Overview article

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Recent advances in the pathophysiology of ovarian cancer and clinical implications for screening and intervention

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Abstract

New evidence in ovarian cancer shows that advanced-stage, high-grade serous tumors often originate from precursor epithelial lesions in the distal fimbriated end of the fallopian tube. This stands in stark contrast to endometrioid tumors and low-grade clear cell tumors, which tend to present early and may originate from borderline serous carcinoma or endometriosis. This article aims to explore novel insights into the pathophysiology of different epithelial ovarian carcinoma groups, with implications for potential screening and intervention methods in the future.

Keywords: TIC (tubal intraepithelial carcinoma), endometriosis, risk-reducing bilateral salpingo-oophorectomy, epithelial ovarian cancer.

1. INTRODUCTION

Ovarian cancer is a gynecologic cancer that has a high prevalence of mortality. Despite many advances in treatment and early screening which combines transvaginal ultrasound (TVUS) and serum CA-125 measurement, it does not seem to lead to a reduction in mortality. Recent clinical observations and new insights into the pathophysiology of ovarian epithelial carcinoma suggest the way for the development of screening and intervention strategies aimed at reducing ovarian cancer incidence within the community.

2. REVIEWS

1. Overview of Ovarian cancer

Ovarian cancer is the second most common gynecological malignancy and is associated with the highest mortality rates in developed countries [1]. Primary ovarian tumors are subdivided into three categories: epithelial, germ-cell, and sex-cord stromal tumors with epithelial tumors being the most common (80%-85%). Unfortunately, most epithelial ovarian cancers are advanced-stage, high-grade serous carcinomas at the time of diagnosis and have a poor prognosis compared with early-stage carcinomas. Epithelial ovarian tumors are primarily classified according to cell type into serous tumors (68-71%), endometrioid tumors (9-11%), clear cell tumors (12-13%), mucinous tumors (3%), transitional tumors (1%), and mixed tumors (6%) [2]. Currently, despite many advances in treatment and early screening (combined with transvaginal ultrasound and serum CA-125), the morbidity and mortality rates of ovarian cancer have not improved. [3]

2. Theories of the origin and Classification of Epithelial Ovarian Carcinoma (EOC)

The etiology of ovarian cancer remains poorly understood and has become a matter of controversy. According to the traditional view, the ovarian surface epithelium is considered the origin of malignant tumors. Indeed, the theory of incessant ovulation presupposes that repetitive involvement of the ovarian surface in the process of ovulation is a significant risk

factor for ovarian cancer, including injury and repair of the ovarian surface epithelium in response to follicle rupture, inflammatory effects of the ovarian environment surrounding ruptured follicle, entrapment of surface epithelial cells leads to the formation of luteal follicles, and high concentrations of sex steroids (such as progesterone, androgens, and estrogens) in the local ovarian during each menstrual cycle [4].

However, current evidence indicates that ovarian carcinoma often originates from the fimbriated end of the fallopian tube. A surgical procedure known as salpingo-oophorectomy, which involves removing the ovaries and fallopian tubes, has been shown to significantly reduce the risk of ovarian cancer in women with BRCA gene mutations or a strong family history of ovarian cancer [5]. Upon serially examining the entire tube, researchers have found foci of small in situ tubal intraepithelial carcinoma (TIC), characterized by high levels of TP53 mutations [6]. Similar TIC lesions have been observed in the fimbria epithelium of a significant number of cases of sporadic ovarian carcinomas. Przybycin et al found TIC in 60% of ovarian cancer cases [7]. However, these precursor lesions were not found in the fimbria epithelium of non-serous ovarian carcinoma.

Afterward, scientists suggested two types of epithelial ovarian cancer: type I and type II. Type I epithelial tumors typically arise from borderline serous tumors or endometriosis including low-grade serous carcinoma, endometrioid, and clear-cell carcinoma. Type I tumors are often in an early stage, demonstrate high differentiation and progress relatively slowly in terms of disease advancement. These tumors are characterized by mutations in genes such as KRAS, BRAF, ERBB2, CTNNB1, PTEN, PIK3CA, ARID1A, PPP2R1A, and BCL2 [8]. Conversely, type II epithelial tumors are more frequent in clinical settings and primarily consist of high-grade serous tumors that are detected at late stages (3 or 4). Up to 60% of type II tumors seem to originate from the tubal epithelium of the fallopian tube [7]. And most type II tumors exhibit TP53 mutations [9].

3. The Role of the fallopian tube and high-grade serous carcinoma

The rapid progression of high-grade serous carcinomas is consistent with the concept of "seeding" in the peritoneal cavity, where malignant cells originate from the distal fimbriated end of the fallopian tube. Today, precursor lesions known as TIC have been identified. These lesions are characterized by a high degree of DNA repair pathway alterations, including BRCA and BRCA-like mutation within the fallopian tube, and usually consist of secretory cells. Additionally, they lack the ciliated cells of a normal fallopian tube and have a TP53 signature. [6]

The results from the surgical intervention arm of Gynecologic Oncology Group (GOG) revealed that TIC or stage 1 or 2 invasive carcinoma was present in 56% of women diagnosed with ovarian/tubal neoplasms undergoing risk-reducing salpingo-oophorectomy before [10]. Since early detection of high-grade serous carcinoma of the ovary using current screening methods of pelvic ultrasound and serum CA-125 is extremely challenging the medical community needs to focus on novel approaches for the early detection of high-grade serous carcinomas, shifting our perspective toward the earliest precursor lesion inside the fallopian tube.

4. The Role of endometriosis and endometrioid and clear cell carcinoma

Despite scientific debates, several epidemiological studies have suggested the association between endometriosis and ovarian cancer [11]. A meta-analysis conducted by Pearce et al. revealed a significant association between endometriosis and the risk of clear cell cancer (OR ratio = 3.05), endometrioid cancer (OR ratio = 2.21), and low-grade serous invasive ovarian cancers (OR = 2.21) [12]. Interestingly, no association was found between endometriosis and the risk of high-grade serous carcinoma. In another meta-analysis, Kim et al. discovered that endometrioid 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 non-endometriosis-associated group (RR, 0.733) [13]. However, the specific biological process responsible for the malignant progression of endometriosis remains uncertain. It may involve genetic, hormonal, and immunological factors that alter the ovarian microenvironment. The microenvironment plays a part in the malignant evolution of endometriosis, according to recent research. Indeed, endometriosis is an inflammatory state, because of retrograde menstruation.

The approaches for the early detection of type I ovarian carcinomas should focus on their precursor lesions, such as endometriosis. Although endometriosis is often classified as a benign lesion, it exhibits features typically associated with malignant diseases, such as invasion into stromal tissue, local growth, distant spread, and high recurrence after treatment.

The correlation between ovarian cancer and ovarian endometriotic lesions is becoming more apparent in current research, especially in clear-cell tumors and endometrioid ovarian carcinomas. Screening by using combined transvaginal ultrasonography and serum CA-125 is helpful, although they are not very good at distinguishing between benign and malignant tumors [14]. A study by Deligdisch et al. found that 39 out of 54 women with stage I non-serous ovarian carcinoma had an endometriotic ovarian cyst, and 33 of the 54 women with stage I non-serous ovarian carcinoma had endometrial carcinoma, hyperplasia, or polyp. Consequently, to rule out the possibility of concurrent cancers, evaluating the endometrium is essential in symptomatic individuals with endometriosis and an ovarian tumor.

5. Methods to Prevent Ovarian Carcinoma

Nowadays, the scientific community understands the origin of ovarian epithelial cancers: low-grade serous carcinomas arise from the surface epithelium of the ovary, while most endometrioid and clear-cell histological subtypes originate from endometriosis. Additionally, certain similarities between endometriosis and ovarian cancer will help create future preventative and treatment plans.

Oral Contraceptives

Oral contraceptives offer a promising preventive strategy for ovarian cancer. Several studies indicate that combined oral contraceptive use reduces the risk of ovarian cancer. Research by Beral et al [16] reported a significant reduction in overall ovarian cancer risk (RR = 0.73; 95% confidence interval = 0.70-0.76) based on data from 23,257 cases and 87,303 controls. Furthermore, each 5 years of oral contraceptive use provides an additional 20% risk reduction. Notably, the risk reduction effect over 5 years is consistent for both epithelial and non-epithelial tumors. However, oral contraceptives appear less effective in cases of mucinous tumors [16].

Tubal Ligation

Two large collaborative studies have recently investigated Tubal ligation to reduce ovarian cancer risk [17]. Recent analyses demonstrate that tubal ligation is most effective in reducing the risk of endometrioid cancers (52%) and clear-cell cancers (48%), compared to high-grade serous ovarian carcinoma (19%) [18]. The protective effect of tubal ligation may result from preventing retrograde menstruation and the “seeding” of endothelial cells from the uterine lining, along with inflammatory cells, into the ovary.

Salpingectomy

Given substantial scientific evidence regarding the Fallopian tube’s role in high-grade ovarian cancer, salpingectomy should be considered as a preventive method, instead of tubal ligation. The Society of Gynecologic Oncology (SGO) recommends that women with BRCA1 or BRCA2 mutations should be counseled regarding bilateral salpingo-oophorectomy when childbearing is finished, as the best strategy to reduce the risk of developing ovarian cancer. [19]. Additionally, the SGO also suggests that women at average risk of ovarian cancer consider salpingectomy during abdominal or pelvic surgery after completion of childbearing [19]. Although Postpartum salpingectomy is considered feasible and safe, some experts express concern that removing the fallopian tubes would compromise collateral circulation to the ovaries and predispose women

to early ovarian failure. However, studies have not established the link between tubal removal and early ovarian failure. Findley et al' study [20] found no significant difference in AMH concentrations between the two groups. the salpingectomy group (with bilateral fallopian tube removal) and the group without tubectomy.

Similarly, Morelli et al [21] compared ovarian function in premenopausal women undergoing simple hysterectomy alone versus hysterectomy accompanied by bilateral salpingectomy for benign diseases. The authors found no difference in ovarian function between the two patient groups, as assessed by AMH and FSH levels, antral follicle count, average follicle diameter, and peak systolic velocity via ultrasound. Despite these benefits, the possibility of tubal re-anastomosis in the future is eliminated, which is one disadvantage of total bilateral salpingectomy. Therefore, patients should receive counseling over regretting being sterilized, especially for women under 25 years old.

6. Management and Monitoring of Ovarian Endometriosis

Although about 0.31-1.6% of women with endometriosis go on to develop ovarian cancer [13], systematic monitoring of risk factors for progression to ovarian cancer remains essential in clinical practice. Key risk factors include long-standing endometriosis, endometriosis diagnosed at an early age, endometriosis associated with infertility, the presence of enlarging ovarian endometrioma, or changing characteristics and mural nodule formation [22]. Women diagnosed with ovarian endometrioma have two options, including medical (hormonal) or surgical treatment. The choice depends on factors such as the patient's age, desire for childbearing, family history, and type and characteristics of endometriomas. Hormonal treatment can lead to incomplete regression of endometriotic lesions and recurrence of endometriomas. Adjuvant hormonal suppressive therapy prevents ovulation, thereby reducing the risk of recurrence in women with type II endometriosis. Research by Melin et al indicated that women who underwent unilateral oophorectomy due to endometriosis had a significantly reduced risk of subsequent ovarian cancer (OR = 0.19, 95% CI 0.08-0.46) compared to the non-surgical control group. Moreover, women who received radical surgical removal of all visible endometriosis had a considerably lower risk of developing ovarian cancer. (OR = 0.30, 95% CI 0.12-0.74)

3. CONCLUSION

Recent clinical findings and novel discoveries of the pathophysiology of ovarian epithelial carcinoma have set the ground for implementing new approaches for screening and prevention programs to reduce the incidence of epithelial ovarian cancer. Because of the connection between endometriosis and ovarian cancer, it is essential to monitor women with endometriosis closely and choose suitable treatments to decrease the risk of ovarian cancer. When considering surgical diagnosis and treatment options, such as total excision of pelvic endometriosis, salpingectomy, oophorectomy, or hysterectomy, it is important to personalize the approach based on the patient's age, desire for future fertility, and preoperative consultation regarding endometriosis.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: pp 9-29.
2. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. Pathology 2011; 43: pp 420-32.
3. Buys S, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening randomized controlled trial. JAMA 2011; 305: pp 2295-303.
4. Erickson BK, Conner MG, Landen CN. The role of the fallopian tube in the origin of ovarian cancer. Am J Obstet Gynecol 2013; 209: pp 409-14.
5. Piek JM, van Diest PJ, Zweemer RP, et al. Dysplastic changes in prophylactically removed fallopian tubes of women predisposed to developing ovarian cancer. J Pathol 2001; 195: pp 451-6.

6. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. Am J Surg Pathol 2007; 31: pp 161-9.
7. Przybycin CG, Kurman RJ, Ronnett BM, Shih IM, Vang R. Are all pelvic (non-uterine) serous carcinomas of tubal origin? Am J Surg Pathol 2010; 34: pp 1407-16.
8. Nezhat FR, Pejovic T, Reis FM, Guo SW. The link between endometriosis and ovarian cancer: clinical implications. Int J Gynecol Cancer 2014; 24: pp 623-8.
9. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carci- noma. Nature 2011; 474: 609-15.
10. Sherman ME, Piedmonte M, Mai PL, et al. Pathologic findings at risk-reducing salpingo-oophorectomy: primary results from Gynecologic Oncology Group Trial GOG-0199. J Clin Oncol 2014; 32: pp 3275-83.
11. Sampson JA. Endometrial carcinoma of ovary arising in endometrial tissue in that organ. Arch Surg 1925; 10: pp 1-72.
12. 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 2012; 7: pp 385-94.
13. Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis. Br J Cancer 2014; 110: pp 1878-90.
14. Agency for Healthcare Research and Quality. Management of adnexal mass. Evidence based report / technology assessment no. 130. AHRQ Publication no. 06-E004. Rockville, 2006.
15. Deligdisch L, Penault-Llorca F, Schlosshauer P, Altchek A, Peiretti M, Nezhat F. Stage I ovarian carcinoma: different clinical pathologic patterns. Fertil Steril 2007; 88: pp 906-10.
16. Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008; 371: pp 303-14.
17. Rosenblatt KA, Thomas DB. Reduced risk of ovarian cancer in women with a tubal ligation or hysterectomy. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Cancer Epidemiol Biomarkers Prev 1996; 5: pp 933-5.
18. Rice MS, Hankinson SE, Tworoger SS. Tubal ligation, hysterectomy, unilateral oophorectomy and risk of ovarian cancer in the Nurses Health Studies. Fertil Steril 2014; 102: pp 192-8.
19. Society of Gynecologic Oncology. SGO clinical practice statement: salpingectomy for ovarian cancer prevention. Chicago, IL: Society of Gynecologic Oncology; 2013.
20. Findley AD, Siedhoff MT, Hobbs KA, et al. Short-term effects of salpingectomy during laparoscopic hysterectomy on ovarian reserve: a pilot randomized controlled trial. Fertil Steril 2013 ; 100 : pp 1704-8.
21. Morelli M, Venturella R, Mocciaro R, et al. Prophylactic salpingectomy in premenopausal low-risk women for ovarian cancer: primum non nocere. Gynecol Oncol 2013; 129: pp 448-51.
22. Takeuchi M, Matsuzaki K, Uehara H, Nishitani H. Malignant transformation of pelvic endometriosis: MR imaging findings and pathologic correlation. Radiographics 2006; 26: pp 407-17.
23. Nezhat F, Nezhat C, Allan CJ, Metzger DA, Sears DL. Clinical and histologic classification of endometriomas. Implications for a mechanism of pathogenesis. J Reprod Med 1992; 37: pp 771-6.
24. Melin AS, Lundholm C, Malki N, Swahn ML, Sparèn P, Bergqvist A. Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer. Acta Obstet Gynecol Scand 2013; 92: pp 546-54.