

Editorial

For reprint orders, please contact: reprints@futuremedicine.com

Is endometriosis a preneoplastic condition?

“Ovarian cancer risk increased significantly over time, and the risk was particularly elevated among women with a long-standing history of ovarian endometriosis...”

Keywords: breast cancer • cancer • cervical cancer • endometrial cancer • endometriosis • genetic alteration • inflammation • ovarian cancer

Endometriosis is a condition that is characterized by the presence of endometrial tissue implants that are outside the uterine lining. It is presented in 10–15% of women in the reproductive age group, 2–5% of postmenopausal women, 25–30% of infertile women and 40–70% of women with chronic pelvic pain. The natural course of endometriosis starts with ectopic tissue implantation and bleeding occurs in this ectopic tissue. In this area, inflammation and fibrin deposition are seen. The final results of these events are adhesion, scar formation and distortion of peritoneal surfaces.

In 1925, Sampson firstly described a case with an ovarian carcinoma derived from an endometriotic lesion [1]. Since then, many retrospective studies have documented an increased rate of endometriosis in women with ovarian cancer, especially ovarian cancer with endometrioid adenocarcinoma and clear cell carcinoma. It has been understood that there are many histological, molecular and genetic alterations in the ectopic endometrial tissue. There are two pathways in the course of human endometriosis. The first and usual pathway is that ectopic endometriotic tissue on the ovarian surface encounters an unfavorable microenvironment and progresses regression with scar formation. However, the second and unusual pathway is that endometriotic tissue encounters a favorable microenvironment and continues growth to form endometriotic cysts/masses. This evolution causes an increased risk of accumulating additional genetic alterations that may lead to the development of ovarian cancer. The

relationship between endometriosis and cancer is an important matter. The points of discussion in this article are to clarify whether endometriosis should be considered a precursor lesion of cancer such as ovarian, uterine and mammary cancer.

Endometriosis & ovarian cancer

Interestingly, there are many clinical similarities between endometriosis and ovarian cancer. The most remarkable one is that similar factors affect the incidence of ovarian cancer and endometriosis. For example, tubal ligation, hysterectomy, oral contraceptives (OCs) and pregnancy decrease the risk of endometriosis and ovarian carcinoma. In contrast, infertility, early menarche, late menopause increase the risk of endometriosis and as well as ovarian cancer.

There are many studies that have addressed the relation between endometriosis and OCs. The first largest epidemiologic study was published from Swedish by Brinton *et al.* at 1997 [2]. This study reviewed more than 20,000 women (20,686) hospitalized with endometriosis, with a mean follow-up of 11.4 years. They found significant elevation for ovarian cancer in these patients (relative risk [RR]: 1.92). Ovarian cancer risk increased significantly over time, and the risk was particularly elevated among women with a long-standing history of ovarian endometriosis (follow-up of ≥ 10 years). Melin *et al.* published two cohort studies comprised of more than 120,000 women with endometriosis in 2006 and 2007 [3,4]. The average follow-up time was 13 years. There was an



Fuat Demirkiran
Department of OB & GYN,
Division of Gynecologic
Oncology, Istanbul
University, Cerrahpasa
Medical Faculty, Turkey
demirkiranfuat@gmail.com

increased risk of ovarian cancer (standardized incidence ratio [SIR]; 1.43–1.37). Similarly, women with early diagnosis and long-standing endometriosis had a higher risk of ovarian cancer, with SIR of 2.01. In a study from US by Brinton *et al.*, infertile patients were found to have a significantly higher risk of ovarian cancer [5]. Among infertile women, patients with endometriosis had the highest risk of ovarian cancer compared with the general population (RR: 2.48). Primary infertile patients with endometriosis had obvious increased risk of ovarian cancer (RR: 4.19). In another study from Japan, it was found that significantly increased ovarian cancer risk was seen in women having endometriosis [6]. The SIR was 8.95. This risk increased with increasing age at the time of diagnosis of ovarian endometrioma, with a SIR of 13.2. By contrast, in 2002, Olsen *et al.* could not show any relation between endometriosis and ovarian cancer [7]. If we look at the results of case–control studies addressing the relation between endometriosis and ovarian cancer, we can find similar results to that were found in cohort studies. Many case–control studies detected higher risk of ovarian cancer in patients with endometriosis. The RRs were changing from 1.32 to 1.73 [8–10].

The most recent study on this issue evaluated the results of English language papers published between 1973 and 2011 [11]. In that study, dataset consisted of data from 23,144 women. Seven thousand nine hundred and eleven cases had invasive ovarian cancer, 1907 had borderline ovarian cancer and there were 13,326 control cases. Authors reported that no association was noted between the history of endometriosis and borderline ovarian cancer. They also found that the history of endometriosis was associated with an increased risk of invasive epithelial ovarian cancer and there was two- to three-fold increase in the risk of clear-cell, low-grade serous and endometrioid invasive ovarian cancer in patients with endometriosis.

There are some known clinicopathologic characteristics of endometriosis-associated ovarian cancer. These cancers tend to be to be at younger age, to be diagnosed at earlier stages, to be lower grade lesions, to have better survival and to be endometrioid and clear-cell subtypes. So, these findings suggest that endometriosis-associated ovarian cancers have distinct clinicopathologic characteristics compared with nonendometriosis-associated ovarian cancer.

Endometriosis & breast cancer

There are many cohort and case–control studies addressing the association between endometriosis and breast cancer. Endometriosis and breast cancer appear to have common risk factors such as endogenous estrogen, reproductive characteristics, obesity and use of

hormone replacement therapy. However, the studies published so far have provided inconsistent results. For example, Brinton, Scairer and Weiss documented a significantly increased risk of breast cancer in patients with endometriosis [2,12–13], whereas the other authors could not find any relation [14,15].

This relation may be based on that both endometriosis and breast cancer have a hormone-dependent etiology. Endometriosis is a cause of infertility thereby leading to nulliparity or delayed childbearing. These events are also known risk factors for breast cancer.

Endometriosis & cervical cancer

A few studies have reported that the risk of cervical cancer decreases in patients having endometriosis. Also, some studies reported that there was nearly 40% risk reduction of cervical cancer in patients with endometriosis compared to the general population [16].

There are some explanations for this reduced risk of cervical cancer in patients with endometriosis. The first is that the patients with endometriosis have been controlled frequently, so they have more regular Pap tests. The second is that the inflammatory reaction and high levels of cytokines associated with endometriosis may play a protective role against viral infection with human papillomavirus, a causative factor for cervical cancer.

Endometriosis & endometrial cancer

There are some studies addressing the association between endometriosis and endometrial cancer. The most of them have conflicting findings [7,17]. Actually, no clear association has been found between endometriosis and endometrial cancer.

In conclusion, there is a relation between endometriosis and ovarian cancer, and endometriosis increases the risk of ovarian cancer.

It is not clearly understood certain molecular mechanisms related to malignant transformations of endometrial tissue. There are many clinical similarities between endometriosis and ovarian cancer. The most signal similarity is that similar factors affect the incidence of ovarian cancer and endometriosis. In contrast with infertility, early menarche, late menopause are for example, tubal ligation, hysterectomy, OCs, pregnancy are decreased risks of endometriosis increased risk of endometriosis and also ovarian cancer. So, the potential etiologic factors showing distinct association between endometriosis and ovarian cancer are thought to be multifactorial. It is well known that endometriosis is a common disorder of women, especially in reproductive age group. Another fact is that there is high mortality rate of ovarian cancer. With these findings, the potential association has important public health implications. So, gynecologists

should be aware of the apparently increased risk of ovarian cancer among patients with endometriosis, and they should make a point of evaluation the patients having long-standing history of endometriosis for ovarian pathology related to ovarian cancer.

Conclusion

Actually endometriosis is a benign disease and it is a common pathology for women in their reproductive period. In meantime, it is well known that there is close relation between ovarian endometriosis and cancer. With these findings, surgical management

can be considered for women having endometriosis forming ovarian mass at late reproductive period.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Endometriosis is not uncommon pathology seen in women and usually causes chronic pelvic pain and infertility.
- Ectopic endometriotic tissues initiate inflammatory reaction and this situation may induce some histological and genetic alteration.
- These alterations related to endometriotic tissues may increase the incidence of some kind of cancer, especially ovarian cancer.

References

- 1 Sampson JA. Endometrial carcinoma of the ovary arising in endometrial tissue in that organ. *Arch. Surg.* 10(1), 1–72 (1925).
- 2 Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am. J. Obstet. Gynecol.* 176(3), 572–579 (1997).
- 3 Melin A, Sparen P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. *Hum. Reprod.* 21(5), 1237–1242 (2006).
- 4 Melin A, Sparen P, Bergqvist A. The risk of cancer and the role of parity among women with endometriosis. *Hum. Reprod.* 22(11), 3021–3026 (2007).
- 5 Brinton LA, Lamb EJ, Moghissi KS *et al.* Ovarian cancer risk associated with varying causes of infertility. *Fertil. Steril.* 82(2), 405–414 (2004).
- 6 Kobayashi H, Sumimoto K, Kitanaka T *et al.* Ovarian endometrioma – risks factors of ovarian cancer development. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 138(2), 187–193 (2008).
- 7 Olson JE, Cerhan JR, Janney CA, Anderson KE, Vachon CM, Sellers TA. Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. *Cancer* 94(5), 1612–1618 (2002).
- 8 Ness RB, Cramer DW, Goodman MT *et al.* Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case–control studies. *Am. J. Epidemiol.* 155(3), 217–224 (2002).
- 9 Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am. J. Obstet. Gynecol.* 191(3), 733–740 (2004).
- 10 Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS. Risk of epithelial ovarian cancer in relation to benign ovarian conditions and ovarian surgery. *Cancer Causes Control* 19(10), 1357–1364 (2008).
- 11 Pearce CL, Templeman C, Rossing MA *et al.* Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case–control studies. *Lancet Oncol.* 13(4), 385–394 (2012).
- 12 Schairer C, Persson I, Falkeborn M, Naessen T, Troisi R, Brinton LA. Breast cancer risk associated with gynecologic surgery and indications for such surgery. *Int. J. Cancer* 70(2), 150–154 (1997).
- 13 Weiss HA, Brinton LA, Potischman NA *et al.* Breast cancer risk in young women and history of selected medical conditions. *Int. J. Epidemiol.* 28(5), 816–823 (1999).
- 14 Baron JA, Weiderpass E, Newcomb PA *et al.* Metabolic disorders and breast cancer risk (United States). *Cancer Causes Control* 12(10), 875–880 (2001).
- 15 Bertelsen L, Mellekjaer L, Frederiksen K *et al.* Risk for breast cancer among women with endometriosis. *Int. J. Cancer* 120(6), 1372–1375 (2007).
- 16 Borgfeldt C, Andolf E. Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis. *Acta Obstet. Gynecol. Scand.* 83(4), 395–400 (2004).
- 17 Brinton LA, Sakoda LC, Sherman ME *et al.* Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. *Cancer Epidemiol. Biomarkers Prev.* 14(12), 2929–2935 (2005).