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Precursors of ovarian cancer in the fallopian tube: Serous tubal intraepithelial carcinoma – an update

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Abstract

Ovarian tumors comprise a wide variety of entities. The largest group, epithelial ovarian carcinoma, can be classified into two main groups, type I and type II tumors. Recent advances in the understanding of ovarian cancer development have resulted in the finding of ‘serous tubal intraepithelial carcinoma’, which is believed to represent the precursor lesion in high-grade serous ovarian carcinoma. In this review, lines of evidence for this are discussed and possible future implications for clinical and research settings are outlined.

Keywords

epithelial ovarian cancer; fallopian tube; high-grade serous carcinoma; precursor; serous tubal intraepithelial carcinoma

Introduction

Despite intensive research, advances in techniques and intransigency of surgery, and optimized cytotoxic chemotherapy regimens, the overall survival rate in ovarian cancer patients has not profoundly improved over the last few decades. This is largely due to the fact that patients are still diagnosed at advanced stages due to the lack of effective screening strategies.^{1,2} Fortunately, in recent years important progress has been made that has advanced our understanding of ovarian cancer and its potential precursor lesions that will hopefully improve the outcome in the future. Ovarian tumors comprise a very heterogeneous group of diseases. Four main categories can be distinguished: epithelial ovarian cancer (EOC), gonadal tumors (deriving from the ovarian stromal component), germ cell tumors (like dysgerminomas, choriocarcinomas, and teratomas deriving from the gametes), and metastatic neoplasms (classically from gastrointestinal tract tumors).³ EOC represent the most common type.

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Recent molecular genetics and morphologic studies have resulted in the proposition of a dualistic model to classify EOC, grouping them into two categories, designated types I and II.^{4,5} Type I tumors comprise low-grade serous, low-grade endometrioid, mucinous, and clear cell carcinomas. This type usually manifests large cystic masses confined to one ovary with a relatively benign course. They are thought to develop in a stepwise progression, similar to the adenoma carcinoma sequence in colorectal cancer: from benign lesions via atypia and precursor lesions to noninvasive borderline tumors, and invasive low-grade carcinoma. Typical mutations include *KRAS*, *BRAF*, *ARID1A*, *PTEN*, *PIK3CA*, *CTNNB1*, and *PPP2R1A*. Mutations in *BRCA1*, *BRCA2*, and *TP53* are rarely seen in type I tumors. Type II tumors comprise high-grade serous and endometrioid carcinomas, malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinomas. They are more aggressive and typically present in advanced stages. As high-grade serous tumors are the most common form, this review will focus on that group and describe the existing evidence for a tubal origin, rather than ovarian, for at least a majority of EOC.

Precursors in High-grade Serous Carcinoma

Several precursors have been proposed for EOC. Originally EOC have been thought to arise from ovarian surface epithelium (OSE). The OSE forms a single layer of epithelium covering the ovarian germ and stromal cells. It is a form of mesothelium, morphologically and histochemically identical to the peritoneal epithelium, with which it is continuous. Both share a common embryonic origin deriving from the mesonephros. The fallopian tubes, endometrium, endocervix, and upper vagina are related to the paramesonephros (Müllerian duct). In the ovarian cortex, small cysts can be found. They are termed ‘cortical inclusion cysts’ (CIC) and are thought to develop from invaginations of the OSE. Investigators hypothesized that ovarian cancer might originate from those OSE cells that form CIC. Also, it has been known for a long time that the number of ovulations is linked to ovarian cancer development. Epidemiologic studies reproducibly showed that the number of lifetime ovulations correlates with the risk of ovarian cancer.^{6–8} Parity and oral contraceptive use are both associated with a lower risk of ovarian cancer. In 1971, Fathalla proposed his theory of ‘incessant ovulation’.⁹ With this concept, it is argued that the rupture of the OSE during consecutive bouts of ovulation cause DNA damage and can eventually induce neoplastic transformation of the OSE and/or the CIC.

As EOC cells show a Müllerian phenotype (in fact the term ‘serous’ in high-grade serous ovarian carcinoma [HGSC] can be attributed to the morphologic resemblance of tumor cells to the fallopian tube epithelium), the (mesonephric) OSE must undergo metaplastic changes during carcinogenesis. Convincing evidence for this event however is lacking. Although numerous studies have explored the ovaries for possible precursor lesions of ovarian cancer, none have been found. Tumors arising from the fallopian tube had already been described in the 1950s,¹⁰ but it was not until the 2000s that the important role of fallopian tube epithelium in ovarian tumors carcinogenesis was further investigated. In 2001, Piek *et al.* described hyper or dysplastic changes in the fallopian tubes of women who underwent risk-reducing bilateral salpingo-oophorectomy (RRBSO) due to a known *BRCA1* mutation. The changes were similar to high-grade serous carcinoma and only found in the fallopian tubes

but not in the ovaries.¹¹ These changes did not exist in the control group of women who had salpingectomies for benign causes.

This forwarded the use of the ‘Sectioning and Extensively Examining the Fimbriated End’ (SEE-FIM)-protocol or similar protocols in pathologic practice that ensure the careful evaluation of the fallopian tube, especially the fimbriated end, which is found to be the most common site of serous tubal intraepithelial carcinoma (STIC).¹² The morphological characteristics of STIC are: disorganized, pleomorphic, hyperchromatic, and enlarged epithelial cells with highly atypical nuclei (overview in Kurman¹³) (Fig. 1).

With regards to terminology, some authors have suggested the use of the term ‘high-grade tubal intraepithelial neoplasm’ (HGTIN) instead of STIC.¹⁴ The term tubal intraepithelial carcinoma (TIC) has also been used synonymously. Furthermore, there is some overlap with the term TILT for serous tubal intraepithelial lesions in transition. In addition, cellular outgrowths in the whole tube, including the proximal part without p53 mutation, have been termed secretory (stem?) cell outgrowths (SCOUT). As they are believed to be associated with HGSC but not directly participating in carcinogenesis, they are supposed to be best viewed as ‘surrogate precursors’ (overview in Crum *et al.*¹⁵). Use of the term ‘pelvic serous carcinoma’ has been suggested due to the fact that HGSC of the ovary, fallopian tube carcinoma, and primary peritoneal carcinoma seem to share the same pathogenesis and molecular biomarkers.

The actual frequency of STIC in asymptomatic BRCA mutation carriers, based on two retrospective studies from Europe and the USA with over 350 patients each, is estimated to be between 2% and 6%.^{14,16} The latter group hypothesizes that the difference in frequencies might be based on the cohort age, as they demonstrate that the detection frequency for precursors/neoplasia in asymptomatic BRCA-mutation carriers increases with age.¹⁴ It appears that in line with the earlier age at onset of disease in BRCA1 carriers versus BRCA2 carriers, the same pattern holds true for STIC detection. The mean age of asymptomatic BRCA1 patients with detection of STIC was younger than that of BRCA2 patients. The STIC frequency in non-BRCA mutation carriers is estimated to be much lower, but is difficult to evaluate. This can be attributed to several reasons. To date, it has not become common practice to perform salpingectomy in female sterilization procedures or hysterectomies performed for benign reasons. Also, the protocols with thorough pathologic examination of the tubes in non-risk populations are labor-intensive and have not reached the status of common practice in a nationwide setting.

Fallopian Tubes as Site of Origin of HGSC

Several lines of evidence support the tube as the site of origin of HGSC. STIC are not only found in specimens of high-risk patient populations like the BRCA1-carriers but also in up to 60% of sporadic cancer cases.^{17–19} Interestingly, in documented RRBSO-specimens from high-risk cases so far, only STIC in the fallopian tubes have been found but never intraepithelial carcinoma in the ovaries.²⁰ STIC and HGSC are clonally related as they harbor the same TP53 mutations.^{21,22} Apart from TP53, STIC express tumor-associated

oncoproteins like fatty acid synthase, Rsf-1, and cyclin E1, which is rarely seen in the adjacent normal tubal epithelium.²³

The gene expression profiles of HGSC resemble the fallopian tube profile more than the OSE. This can be seen on the protein level, as immunohistochemistry analysis shows that HGSC stain positive for PAX8, a Müllerian marker, but negative for calretinin, a mesothelial marker. A recent study in genetically engineered mice further corroborates these findings; the authors were able to drive Cre-mediated recombination of *BRCA1* or *BRCA2*, *TP53*, and *PTEN* in murine fallopian tube cells. Following this, STIC-like lesions formed and HGSC invaded the ovaries and the peritoneum in these mice. Apart from being a good model for further research, including therapeutic studies for *BRCA*-mutation carriers, this serves as a proof-of-concept that HGSC can arise from fallopian tube cells.²⁴

To support the hypothesis that the fallopian tubes are actually the primary site of origin and not of secondary involvement and that STIC formation is an early event in carcinogenesis, examination of the telo-mer length revealed telomere shortening in STIC compared to the adjacent normal tubal epithelium.²⁵ Telomere shortening is known as a main genetic manifestation in cancer. Interestingly, the telomeres in STIC were even shorter than in the corresponding HGSC, underpinning the idea of STIC formation as an early event in carcinogenesis.

Despite these evidences supporting the fallopian tube and STIC as the precursor lesions in many HGSC, there still remain several uncertainties and questions to be answered.

Even if STIC can be found in up to 60% of sporadic HGSC, what about the remaining 40% of cases? It might be argued that in some cases, the original STIC site has been overgrown by the tumor. Some might not have been found and missed by leveling, although careful examination was ensured. It might also be that there is an alternative pathway leading to HGSC. It still remains possible that some of the STIC that are associated with HGSC are in fact the lateral dissemination or spread from the adjacent HGSC (Fig. 2). As aforementioned, metaplastic changes could cause OSE cells to become tube-like. It remains uncertain which steps happen between STIC development and tumor formation in the ovaries or the peritoneum. Are STIC-cells shed from the fallopian tube and then floating through the peritoneal cavity, attaching to the best tumor bed in sight? And if so, why do ovarian cells serve as the preferred location? Is it only due to the anatomically close relationship between the fallopian tube and the ovaries or do other factors play a role?

Despite possible advances and potential early detection of STIC, it must be noted that no valid data exist on patients that show STIC but no adjacent carcinoma.²⁶ Is it sufficient to remove the STIC-bearing fallopian tube? Do patients need additional treatment, for example, intensive peritoneal washings during surgery or even cytotoxic therapy? First estimations for STIC alone estimate a 9% recurrence rate (one of 11 patients) in a 5-year follow-up.¹⁴ Another study did not record any recurrence in 12 STIC in a shorter follow-up.²⁶ Of course, these data are still insufficient for a general clinical recommendation, but so far it does not urge to support prophylactic cytotoxic therapy for isolated STIC.

Also, it should be mentioned that for the less common ovarian endometrioid and clear cell carcinomas, precursor lesions are thought to be originally derived from endometrial cells. It is hypothesized that retrograde menstruation and implantation of endometrial cells, possibly forming endometriosis nests, can lead to cancer formation. This is supported not only by studies showing that tubal ligation or tubal removal can decrease the cancer risk of these subtypes, but also by studies demonstrating the clonal relation between tumor cells and endometriosis cells with the same mutations in *ARID1A*.^{27–29}

Implications for Research and Clinical Practice

Accepting an extraovarian origin for many if not all EOC will have a profound impact on future research and on clinical management, especially regarding early detection and prevention of HGSC. Although preventive strategies in BRCA-mutation carriers have been adjusted over recent years, the general principle still remains to recommend RRBSO before the age of 40 with all the impact not only on fertility but also effects on bone and heart health as consequence of iatrogenic early menopause. A fallopian tube origin of ovarian cancer could allow treating physicians to perform salpingectomy without the removal of the ovaries during the reproductive age. Oophorectomy could be delayed until after menopause or even omitted completely.³⁰ The effectiveness of such strategies should of course be monitored in a study setting. The advances in assisted reproductive technologies even promise high success rates in conceiving after having such a procedure performed early in adulthood. For sterilization procedures performed, from a cancer prevention perspective, salpingectomy should be preferred over tubal ligation procedures. Also, concurrent salpingectomy at the time of hysterectomy in women with low risk for ovarian cancer has been advocated for by some providers while others quote potential risks of decreased ovarian blood supply and consecutive earlier menopause with its impact on bone and cardiovascular health or psychiatric well-being. A recent pilot study supporting the former could demonstrate that anti-Müllerian hormone (AMH) levels did not change 3 months after hysterectomy with or without salpingectomy, indicating no change in ovarian reserve as a surrogate for onset of menopause.³¹ Similar results could be demonstrated in a retrospective study setting.³² Although data on cancer-risk-reducing effects as well as longer follow-up are still needed, we believe the potential benefits and risks of salpingectomy should be discussed with all suitable patients and should be best performed within the setting of a clinical trial.

With a better understanding in STIC development, new and better biomarkers for screening purposes can be envisioned. Although in their infancy, newly developed techniques in detecting the smallest fragments of tumor DNA, even in noninvasive examining techniques, like liquid-based pap-smears, reveal promising results considering future detection of cancer and in the long run maybe even ovarian cancer precursors.³³ This could help in identifying high-risk patients who do not carry the known cancer-associated gene mutations, like *BRCA1* or *BRCA2*, and include them in risk-reducing (ovarian preserving) preventive and treatment strategies. Without the right tools to detect ovarian cancer precursors yet, seeking answers to questions such as why STIC develop in the tube holds potential targets for preventive strategies; there may be signaling molecules or pathways that can be targeted and blocked.

To address the knowledge deficit and perhaps improve research efficacy, new models must be considered. Currently, animal models used to study ovarian cancer have mainly used rodents, especially mice. As mouse anatomy in the ovarian region with the ovarian bursa, a thin layer surrounding the ovary and the oviduct, is slightly different from the situation in humans, it is worthwhile to even look for more equivalent models.³⁴ For example, it has been shown that a hen model, although much more labor-intensive, develops ovarian adenocarcinomas with morphological features similar to human ovarian cancer.^{35,36}

Even with different approaches and recent breakthroughs, it remains to be determined what factors originally cause ovarian cancer. A huge portion of epithelial cancer has been linked to certain infectious events,³⁷ with one of the major success stories of recent medicine developments seen in gynecologic cancers by preventing precursor lesions of cervical and vulvar cancer using the HPV-vaccination. Data for long-term effects in decreasing cancer incidence are expected within the coming decade. Also, epidemiologic studies show a preventing effect of NSAID use for ovarian cancer.³⁸ As we know that the use of oral contraceptives can result in the prevention of many ovarian cancer cases, their use, coupled with NSAID/aspirin, needs to be re-evaluated in terms of possible preventive strategies. In this regard, apart from improving screening strategies, more effort is needed to improve our etiologic knowledge and with this, therapeutic and preventive approaches.

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Figure 1. Morphologic features of serous tubal intraepithelial carcinoma (STIC). (a) Hematoxylin–eosin stain shows a focal epithelial proliferation but no invasion is detected. (b) Immunostaining with an anti-p53 antibody demonstrates STIC cells are diffusely and strongly positive, suggesting a TP53 missense mutation in this STIC.

Figure 2. p53 staining of a high-grade serous carcinoma and associated serous tubal intraepithelial carcinoma (STIC). It is uncertain if the STIC develops into the invasive carcinoma or the ‘STIC’ represents a lateral extension and intraepithelial growth from the adjacent high-grade serous carcinoma.