID1A gene , which may also have future clinical applications.* *(Bitler , BG … 2017)*

- In recent years, basic and epidemiological data suggesting that genetic mutations in the eutopic endometrium may be responsible for EAOC have been accumulating.

- *Eutopic endometrial glandular epithelial cells with sufficient oncogenic mutations that are refluxed to engraft in the ovary. That is, "ECs" in which EAOC occurs during follow-up is considered to be "cancer from the beginning".*

- Targeted therapy

- endometrial glandular epithelial cells serve as a carcinogenic site.

The Association between Endometriomas and ovarian cancer

- In spite of about 90 years of research, pathogenesis of this disease is still largely unknown .(Giovann.G…2015)

- Although endometriosis frequently involves multiple sites in the pelvis , malignancies associated with this disease are mostly confined to the ovaries , evolving from an endometrioma .

- Regurgitated endometrium. Conversely, the mechanism of cyst development is different among these theories .

- Endometrial implants , local on the surface of the ovary , cause a gradual invagination of the ovarian cortex , which results in a pseudocyst .

- Endometriomas may develop as a result of secondary involvement of functional ovarian cysts .

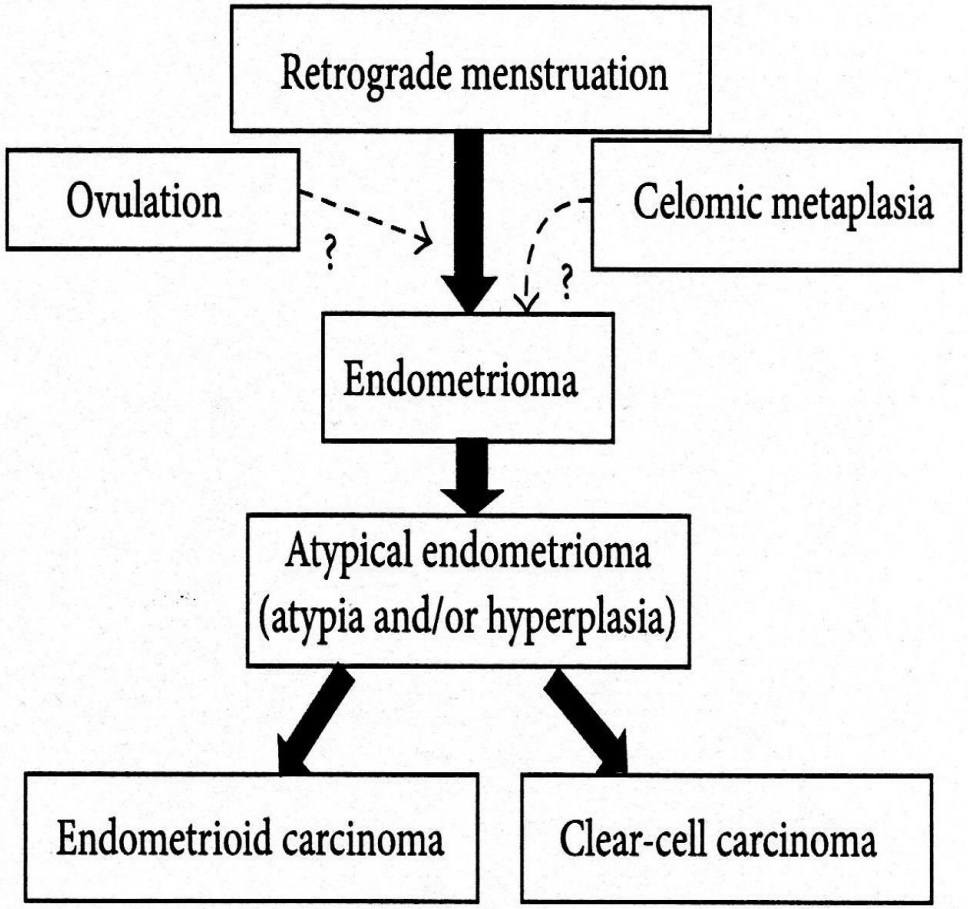
(Hughesdom , Brosens et al , Nezhat et al . , Vercellini et al .

- Celomic metaplasia .

- The presence of hyperplasia in the glandular epithelium is less common but is described in some atypical endometriomas

Figure 2

The proposed step by step process of transformation from retrograde menstruation to typical endometrioma, through atypical endometrioma, and finally to endometrioid or clear-cell ovarian cancer.



- Several studies have demonstrated the important reduction of cyst recurrence after surgery for cystectomy in case of prolonged ovulation inhibition,

- Estroprogestin contraceptive pills.

- Progestin

- GnRh(a)

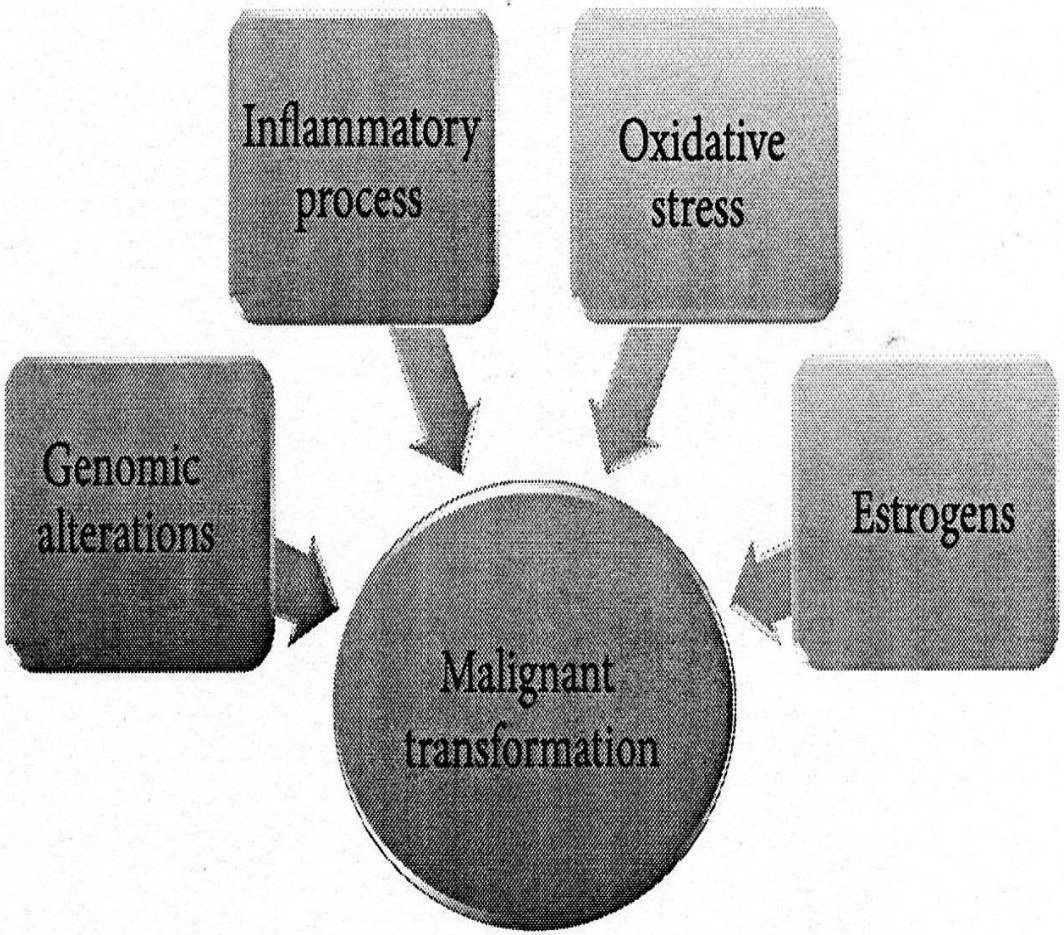
Sampson :

- 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.
- Scott: histology – Proven transition from benigin end to cancer .

- EAOC is described as an ovarian cancer having both cancer cells and endometriosis in the same ovary
- presence of ovarian cancer and pelvic endometriosis.
- Recent molecular studies have linked endometriosis with ovarian cancer through pathways related to oxidative stress, inflammation, and hyperestrogenism and finally to genomic alterations .

Figure 4

Different mechanisms involved in the malignant transformation of an endometrioma.



- Histologically benign endometriosis may harbor genetic abnormalities that predispose for malignant transformation .

- Chronic inflammation has been demonstrated in the establishment and progression of endometriosis, through the secretion of growth factors and proinflammatory cytokines

- *The inflammatory state increases during the menstrual phase, probably as the consequence of the irritative stimulus induced by retrograde menstruation .*

- An association between hyperestrogenism and gynecologic malignancies, including cancers of the breast, endometrium, and ovary .

- The enzyme aromatase is highly present in endometriomas .

- In endometriomas the enzyme 17β-hydroxysteroid-dehydrogenase (17β-HSD) type 2 is lacking.

- This highly proliferative microenvironment in endometrioma presents an enhanced level of reparative activity, with a higher chance for DNA damage and mutations .

- Patients with EAOC have a lower stage of cancer, a distribution of histological subtypes that differs from the general population, predominantly lower-grade endometriosis lesions, and significantly better overall survival as compared with other ovarian carcinomas .

- The preventive effect of hormonal contraceptives is different among several histological subtypes: a lower degree of risk reduction being observed for mucinous invasive cancers.

- *An in vivo model of absence of retrograde menstruation is tubal sterilization. A systematic metaanalysis [39] observed a 34% reduction in the risk of ovarian cancer after tubal sterilization.*

Endometriosis-associated ovarian cancer occurs early duing follow-up of endometrial cysts .

- They reviewed published cases of EAOC considered to have developed from endometrial cysts , and focused on the observation period .

(Kosuke . M …2019)

- DNA damage caused by oxidative stress due to iron in the cyst fluid ARID 1A and PIK3CA mutation .

- *Microenvironmental factors , such as inflammation and tumor immunity , has previouly been proposed as mechanisms of carcinogenesis in endometrial cysts .*

- Patient's age ,
- Size of the cyst ,
- Tumor markers at diagnosis of endometrial cysts and ovarian cancer were investigated .
- The period from the start of follow-up of the endometrial cyst to diagnosis of ovarian cancer was calculated .

- 79 cases in 32 articles .
- *Clear cell carcinoma was the most frequent and it occurred in 60 (76%) .*
- 40s at the time of cancer diagnosis .
- *Median CA125 level was 38 U/ml .*
- The median cyst diameter at the diagnosis of an endometrial cyst was 4 cm (2-11 cm) and that of ovarian cancer was 7.3 cm (3-20cm) .
- *Median period from the diagnosis of endometrial cysts to the diagnosis of ovarian cancer was 36 months .*

- Meta-analysis recently showed that the frequency of ovarian cancer was only increased approximately 1.5 times in patients with endometriosis .

- *European society of Human Reproduction and Embryology guidelines recommend that the risk of ovarian cancer should not be taken into consideration in the management of endometriosis .*

conclusion

- Based on previously published case reports , the number of cases of EAOC tended to decrease with increasing time from diagnosis of an endometrial cyst , and almost allcases of cancer developed within 10 years .

- Clinically detectable cysts subsequently diagnosed as ovarian cancer might already have contained cancer cells (i.e… high-risk endometriosis) , rather carcinogenesis being mainly caused by enviromental factors .

Use of tumor markers to distinguish endometriosis – related ovarian endometrioma

- A case-control study was conducted on 283 women who were diagnosed with confirmed pathology with endometriosis-related ovarian neoplasms (n=21) and ovarian endometrioma (n=262) at a single institution from April 2008 to April 2018.

- *The cut-off value for the serum CA125 level was set at 35 U/mL; CA19-9 level, 37 U/mL; CEA level, 5 ng/mL; SLX level, 38 U/mL; and LDH level, 211 U/mL. The maximum tumor diameter and the presence of mural nodule in the tumor were determined via MRI.* *(Hiroki . S …2020)*

- four patients presented with ovarian clear cell carcinoma; five patients with ovarian endometrioid carcinoma; and 10 patients with seromucinous borderline tumor.

- *A total of 20 patients had stage I endometriosis-related ovarian neoplasms .*

- The median size of endometriosis-related ovarian neoplasms was 79mm

- This study showed that CA19-9, CEA , SLX, and LDH levels were significantly different between patients with endometriosisrelated ovarian neoplasms and ovarian endometrioma.

- *The ROC curves showed that LDH level was a better screening marker for endometriosis-related ovarian neoplasms.*

- Age, tumor size, and the presence of mural nodule were important factors in the preoperative prediction of endometriosis-related ovarian neoplasms .

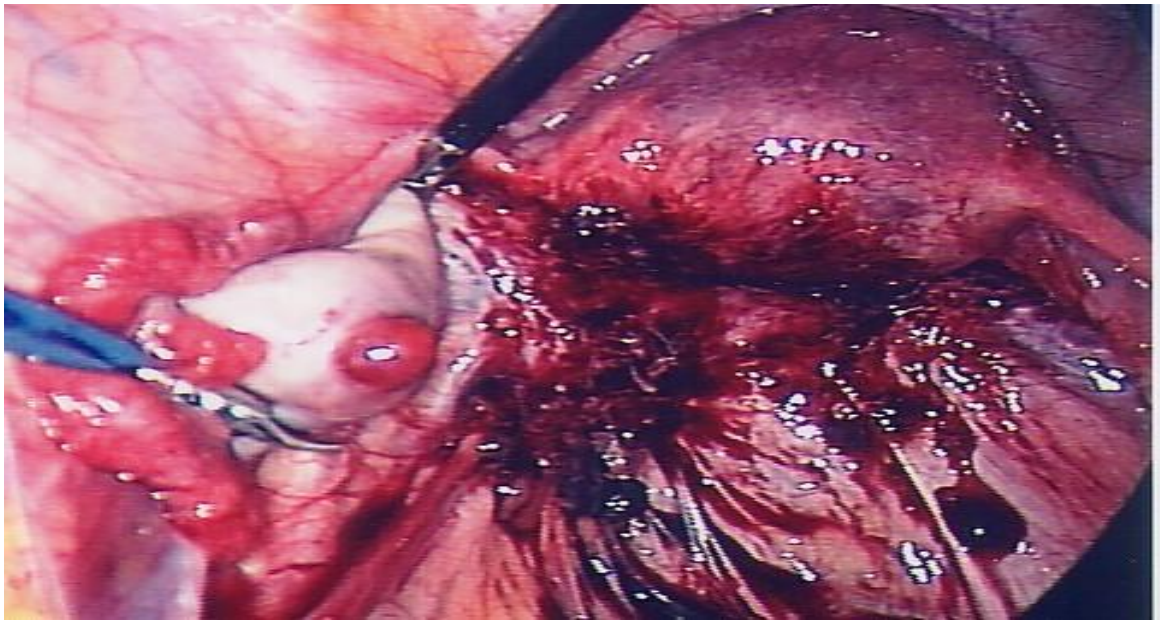
- *Human epididymis protein 4 (HE4) as a tumor maker. Serum HE4 may be a useful biomarker . Differential diagnosis between epithelial ovarian cancer and endometriosis .*

- Age , Tumor size , and the presence of mural nodule were informative factors for the preoperative prediction of endometriosis – related ovarian neoplasms .

Endometriosis and cancer: a systematic review and meta-analysis

Marina Kvaskoff et al conducted a meta-analysis of studies investigating the association between endometriosis and cancer risk and analyzed the results by methodological characteristics (2021).

- They discussed the implications of cancer screening in patients and management challenges faced by clinicians.



Method

- They searched PubMed and Embase databases for eligible studies and included **cohort** and **case-control** studies .
- cross-sectional studies and case reports were excluded.
- **49** Population-based case-control and cohort studies were included.
- **26** studies were scored as having a 'serious'/'critical' risk of bias, and the remaining **23** 'low'/'moderate.

Result

- They stated a positive association between endometriosis and ovarian cancer risk (SRR = 1.93, 95% CI = 1.68-2.22; n = 24 studies) that was strongest for clear cell (SRR = 3.44, 95% CI = 2.82-4.42; n = 5 studies) and endometrioid (SRR = 2.33, 95% CI = 1.82-2.98; n = 5 studies) although with significant evidence of both *heterogeneity* across studies and *publication bias* (Egger's and Begg's P-values < 0.01).

- A robust association was observed between endometriosis and **thyroid cancer** (SRR = 1.39, 95% CI =1.24-1.57; n = 5 studies).

- A very small association with **breast cancer** (SRR = 1.04, 95% CI =1.00-1.09; n = 20 studies).

- No association with **colorectal cancer** (SRR = 1.00, 95% CI =0.87-1.16; n = 5 studies).

- The association with **endometrial cancer** *was not statistically* significant (SRR = 1.23, 95% CI =0.97-1.57; n = 17 studies) .

- The association with cutaneous melanoma was also non-significant (SRR = 1.17, 95% CI =0.97-1.41; **n = 7** studies) but increased in magnitude and was statistically significant when restricted to studies with low/moderate risk of bias (SRR = 1.71, 95% CI = 1.24-2.36, **n = 2 studies**).

- The most robust finding both in terms of statistical significance and magnitude of effect was an **inverse association** with Cervical cancer (SRR = 0.68, 95% CI =0.56-0.82; n = 4 studies)

- This result has a high potential to reflect heightened access to detection of dysplasia for women who reached an endometriosis diagnosis and is thus likely not causal.

CONCLUSION

- Endometriosis was associated with a higher risk of ovarian and thyroid, and minimally (only 4% greater risk) with breast cancer, and with a lower risk of cervical cancer.

- However, this meta-analysis confirms that: a majority of studies had severe/critical risk of bias; there is impactful heterogeneity across studies-and for ovarian cancer, publication bias.


با تشکر از توجه شما