GYNECOLOGY

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

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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

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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).