

## Mini Review

# Oncogenic Risk of Endometriosis

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Endometriosis is a chronic, inflammatory, and estrogen-dependent, with a prevalence of 10% in women of reproductive age; the pathophysiology is explained based on various theories, the most accepted is the retrograde menstruation associated with chronic inflammation, which could be the link between endometriosis and cancer. The symptomatology is characterized by dysmenorrhea, dyspareunia and infertility. Genetic studies provide information on the pathophysiology of epithelial ovarian cancer but there is still much to learn about the cellular origin and the molecular basis of these diseases and their risks. The management of endometriosis is medical and surgical; complete surgical removal of lesions of endometriosis, as well as removal of the affected ovary future decreases the risk of ovarian cancer.

**Keywords:** Endometriosis; Chronic pelvic pain; Retrograde menstruation; Ovarian cancer; Prevention; Hormone therapy; Surgery; Hysterectomy; Oophorectomy

## Introduction

Endometriosis is defined by the presence of endometrial glands and stroma outside of the uterine cavity; which is present in 22% of women and estimated, reported for the general population, prevalence [1] is 4%. The definitive diagnosis of endometriosis is by biopsy and histopathology. Endometriosis affects more often ovarian and peritoneal, secondary surface menstrual reflux through the fallopian tubes during menstruation, causing pelvic inflammation and adhesions that are manifested clinically in chronic pelvic pain, mild to severe, or cyclic and infertility; is an estrogen-dependent chronic, inflammatory disease, which affects 10% of women of reproductive age; Clinical manifestations usually disappear with menopause [2,3].

The pathophysiology is explained based on various theories, the most accepted is the retrograde menstruation or reflux of endometrial fragments strewn across the fallopian tubes during menstruation and implantation of cells into the peritoneal surfaces of the pelvic structures, ovaries, uterus, bladder and bowel, associated with chronic inflammation, which could be the link between endometriosis and cancer [1-3]; considering an independent risk factor for ovarian cancer and other malignancies [4].

## Reason for the Study of Endometriosis and Ovarian Cancer

The importance of studying the possible association of endometriosis with cancer, it is considered a risk factor for epithelial ovarian cancer, gynecological cancer is more lethal [1-6]; although there is controversy respect [6,7].

On the other hand, the definitive treatment of endometriosis is hysterectomy with bilateral salpingo-oophorectomy and complete removal of all endometriosis implants [1,2,8,9] eliminating the probability of epithelial ovarian cancer [1,7-9]. Cancer is the second leading cause of death in women, ovarian cancer is the eighth diagnosed in 1 to 1.5% of women [5], the fifth or sixth decade of life; It is when diagnosed in advanced stages, when treatment is less effective

and endometriosis has been linked to ovarian cancer, especially subtypes clear, low-grade serous cells and endometrioid [2,4] makes it necessary that doctors are aware of and understand the causes that increase the risk, whether genetic or epidemiological analyzes, to differentiate epithelial ovarian cancer in the categories of high, medium and low risk, according to the results, establish mechanisms prevention, early detection and surgical treatment individual [1,8].

## Endometriosis and ovarian cancer

The coexistence of endometriosis and epithelial ovarian cancer in the same ovary has a prevalence of 2.5% and 4.5% of all ovarian endometriosis and extra-ovarian. The prevalence of endometriosis in different histological subtypes of epithelial ovarian cancer are: for serous carcinoma 4.5%, 1.4% mucinous, clear cell, endometrioid 35.9% and 19% from [1,8] to [10] synchronous development of endometriosis and ovarian epithelial cancer subtype is 41% clear cells and epithelial ovarian endometrioid 38 %; other studies report 79% and provide that comes from endometriosis extra ovarian [1].

Epidemiological studies of benign gynecological conditions endometriosis associated with some subtypes of epithelial ovarian cancer [4,10,11-15] not conclusively [4,15] and subtypes mainly clear cell, endometrioid 2 low-grade serous [4,16]; unrelated to serous epithelial subtypes of high grade serous and mucinous borderline; the criteria for the diagnosis of cancer from endometriosis include: 1) endometrial cancer and benign tissue in the same ovary; 2) endometrial cancer that arises in non-metastatic ovarian tissue; 3) Histopathological relationship between benign and invasive components associated with endometriosis.

Ovarian cancer is not one disease but several diseases with different molecular and epidemiological factors that make heterogéneo [2,4], invasive epithelial ovarian cancer consists of five major histological subtypes: epithelial cancer [2,4,17] clear cell, endometrioid cancer epithelial cancer mucinous, serous epithelial cancer and serious high-grade low-grade epithelial cancer; all show molecular, clinical and pathological features differences [2,4]. Evidence suggests that the risk

associated with endometriosis varies according to the subtypes and clearest association was with endometrioid cell subtypes and clear cell [2,4,17-21].

Epidemiological association, tumor behavior, stage, grade of differentiation and risk of ovarian borderline tumors: genetic polymorphisms of risk and the relationship between endometriosis and the five subtypes of epithelial ovarian cancer to evaluate [2,4,21] are being studied. There have been studies of epithelial ovarian cancer and endometriosis [2,4,20,21]. Associated factors included age, ethnicity, use of oral contraceptives and parity; a history of endometriosis is associated with increased risk of epithelial invasive cancer of the ovary, after considering all the variables mentioned above, as reported in studies where the association of endometriosis and risk of epithelial ovarian cancer are different for some histological subtypes and women with a history of endometriosis are at increased risk of developing invasive serous low-grade epithelial cancer, epithelial cancer endometrioid and clear cell. Women with endometriosis who were diagnosed within 3-10 years confirmed epithelial ovarian cancer were cataloged without endometriosis [2,4,19-21].

Synchronous development of epithelial cancer and endometriosis clear cell subtype is 41% and 38% epithelial endometrioid cancer; the transformation is due to the loss of heterozygosity and somatic mutation of tumor suppressor genes, including [2,4] PTEN/MMAC/TEP1. The final confirmation of the association between endometriosis and epithelial cancers clear cell and endometrioid consistent with the results of studies demonstrating molecular ARID1A gene mutations in 46% of clear cell and 30% of endometrioid epithelial cancer in contiguous areas of epithelial ovarian cancer and endometriosis [2,4,8]; the molecular basis of this connection with serous epithelial ovarian cancer of low grade (characterized by mutations in KRAS, BRAF and ERBB2) is not defined and the results of studies of population screening for ovarian epithelial have not shown significant benefit, [2,4,8] undetectable in stages early [2,4].

Although concomitant endometriosis is observed in epithelial ovarian endometrioid and clear cell cancer, some subtypes of serous epithelial cancer arising from endosalpingiosis low grade (benign glandular proliferations) of tubal origin; endosalpingiosis as asymptomatic can be detected only histologically and cannot determine its incidence. On the other hand, the development of endometriosis and endosalpingiosis depends on host susceptibility, similar to the implantation of exfoliated cells Mullerian epithelium, endometrial or uterine tubes and association with endometriosis suggests that it is a precursor lesion, and other precursors associated with a history of endometriosis that increase the risk of epithelial cancers clear cell and endometrioid, although 28% were reclassified as high degree serous epithelial cancer [11,14].

It has been found that endometriosis is a precursor lesion of epithelial ovarian cancer and that this is due to two mechanisms: inflammatory and hormonal. Many of the mutations in the same gene, as  $\beta$ -catenin and PTEN, have been demonstrated in epithelial cancer and endometrial endometrioid cancer [11,22-26], suggesting a shared molecular pathogenesis of epithelial cancer cells do not express receptors clear progesterone or estrogen, so develop endometriosis epithelial cancer clear cell will not be a hormone dependent tumor during the transformation process [2,4,11].

## Discussion

Regardless of the association between endometriosis and risk of serious epithelial cancers, low-grade endometrioid and clear cell, most women with endometriosis do not develop epithelial ovarian cancer; but require close monitoring to establish mechanisms to prevent and, if required, provide treatment opportune [2,4,13,22]. Some studies report on the impact of the management of endometriosis on the risk of epithelial ovarian cancer. In the medical-hormonal treatment of endometriosis there are four main types that have changed over time. Progestogens and combined oral contraceptives, GnRH agonists were introduced.

Of all hormonal treatments alone shows an association with risk of epithelial ovarian cancer is danazol (OR 3.2) [2-4,27-32]. GnRH agonists have never been associated with ovarian cancer and combined oral contraceptives protect against ovarian cancer in women with and without endometriosis, using a prolonged (> 10 years). No association between combined oral contraceptives and ovarian cancer, no association between use of hormone replacement therapy was demonstrated, others have shown an association with relative risk of 1.38 to 3.00 for ovarian cancer compared to nonusers thereof [2,4,22].

The impact of surgery on endometriosis, reported that surgical treatment reduces the risk with the removal of the affected ovary, even when the other ovary is left, and the removal of all visible endometrial tissue even if the ovaries are affected; hysterectomy and bilateral tubal occlusion regardless of a diagnosis of endometriosis, has a protective effect against ovarian cancer [2,4,22]; although it is controversial. Endometriosis is associated with endometrioid cancer, while the fallopian tubes leading to serous epithelial ovarian cancers, thus eliminating most fallopian decrease in the risk of this cancer [2,4,22]; but if the protection of the surgical treatment (removal of the cyst, ovarian resection or oophorectomy) after a diagnosis of a cyst in the ovarian [2,4,30,31].

The protective factor hysterectomy or bilateral tubal occlusion on the risk of ovarian cancer, although 80% of hysterectomies for adenomyosis did not have an increased risk of ovarian cancer, it is possible that women with adenomyosis have no greater risk of ovarian cancer and it failed to show a protective effect of hysterectomy on the future risk of ovarian cancer; when ovarian endometriosis develops no matter whether women will undergo hysterectomy, the damage is already done for ovarian cancer risk increases [22,30-32].

In another report, the unilateral oophorectomy affected ovary and complete removal of all visible lesions endometriosis, had protective effect against epithelial ovarian cancer [2,4,22]; originating two theories, the ability of endometrial cells to become atypical cells and these in atypical endometriosis, observed in 12-35% of ovarian endometriosis and atypical endometriosis occurs in 60-80% of the endometriosis-associated ovarian cancer and about 60% of ovarian cancers are associated with endometriosis cancer occurs directly adjacent or endometrial tissue [2,4,22,30,31]. If endometriosis is responsible risk factor for induction of atypical cells that could suffer malignant changes later, ovarian cancer and hormone treatment time unchanged risk. In these cases, premalignant cells already present in the ovaries at the time that the hormone treatment started.

This theory is also supported by the benefits observed with more radical surgery (complete resection of endometriosis and oophorectomy), in which the abnormal cells are removed along with the injury of the endometrium, these results should be confirmed in studies with larger numbers case. The other theory is the development of chronic inflammation as a result of endometrial tissue. Inflammatory mediators (interleukin-1, interleukin-8, interleukin-6, tumor factor, tumor necrosis-alpha and beta) are involved in endometriosis and in the development of ovarian cancer [2,4,22,30,31], here extraction also reduces the pelvic endometrial tissue swelling and decreases the risk of cancer; It is necessary to make a unilateral oophorectomy in 62 women with ovarian endometriosis to prevent one case of ovarian cancer that demands a significant economic burden, besides the suffering of patients, important to take into account issues.

The lifetime risk of ovarian cancer in a woman is one in 70 and 1.5% endometriosis; surgically removed when all endometriotic lesions risk reduction is 30% for ovarian cancer; 95 women are required to undergo radical surgery to prevent one case of cancer; risk reduction of 81% is reported if affected by unilateral oophorectomy for every 62 women removed ovarian cancer case is prevented ovario [2,4,22,30-32].

## Conclusion

Endometriosis is a multifactorial disease that requires future research should focus on identifying factors associated with malignant transformation of endometriosis and development of serous epithelial cancers, low-grade clear cell and endometrioid, to identify all risk factors, the make decisions about the final management of endometriosis. Genetic studies provide information on the pathophysiology of epithelial ovarian cancer but there is still much to learn about the cellular origin and the molecular basis of these diseases and their risks. Surgical treatment of endometriosis with removal of all endometriotic implants including unilateral oophorectomy protects against epithelial ovarian cancer and hormone therapy showed no protection against epithelial ovarian cancer, including increased risk associated with the use of danazol; patients require close monitoring by the risk of epithelial ovarian cancer. Identifying subtypes of epithelial ovarian cancer affected by endometriosis help define the process and strategy development and will assess the factors effective prevention, treatment and monitoring of epithelial ovarian cancer.

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