Tzu Chi Medical Journal 25 (2013) 203–205

Contents lists available at SciVerse ScienceDirect

Tzu Chi Medical Journal

journal homepage: www.tzuchimedjnl.com

Review Article

The fallopian tube is the culprit and an accomplice in type II ovarian cancer: A review

Mun-Kun Hong [a,b], Tang-Yuan Chu [a,b], Dah-Ching Ding [a,b,*]

[a] Department of Obstetrics and Gynecology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan
[b] Institute of Medical Science, Tzu Chi University, Hualien, Taiwan

ARTICLE INFO

Article history:
Received 21 January 2013
Received in revised form
6 February 2013
Accepted 1 April 2013

Keywords:
Fallopian tube
Ovarian carcinogenesis
Salpingectomy

ABSTRACT

Ovarian cancer is the most lethal gynecologic malignancy in the world. The origin or the pathogenesis of epithelial ovarian cancer is poorly understood, which often leads to failure of early detection. Development of a new approach to reduce mortality is urgent. The fallopian tubes were once seen as an extremely rare site for cancer, but increasing evidence now suggests that they could be involved in initiation of the most aggressive ovarian carcinoma. As a result of evolution to prevent ectopic pregnancy, not only is the fallopian tube "poor soil" for carcinogenesis, but angiogenesis is also inhibited there. However, every cycle of ovulation results in changes in which tubal epithelial cells are dislodged and implanted on the denuded surface of the ovary, resulting in the formation of an inclusion cyst. This is the very beginning of serous ovarian carcinogenesis. To prevent ovarian cancer, a salpingectomy might be recommended during hysterectomy because this procedure can effectively reduce the incidence of ovarian cancer. Application of these new concepts will allow for a more rational approach to screening, treatment, and prevention, which could potentially have a significant impact in reducing mortality from this devastating disease.

1. Introduction

Ovarian cancer is the second most common gynecologic malignancy and the most common cause of gynecologic cancer death in developed countries [1]. Ovarian cancer is often diagnosed when the disease has spread, making it more difficult to treat. This poor prognosis has remained a major issue for the last 50 years. It was previously believed that 95% of ovarian malignancies were derived from epithelial cells, but it is now though that this concept is false according to numerous recent morphologic and molecular genetic studies. Epithelial ovarian cancer (EOC) has various histological types, including serous, mucinous, endometroid, transitional cell, and clear cell types. The question of why the epithelium of the ovary (mesothelium) can develop into tumors of different histological types has led to the proposal that ovarian cancer develops anew [2]. The subsequent question is where these cancer cells come from.

Kurman and colleagues divided ovarian tumors into two groups designated type I and type II [3]. Type I tumors are slow growing and are generally confined to the ovary on diagnosis. They develop from well-established precursor lesions, including low-grade micropapillary serous carcinoma, and mucinous, endometrioid, and clear cell carcinomas. By contrast, type II tumors are rapidly growing and highly aggressive neoplasms without well-defined precursor lesions. Type II tumors include high-grade serous carcinoma, malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinomas. This group of tumors has a high level of genetic instability and is characterized by mutation of *TP53*. Recent studies have shown strong evidence suggesting that what we thought were primary ovarian tumors in the past actually originated from other pelvic organs. It has been proposed that serous tumors arise from implantation of epithelium from the fallopian tube [4].

As a result of evolution to prevent ectopic pregnancy, not only is the fallopian tube "poor soil" for carcinogenesis, but angiogenesis is also inhibited there, which suggests why fallopian tube cancer is rare. By contrast, the ovary is "nourished soil", rich in blood supply and suitable for the survival of imported cells. This review article reports recent research findings on the cells of origin and pathogenesis in EOC. In addition, prevention methods such as prophylactic salpingectomy are discussed.

Conflict of interest: none.

* Corresponding author. Department of Obstetrics and Gynecology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien Taiwan. Tel.: +886 3 8561825x2107; fax: +886 3 8577161.
E-mail address: dah1003@yahoo.com.tw (D.-C. Ding).

1016-3190/$ – see front matter
http://dx.doi.org/10.1016/j.tcmj.2013.04.002

2. Epidemiologic evidence of the role of the fallopian tube and ovulation on EOC

To prevent ovarian cancer, tubal ligation was recommended for carriers of *BRCA1* or *BRCA2* mutations who have undergone childbirth [5]. Moreover, salpingectomy is strongly recommended by experts for women opting for tubal ligation [6]. A recent meta-analysis of 30 studies on correlation between tubal ligation and risk of ovarian cancer demonstrated a significant inverse association [7]. There is an approximately 26–30% decrease in ovarian cancer for women who have had a tubal ligation compared to those who have not had the procedure. In secondary analyses in the same study, the ovarian cancer risk was higher for endometrioid tumors (relative risk 0.45, 95% confidence interval 0.33–0.61) compared with serous tumors. This implies that the cells of origin for ovarian cancer travel to the ovary via the fallopian tubes. Functional or structural disorders of the fallopian tube cannot prevent retrograde movement of the cells of origin, so the fallopian tubes act as an "accomplice" in ovarian carcinogenesis.

According to numerous observational epidemiologic studies, ovulation plays a pivotal role in the very beginning of EOC pathogenesis. Both early menarche and late menopause have been associated with increased risk of EOC [8,9]. Women who have never gone through pregnancy seem to have an increased risk of EOC [10]. A decreased risk of EOC has been associated with women who have had a full-term pregnancy [10–12]. A higher ovarian cancer risk is also seen in women who are infertile [13,14] and in women who have endometriosis or polycystic ovarian syndrome. These studies demonstrate a significant positive correlation between the total number of ovulations and the risk of EOC: the higher the number of ovulations, the greater the risk of EOC.

3. Most EOC does not originate from the ovary

The theory of ovarian carcinogenesis has long been debated. The traditional view suggests that the cells of origin for different malignant ovarian tumors all arise from ovarian surface epithelium and subsequent metaplastic changes lead to various cancer cell types. In the embryonic development of the human reproductive system, the Müllerian ducts (or paramesonephric ducts) develop into the upper vagina, cervix, uterus, and fallopian tubes in females. The ovaries develop from mesodermal epithelium on the urogenital ridges separate from the Müllerian ducts. Therefore, it is quite unreasonable that ovarian cancer would have different cell types. Thus, it has been proposed that serous tumors arise from implantation of epithelium from the fallopian tube. It is assumed that endometrioid and clear cell tumors are related to endometriosis, which develops from endometrial tissue by retrograde menstruation. Thus, endometriosis is regarded as the precursor of endometrioid and clear cell tumors [4].

4. Histological and molecular evidence

Serous tubal intraepithelial carcinoma (STIC) is the earliest morphologically recognizable form of tubal high-grade serous carcinoma (Fig. 1). These precancerous or cancerous lesions in the fallopian tubes have long been ignored by pathologists. During the last few years, there has been a dramatic shift in attention to STIC. It is now considered the precursor of serous ovarian or peritoneal carcinoma [15,16]. It is particularly interesting that at least half of papillary serous peritoneal carcinoma cases are associated with STIC [16]. These tumors always exhibit abnormal immunohistochemical expression of p53 [17]. The p53 signature has recently been described and proposed as a precursor of STIC (Fig. 1). It can be characterized by p53 overexpression and low Ki-67 labeling. One study demonstrated that 57% of p53 signatures contain a *TP53* mutation, which is the most common gene mutation found in ovarian cancer [15].

High similarity in morphology and gene expression between fallopian tube epithelium and serous borderline ovarian tumors (SBT) further indicates the close relation between these two organs [18]. Both ciliated and secretory cells are found in SBT, similar to the fallopian tube epithelium. Paired box 2 (PAX2) is expressed throughout the female genital tract, particularly in secretory cells of the fallopian tube epithelium. Secretory cell outgrowths (SCOUTs) exist in the whole length of the fallopian tube. SCOUTs lacking PAX2 expression have been observed in benign fallopian tubes and are more common in the fallopian tubes of patients with SBT or high-grade serous cancer [19,20]. These findings do not definitively establish that SBT is derived directly from SCOUT, but there must be a relationship between these organs.

Another recent gynecological pathology study demonstrated that gene expression profiles of tubal and ovarian serous carcinoma are similar. p53 was highly expressed but PAX2 and phosphatase and tensin homolog (PTEN) expression was markedly reduced or absent in high-grade endometrioid and serous carcinomas of the ovary and in fallopian tubes [21]. These findings led to the conclusion that high-grade fimbrial–ovarian carcinomas all have altered p53, PTEN, and PAX2 regulation.

Dicer, an essential gene for microRNA synthesis and PTEN, is a key negative regulator of the phosphoinositol 3-kinas (PI3K) pathway. These genes related to fallopian tube cancer are also up- or down-regulated in human serous ovarian cancers, as mentioned above. Dicer–Pten double-knockout mice were successfully used to show that high-grade serous carcinomas arise from the fallopian

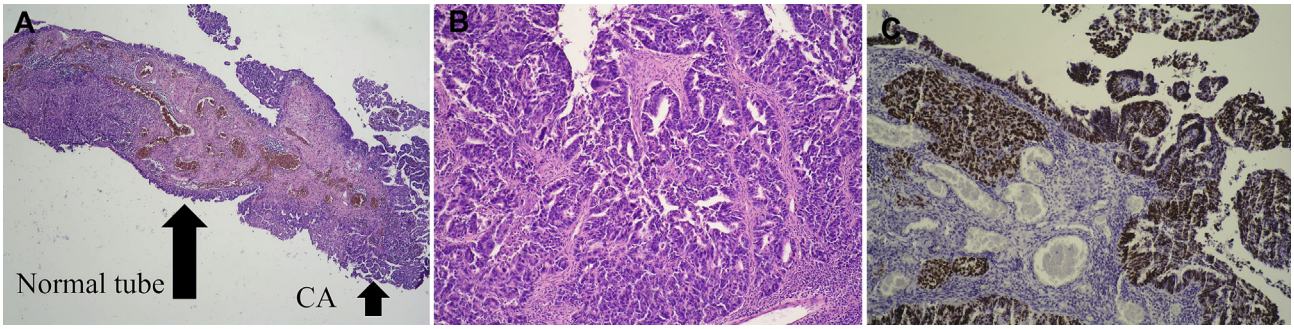

Fig. 1. Histologic and molecular evidence shows that ovarian cancer originated from the fallopian tube epithelium in this case. (A) Serous fallopian tube carcinoma (CA) was found in the lumen of the left fallopian tube (40×, hematoxylin and eosin staining). (B) Serous carcinoma of the ovary (200×). (C) Immunohistochemical stain for p53 over the fallopian tube cancer (brown color, 100×).

tube [22]. Primary fallopian tube tumors spread to engulf the ovary and then aggressively metastasized throughout the abdominal cavity, causing ascites and killing 100% of the mice. After removal of the fallopian tube at an early age there was no cancer formation, implying that the fallopian tube is the origin of ovarian cancer. Interestingly, primary carcinomas were first observed in the stroma of the fallopian tube, suggesting that these epithelial cancers have a mesenchymal origin. Thus, this mouse model represents a paradigm for the origin and initiation of high-grade serous ovarian cancer [22].

5. Prevention: performing salpingectomy during pelvic surgery

Given the obstacles in early detection (screening) and the significant but relatively limited success in treatment, attention should be directed to primary prevention. This takes on particular relevance with the recognition that the majority of ovarian carcinomas are derived from cells in the fallopian tube or from passage of endometrial tissue through the fallopian tubes, and the important role of ovulation in ovarian carcinogenesis. Salpingectomy alone may be sufficient to accomplish this, because removal of the fallopian tubes would reduce the risk of ovarian cancer while preserving ovarian function [23].

Any method that can reduce ovulation or prevent the passage of cells of "foreign origin" to the ovary or peritoneum should be encouraged, such as increased gravidity, breastfeeding, and routine bilateral salpingectomy or fimbriectomy during a hysterectomy. Instead of tubal ligation, bilateral salpingectomy is suggested to prevent this devastating cancer, even if a woman is not at high risk for ovarian cancer [6–9]. Moreover, to prevent premature ovarian failure caused by salpingectomy, the procedure should be performed carefully. The vessels supplying the fallopian tube include branches from the ovarian or uterine artery, which form arcades at the mesosalpinx and meso-ovary while also supplying the ovary. Therefore, complete excision of the tubes should be carried out with caution, starting with the mesosalpinx at the fimbrial end and performing ligation close to the fallopian tube as far as possible from the ovary. Ovarian blood flow and function can be preserved using this approach.

6. Conclusion

The fallopian tube is undoubtedly the site of origin of EOC. The fallopian tube also acts as a conduit, connecting the lower genital tract to the peritoneal cavity. Functional disorders of the fallopian tubes may even enhance retrograde endometrium or cervical cells, facilitating factors that induce local inflammation. Salpingectomy can reduce the incidence of ovarian cancer. All female patients should be given this information before receiving pelvic surgery and the patient herself should make the best treatment choice. Other approaches such as oral medication should also be explored based on these new insights into ovarian carcinogenesis. New diagnostic, prevention and therapeutic approaches should be developed based on our evolving understanding of ovarian carcinogenesis.

Acknowledgments

We thank Dr. Yung-Hsiang Hsu for help with the pathology images.

References

[1] Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–36.
[2] Bell DA, Scully RE. Early *de novo* ovarian carcinoma. A study of fourteen cases. Cancer 1994;73:1859–64.
[3] Kurman RJ, Shih IM. Pathogenesis of ovarian cancer: lessons from morphology and molecular biology and their clinical implications. Int J Gynecol Pathol 2008;27:151–60.
[4] Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 2010;34:433–43.
[5] Narod SA, Sun P, Ghadirian P, Lynch H, Isaacs C, Garber J, et al. Tubal ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet 2001;357:1467–70.
[6] Jenks S. Tying fallopian tubes to ovarian cancer risk. J Natl Cancer Inst 2012;104:578–9.
[7] Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: a meta-analysis. J Ovarian Res 2012;5:13.
[8] Tsilidis KK, Allen NE, Key TJ, Dossus L, Lukanova A, Bakken K, et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 2011;105:1436–42.
[9] Pieta B, Chmaj-Wierzchowska K, Opala T. Past obstetric history and risk of ovarian cancer. Ann Agric Environ Med 2012;19:385–8.
[10] Tung KH, Goodman MT, Wu AH, McDuffie K, Wilkens LR, Kolonel LN, et al. Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study. Am J Epidemiol 2003;158:629–38.
[11] Sueblinvong T, Carney ME. Current understanding of risk factors for ovarian cancer. Curr Treat Options Oncol 2009;10:67–81.
[12] Hemminki K, Granstrom C. Familial clustering of ovarian and endometrial cancers. Eur J Cancer 2004;40:90–5.
[13] Kashyap S, Moher D, Fung MF, Rosenwaks Z. Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis. Obstet Gynecol 2004;103:785–94.
[14] Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, et al. Ovarian cancer risk associated with varying causes of infertility. Fertil Steril 2004;82:405–14.
[15] Vang R, Shih IM, Kurman RJ. Fallopian tube precursors of ovarian low- and high-grade serous neoplasms. Histopathology 2013;62:44–58.
[16] Seidman JD, Zhao P, Yemelyanova A. "Primary peritoneal" high-grade serous carcinoma is very likely metastatic from serous tubal intraepithelial carcinoma: assessing the new paradigm of ovarian and pelvic serous carcinogenesis and its implications for screening for ovarian cancer. Gynecol Oncol 2011;120:470–3.
[17] Lee Y, Miron A, Drapkin R, Nucci MR, Medeiros F, Saleemuddin A, et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. J Pathol 2007;211:26–35.
[18] Marquez RT, Baggerly KA, Patterson AP, Liu J, Broaddus R, Frumovitz M, et al. Patterns of gene expression in different histotypes of epithelial ovarian cancer correlate with those in normal fallopian tube, endometrium, and colon. Clin Cancer Res 2005;11:6116–26.
[19] Laury AR, Ning G, Quick CM, Bijron J, Parast MM, Betensky RA, et al. Fallopian tube correlates of ovarian serous borderline tumors. Am J Surg Pathol 2011;35:1759–65.
[20] Chen EY, Mehra K, Mehrad M, Ning G, Miron A, Mutter GL, et al. Secretory cell outgrowth, PAX2 and serous carcinogenesis in the fallopian tube. J Pathol 2010;222:110–6.
[21] Roh MH, Yassin Y, Miron A, Mehra KK, Mehrad M, Monte NM, et al. High-grade fimbrial-ovarian carcinomas are unified by altered p53, PTEN and PAX2 expression. Mod Pathol 2010;23:1316–24.
[22] Kim J, Coffey DM, Creighton CJ, Yu Z, Hawkins SM, Matzuk MM. High-grade serous ovarian cancer arises from fallopian tube in a mouse model. Proc Natl Acad Sci U S A 2012;109:3921–6.
[23] Kurman RJ, Shih IM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer – shifting the paradigm. Hum Pathol 2011;42:918–31.