GYNECOLOGY

# New insights in the pathophysiology of ovarian cancer and implications for screening and prevention

Farr R. Nezhat, MD; Radu Apostol, DO; Camran Nezhat, MD; Tanja Pejovic, MD, PhD

Despite advances in medicine, ovarian cancer remains the deadliest of the gynecological malignancies. Herein we present the latest information on the pathophysiology of ovarian cancer and its significance for ovarian cancer screening and prevention. A new paradigm for ovarian cancer pathogenesis presupposes 2 distinct types of ovarian epithelial carcinoma with distinct molecular profiles: type I and type II carcinomas. Type I tumors include endometrioid, clear-cell carcinoma, and low-grade serous carcinoma and mostly arise via defined sequence either from endometriosis or from borderline serous tumors, mostly presenting in an early stage. More frequent type II carcinomas are usually high-grade serous tumors, and recent evidence suggests that the majority arise from the fimbriated end of the fallopian tube. Subsequently, high-grade serous carcinomas usually present at advanced stages, likely as a consequence of the rapid peritoneal seeding from the open ends of the fallopian tubes. On the other hand, careful clinical evaluation should be performed along with risk stratification and targeted treatment of women with premalignant conditions leading to type I cancers, most notably endometriosis and endometriomas. Although the chance of malignant transformation is low, an understanding of this link offers a possibility of prevention and early intervention. This new evidence explains difficulties in ovarian cancer screening and helps in forming new recommendations for ovarian cancer risk evaluation and prophylactic treatments.

**Key words:** endometriosis, fallopian tube, ovarian cancer, prevention, risk-reducing bilateral salpingo-oophorectomy, salpingectomy, screening

Ovarian cancer is the second most common gynecological malignancy in developed countries and the most lethal. In the United States, there are approximately 22,000 new cases of ovarian cancer diagnosed each year and 14,000 cancer-related deaths.[1]

The majority of ovarian cancers are of epithelial origin, whereas fewer ovarian cancers develop from the remaining cell types, such as sex-cord stromal, germ cell, or mixed cell–type tumors.[2] The most common histological subtypes of epithelial ovarian carcinomas are serous (68-71%), endometrioid (9-11%), clear cell (12-13%), mucinous (3%), transitional (1%), and mixed histologies (6%).[3] At the time of diagnosis, the majority of epithelial ovarian cancers are advanced-stage, high-grade serous carcinomas and have a poor prognosis compared with early-stage carcinomas.

In the last 50 years, despite advances in cytoreductive radical surgery and cytotoxic chemotherapy, marginal improvement has been seen in the overall survival of patients with ovarian cancer. Attempts at early detection strategies in the last 2 decades have failed to provide survival benefit. Although the potential benefit of an effective screening strategy for ovarian cancer is great, to date studies have not shown any decrease in morbidity and mortality.

The best example is the Prostate, Lung, Colorectal, and Ovarian cancer screening trial, which evaluated the effect of combined modality screening (ie, transvaginal ultrasound and CA-125 serum level) for ovarian cancer.[4] The Prostate, Lung, Colorectal, and Ovarian trial did not find any reduction in ovarian cancer mortality using screening with cancer antigen 125 and transvaginal ultrasound.

Another large multicenter, randomized controlled trial currently looking at not only mortality but also cost, acceptance by patients, and physical and psychosocial morbidities associated with transvaginal ultrasound and CA-125 screening is the United Kingdom Collaborative Trial of Ovarian Cancer Screening.[5]

New evidence suggests that high-grade serous carcinoma, frequently presenting as an advanced stage, often originates from the fimbriated end of the fallopian tube. This is in contrast to low-grade serous endometrioid and clear cell histology, which mostly presents in the early stage and mostly originates from borderline serous carcinoma or endometriosis.[6,7] Herein we will discuss new perspectives in the pathophysiology of different histologies of epithelial ovarian cancer and present some possible preventative steps in decreasing the risks of this malignancy and possible future screening methodologies.

## Etiology

The etiology of ovarian cancer remains poorly understood, and the source

From the Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Mount Sinai Roosevelt, Division of Minimally Invasive Gynecologic Surgery, Winthrop University Hospital, State University of New York at Stony Brook, College of Medicine, New York, NY (Dr F. R. Nezhat); Department of Obstetrics and Gynecology, Division of Minimally Invasive Gynecologic Surgery, Mount Sinai–St. Luke's and Roosevelt Hospital System, New York, NY (Dr Apostol); Center for Special Minimally Invasive and Robotic Surgery, Palo Alto, CA (Dr C. Nezhat); and Division of Gynecologic Oncology, Oregon Health and Science University, Portland, OR (Dr Pejovic).

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Corresponding author: Farr R. Nezhat, MD, FACOG, FACS. FNezhat@chpnet.org

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population of epithelial ovarian cancer progenitors has become a matter of controversy. Traditionally, the ovarian surface epithelium was thought to be the primary source of ovarian malignancies. Indeed, the theory of incessant ovulation presupposes that repetitive involvement of the ovarian surface in the process of ovulation is a risk factor for ovarian cancer.

Factors associated with ovulation include injury and repair of the ovarian surface epithelium in response to follicle rupture, inflammatory effects of the ovarian environment surrounding ruptured follicle, entrapment of ovarian surface epithelium cells within the ovary with resulting inclusion cyst formation, and steroid hormone effects of the uniquely high concentrations of progesterone, androgens, and estrogen in the local ovarian environment during each menstrual cycle.[8] Evidence has accumulated, however, to suggest that many cases of epithelial ovarian cancer originate in the distal portion of the fallopian tube, more precisely the fimbrial epithelium.

The initial evidence implicating the fimbrial epithelium came from risk-reducing salpingo-oophorectomies in women who had either *BRCA* gene mutations or a strong family history of ovarian cancer.[9] When the entire tube was serially examined, foci of small in situ tubal intraepithelial carcinoma (TIC) were found.[10,11] These are regions of dysplasia within tubal epithelium that demonstrate high levels of *TP53* mutations.

Later similar lesions were found in the fimbrial epithelium of a significant number of cases of sporadic ovarian carcinomas.[11] Przybycin et al[12] identified TIC in 60% of consecutive ovarian cancer cases when tubes were systematically examined. Yet these precursor lesions were not found in the fimbrial epithelium of nonserous types of ovarian carcinoma.

## Classification and new theories

Several groups have now convincingly established that there are 2 distinct types of epithelial ovarian carcinoma: type I and type II.[13-15] Type I tumors arise via well-recognized sequence either from borderline serous tumors or from endometriosis and include low-grade serous carcinoma, endometrioid, and clear-cell carcinoma. These tumors are often early stage and low-grade tumors, with a relatively indolent disease course. Type II carcinomas are more frequent, usually of serous histology, are high grade, and seem to originate from the fimbrial epithelium in up to 60% of the cases.[12] Subsequently, high-grade serous carcinomas present clinically as stage 3 or 4 disease, consistent with the hypothesis of peritoneal seeding by malignant cells from the fimbriated end of the tubes.

The molecular profile of the 2 types are different and correlate well with the distinct nature of type I and type II carcinomas. Type I carcinomas are characterized by *KRAS*, *BRAF*, *ERBB2*, *CTNNB1*, *PTEN*, *PIK3CA*, *ARID1A*, *PPP2R1A*, and *BCL2* mutations.[15-17] On the other hand, the majority of type II tumors are characterized by *TP53* mutations. Indeed, the *TP53* mutations are present in almost 96% of high-grade serous ovarian carcinomas of the Cancer Genome Atlas dataset.[18]

### Role of the fallopian tube and high-grade serous carcinoma

Today we understand that the rapid progression of high-grade serous carcinomas is consistent with seeding of the peritoneal cavity by malignant cells from the fimbriated ends of the fallopian tubes. What not so long ago was thought to be a precursor lesion in the fimbrial epithelium of *BRCA* carriers is now found in up to 60% of all cases of epithelial ovarian cancer.[12] The precursor lesion, serous TIC, has now been defined and it typically consists of secretory cells, lacks the ciliated cells of a normal fallopian tube, has a TP53 signature, and is associated with a high degree of DNA repair pathway alterations including *BRCA* and *BRCA*-like mutation.[11]

The Gynecologic Oncology Group is currently completing a nonrandomized prospective trial comparing longitudinal screening with CA-125 and ultrasound to risk-reducing bilateral salpingo-oophorectomy in a high genetic risk population. The results from the surgical intervention arm of Gynecologic Oncologic Group (GOG-0199) found that 2.6% of women undergoing risk reducing salpingo-oophorectomy were diagnosed with ovarian/tubal neoplasm's (4.6% of BRCA1 mutation carriers, 3.5% of BRCA2 mutation carriers, and 0.5% of noncarriers). Overall, 56% of women with ovarian/tubal neoplasia had serous TIC or stage I or II invasive cancer.[19]

## Role of endometriosis and endometrioid and clear cell carcinoma

The association between endometriosis and ovarian cancer has perplexed clinicians and scientists for many years since it was first reported by Sampson.[20] Several epidemiological studies have suggested the link between endometriosis and ovarian cancer. This was recently corroborated by the study assessing the association between self-reported endometriosis and risk of ovarian cancer.[21]

Data collected from 13 original studies analyzed a total of 13,226 controls and 7911 women with invasive ovarian cancer, of which 818 (6.1%) and 738 (9.3%), respectively, reported a history of endometriosis. Self-reported endometriosis was associated with significantly increased risk for clear cell cancer (odds ratio [OR], 3.05), endometrioid cancer (OR, 2.21), and low-grade serous invasive ovarian cancers (OR, 2.21). There was no association between endometriosis and a risk for high-grade serous carcinoma.

In another metaanalysis, Kim et al[22] investigated the impact of endometriosis on the risk and prognosis for ovarian cancer and evaluated the clinicopathological characteristics of endometriosis-associated ovarian cancer in comparison with nonendometriosis-associated ovarian cancer. Again, it was confirmed that endometriod and clear-cell carcinomas are more common in endometriosis-associated ovarian cancer (relative risks [RRs], 1.759 and 2.606, respectively), whereas serous carcinoma was less frequent in endometriosis-associated ovarian cancer than in the nonendometriosis-associated group (RR, 0.733).

The causes of malignant transformation of endometriosis are not clear, but several genetic, immunological, and hormonal factors have been implicated.[8,15,23] Recent evidence links the role of microenvironment to the process of malignant transformation of endometriosis. Indeed, endometriosis is an inflammatory state, as a result of retrograde menstruation. Suryawanshi et al[24] implicated a role of a complement system in malignant transformation. Specifically the group has reported for the first time the up-regulation of chronic activation of the complement pathway in women with endometriosis and its protumorigenic role.

## Clinical implications

Keeping in mind these new findings, it is not surprising that early detection of high-grade serous carcinoma of the ovary is extremely challenging using current methods of mainly pelvic ultrasound and serum CA-125. The occult early lesion in the fallopian tube and the rapid seeding of the peritoneal cavity via the tubes are some of the theories proposed to describe the emergence of impressive ovarian masses as well as other peritoneal tumors. Thus, at the time of diagnosis, clinicians are faced with already advanced disease. In light of these findings, we need to focus on new strategies for the early detection of high-grade serous carcinomas, shifting our thinking toward the earliest precursor lesion within the fallopian tube.

Similarly, the methods for the early detection of type I ovarian carcinomas parallel our understanding of their precursor lesions and biology of their development. Endometriosis, defined as the presence of endometrial-like glands and stroma at extrauterine sites, is a chronic disease occurring in approximately 10% of women.[25] Although endometriosis is considered a benign disease, it has several features that are characteristic of invasive cancers. Some of these features include invasion of the stroma of the organ in which it involves, development of local and distant foci, and high recurrence rate after treatment.

One of the most common sites of endometriosis is the ovary. Ovarian endometriosis is of particular interest because a proportion of ovarian cancers arise from ovarian endometriotic lesions, particularly clear-cell and endometrioid ovarian carcinomas.[26,27] Although useful, both serum CA-125 and transvaginal ultrasound are poor screening modalities in differentiating malignant tumors from benign ones.[28]

Clinical presentation of ovarian cancer associated with endometriosis includes symptoms that are typically attributed to endometriosis, including pelvic pain, exacerbation of dysmenorrhea, dyspareunia, and vaginal bleeding.[29] In a series reported by Deligdisch et al, [7] all stage I nonserous ovarian carcinomas were diagnosed based on associated symptomatology, such as pelvic pain with endometriosis/adnexal masses or vaginal bleeding associated with an underlying endometrial pathology. Pathology revealed an endometriotic ovarian cyst in 39 of 54 women with stage I nonserous ovarian carcinoma compared with 1 of 22 with stage I serous ovarian carcinoma. Furthermore, 33 of 54 women with stage I nonserous ovarian carcinoma proved to have endometrial carcinoma, hyperplasia, or polyp, compared with 4 of 22 women with stage I serous ovarian carcinoma. Therefore, we recommend the evaluation of the endometrium in symptomatic patients with endometriosis and an ovarian mass to rule out possible coexisting malignancies.[7,30]

Endometrioid and clear-cell ovarian carcinomas associated with endometriosis usually present with an adnexal mass that may be associated with endometrioma. It appears therefore that a discreet set of symptoms associated with different ovarian carcinoma histologies exist and may be helpful in establishing programs for early detection of cancers associated with endometriosis.

## Options for prevention

Both endometriosis and ovarian cancer share certain characteristics, valuable in developing strategies for future prevention and treatment.[31]

This becomes even more critical because now we understand that low-grade serous carcinomas originate from ovarian surface epithelium and most endometrioid and clear-cell histological subtypes originate from endometriosis.[32]

Oral contraceptives are a potentially promising primary prevention strategy for ovarian cancer. The majority of studies that have examined the relationship between combined oral contraceptive use and ovarian cancer have reported a decreased risk with their use. Beral et al[33] looked at 23,257 cases and 87,303 controls and found a significant reduction of overall ovarian cancer risk (RR, 0.73; 95% confidence interval [CI], 0.70−0.76) with an additional 20% reduction for every 5 years of use. Furthermore, the reductions in risk per 5 years of oral contraceptive use were broadly similar for epithelial and nonepithelial tumors. Oral contraceptives also seem to have little effect on mucinous tumors.[33]

Two large collaborative studies have recently called attention to the role of tubal ligation on reducing the ovarian cancer risk. Tubal ligation has been known for a long time to reduce the risk of ovarian cancer.[34] Most recent analyses show that this risk reduction is the greatest for endometrioid and clear-cell carcinoma, rather than high-grade serous ovarian carcinoma, 52% and 48% vs 19% reduction, respectively.[35-37] The protective effect of tubal ligation on these 2 subtypes of invasive ovarian cancer is thought to be associated with the prevention of retrograde menstruation, ovarian seeding by endometrial cells, and inflammation.

Given the overwhelming evidence suggesting the possibility of the fallopian tube as the origin of high-grade ovarian cancer, salpingectomy should be considered as a method of prophylaxis, even in women at average risk for ovarian cancer, instead of tubal ligation.

The Society of Gynecologic Oncology recommends that women who have *BRCA1* or *BRCA2* germline mutations should be counseled regarding bilateral salpingo-oophorectomy, after completion of child-bearing, as the best strategy for reducing their risk of developing ovarian cancer. In the event that these women opt to delay risk-reducing bilateral salpingo-oophorectomy, they should be counseled regarding a 2-step

procedure: initial risk-reducing salpingectomy followed by oophorectomy in the future, although the safety of this approach has not been studied.[38] Serial sectioning of the ovaries and fallopian tubes, especially the fimbriae, is crucial. Furthermore, the Society of Gynecologic Oncology also recommends that for women at average risk of ovarian cancer, risk-reducing salpingectomy should also be discussed and considered in patients at the time of abdominal or pelvic surgery, after completion of childbearing.[38]

This recommendation should also be considered by other disciplines, in addition to the gynecologist, especially when the fallopian tubes are found to be damaged by endometriosis and/or pelvic inflammatory disease. Countries like Canada even went so far as to initiate a province-wide ovarian cancer prevention initiative.[39] Obstetricians and gynecologists, in the province of British Columbia, were educated on the current evidence outlying the role of the fallopian tube in ovarian cancer and explained the association of high-grade serous cancer with inherited *BRCA1* and *BRCA2* mutations.

The interventions called for salpingectomy at the time of hysterectomy, salpingectomy for permanent sterilization instead of tubal ligation, and referral for all patients with high-grade serous cancer for hereditary cancer counseling and genetic testing for *BRCA1* and *BRCA2* mutations. Although still in its infancy, these 3 recommendations are projected to reduce ovarian cancer rates in this province by 40% over the next 20 years.[39]

### Pros and cons of salpingectomy

Other advantages of complete bilateral salpingectomy include a decrease in the risk of hydrosalpinx, tubal ligation failure, and ectopic pregnancies.

The Rochester Epidemiology Project evaluated women after hysterectomy with adnexal preservation over a 56 year study period and found that the incidence of women requiring removal of one or both adnexa was 12.8%.[40] Furthermore, the risk of developing a hydrosalpinx was 2.6 per 1000 women-years. Assuming 30 years of life after hysterectomy, the lifetime risk of surgery for hydrosalpinx alone would be 7.8%.[40]

Historically, postpartum salpingectomy has been considered to have the lowest failure rate of all sterilization methods as well as the lowest cumulative probability of ectopic pregnancies.[41,42] The feasibility and safety of postpartum distal salpingectomy has recently been reported.[43]

Although a relatively simple procedure that could potentially be implemented in women who have completed child-bearing, there is a concern that salpingectomy would compromise collateral circulation to the ovaries and predispose women to early ovarian failure. However, multiple studies have failed to show the association between tubal ligation and early ovarian failure.

Findley et al[44] randomized 30 premenopausal women undergoing laparoscopic hysterectomy with ovarian preservation for benign indication into 2 groups: bilateral salpingectomy vs no salpingectomy. Anti-Mullerian hormone (AMH) levels were measured preoperatively and at 4-6 weeks and 3 months postoperatively. Given that there was no statistical difference between the AMH levels, they concluded that salpingectomy at the time of the laparoscopic hysterectomy with ovarian preservation is a safe procedure that does not appear to have any short-term deleterious effects on ovarian reserve.

In another recent study, Morelli et al[45] also compared ovarian function in premenopausal women undergoing hysterectomy alone vs hysterectomy with bilateral salpingectomy for benign disease. The authors found no difference in ovarian function between the patient groups, as determined by AMH, FSH, antral follicle count, mean ovarian diameter, and peak systolic velocity. They also found no difference in operative time, postoperative stay, time to return to normal activity, and postoperative hemoglobin between the 2 groups.

One of the drawbacks of complete bilateral salpingectomy is eliminating the option of future tubal reanastomosis.[46] Subsequently, patients should be counseled regarding sterilization regret, especially for women under the age of 25 years. Furthermore, the local and state policies should be reviewed and taken into consideration.

Based on the available evidence, we can hypothesize that a compromised collateral circulation to the ovaries, resulting in early ovarian failure, would be caused only by poor surgical technique. Therefore, salpingectomy at the time of hysterectomy, instead of tubal ligation, and also at the time of other abdominopelvic surgery would be in the best interest of the patient.

### Endometriosis management consideration

As with the changes in our thinking about screening and preventative measures in high-grade ovarian cancer, there is also mounting evidence for type I carcinomas associated with endometriosis that requires new consideration for a possible change in clinical practice guidelines regarding screening and prevention of endometriosis associated ovarian cancer. Although ovarian cancer develops in only 0.3−1.6% of women with endometriosis,[22] it is important to assess, document, and systematically follow up the risk factors that may predispose patients to developing ovarian cancer. These include the following: (1) long-standing endometriosis, (2) endometriosis diagnosed at an early age, (3) endometriosis associated with infertility, and (4) the presence of enlarging ovarian endometrioma or changing characteristics and mural nodule formation.[5,47,48]

Women found to be at an increased risk of ovarian endometrioma have options of medical (hormonal) or surgical treatment. The treatment should be personalized based on patient's age, desire for child-bearing, family history, and type and characteristics of endometriomas. Nezhat et al[49] have described 2 types of endometriomas: type I and type II.

Type I endometriomas are characterized by small lesions that spread across peritoneal and ovarian surfaces, whereas type II endometriomas originally start as functional ovarian cysts that are invaded by cortical endometriosis and gradually

develop into endometriomas. Hormonal treatment often results in incomplete regression of endometriotic lesions and recurrence of endometriomas.

Additionally, in type II endometriomas, adjuvant hormonal suppressive therapy that prevents ovulation can decrease the risk of recurrent ovarian endometrioma formation.[50-52] Interestingly, Melin et al[53] showed that women who underwent unilateral oophorectomy for endometriosis had a significantly reduced risk of later development of ovarian cancer, with an OR of 0.19 (95% CI, 0.08−0.46) compared with controls. In addition, ovarian cancer was significantly less likely to develop in women who underwent radical surgical excision of all visible endometriosis, with an OR of 0.30 (95% CI, 0.12−0.74).[53] Considering the previously cited information, different surgical strategies should be used at the time of surgical treatment of patients with pelvic endometriosis.

## Conclusion

These clinical observations and the new recent evidence for the dual pathogenesis of ovarian cancer have set ground for implementing new strategies for screening and prevention programs to reduce the incidence of epithelial ovarian cancer. Until specific markers are developed, able to detect different histological epithelial ovarian cancers, it seems reasonable to undertake certain steps, such as bilateral salpingectomy, to reduce the risk of these types of cancers based on the current evidence.

In light of the accumulated data and observations regarding endometriosis and ovarian cancer, we propose that it is time to establish criteria for identifying and monitoring women with endometriosis for risk factors and to pursue risk-reducing medical and surgical treatment options in these women. At the time of surgical diagnosis and treatment, consideration for complete resection of pelvic endometriosis, salpingectomy, oophorectomy, or hysterectomy should be individualized based on a patient's age, desire for future fertility, and preoperative consultation with the patient.

These initiatives, if validated by level 1 evidence, should substantially reduce the risk of ovarian cancer as well as the total mortality risk. As new research becomes available, the recommendations may be refined in terms of both screening and prevention. ■

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