Review Article

Advances in serous tubal intraepithelial carcinoma: correlation with high grade serous carcinoma and ovarian carcinogenesis

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Abstract: Early serous carcinoma in fallopian tube or serous tubal intraepithelial carcinoma (STIC), an early lesion limited to the epithelium of the fallopian tube and firstly identified from specimen obtained by prophylactic salpingo-oophorectomy, has provided insight into pelvic high grade serous carcinoma (HGSC). Increasing evidence indicates that STIC is a likely precursor for HGSC and several studies have focused on this lesion and its clinical significance. This review addresses recent advances in recognizing STIC and its correlation with HGSC and ovarian carcinogenesis. It also describes evidence regarding the fallopian tube as a source of some HGSCs, the protocol for optimizing histological evaluation of the tubes, the spectrum of tubal lesions from benign to noninvasive carcinoma, changes in diagnostic criteria from purely morphologic characteristics to a combination of morphologic features and molecular biomarkers, and new studies about potential biomarkers. However, the direct evidence regarding STIC as the precursor of HGSC is still tantalizing due to other possibilities that may also explain the origin of pelvic HGSC. Further molecular genetic studies are required to address this important question.

Keywords: Serous tubal intraepithelial carcinoma, fallopian tube, high grade serous carcinoma, ovarian cancer, carcinogenesis

Introduction

Pelvic high-grade serous carcinomas (HGSCs), including ovarian, tubal, and “primary” peritoneal carcinomas, receive much attention from clinician and researchers because of their usually advanced stage at presentation, rapid progression, poor prognosis, and high fatality rate. Theories about the origin of these cancers are controversial. Serous tubal intraepithelial carcinomas (STICs), a lesion limited to the epithelium of the fallopian tube and first identified from specimens obtained by prophylactic salpingo-oophorectomies, have provided some insight into HGSCs. Accumulating evidence suggests that the distal fallopian tube is a potential primary site of the origin of primary ovarian or pelvic carcinoma. Many studies have focused on STIC and its clinical significance. So this review addresses recent advances in this field.

Definition of STIC

STIC is a lesion limited to the epithelium of the fallopian tube. Normal fallopian tube consists primarily of two types of epithelial cells, ciliated and secretory. The histologic diagnostic criteria of STIC are as follows: a discretely different population of malignant cells replacing the normal tubal epithelium; disorganized growth pattern and lack of cell polarity without ciliated cells; in malignant cells, elevated nuclear-to-cytoplasmic ratio with more rounded nuclei; marked nuclear pleomorphism with prominent nucleoli; and...
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high mitotic index and sometimes abnormal mitotic figures [1].

STICs were first observed in distal fallopian tubes (fimbria) prophylactically removed from women at high risk of developing ovarian cancer because of BRCA mutations [2, 3]. Several studies of risk-reducing salpingo-oophorectomies in women with BRCA1/2 mutations or a strong history of ovarian cancer have identified the fallopian tube as a frequent source of early serous carcinoma; about 10-15% of fallopian tube STICs have been detected in this way [4-8]. In addition, STICs are detected in 50-60% of cases of sporadic pelvic HGSCs (ovarian, tubal, or “primary” peritoneal carcinomas) [9, 10].

Clinical significance of STIC and correlation with HGSC

Generally, HGSCs are classified according to their clinical location. Lesions in the ovaries, fallopian tubes, and peritoneum are called pelvic HGSCs. These pelvic lesions frequently involve mutations of the p53 tumor suppressor gene and typically evolve quickly, often in the absence of a definitely preexisting benign precursor condition [11]. Because of their propensity for rapid peritoneal spread, serous carcinomas are the most lethal form of pelvic cancer [12].

The principal criteria for distinguishing HGSCs are the tumor distribution pattern and the presence or absence of a precursor lesion. Because a precursor condition is usually absent, ovarian and peritoneal serous carcinomas are mainly classified by pathologists on the basis of tumor distribution. Large ovarian tumors with parenchyma involvement are usually designated as ovarian, whereas tumors with little or no ovarian surface involvement or with a dominant tubal mass (or both) are termed “peritoneal primaries”. However, assignment of a primary site for a pelvic serous tumor is frequently made in the absence of a defined precursor lesion, so the classification of these tumors- and the interpretation of sophisticated studies attempting to distinguish these groups are often subject to error [13].

Before it becomes invasive, HGSC is believed to have a poorly defined precursor lesion that develops de novo [14]. Three origins for HGSC have been proposed: the ovarian surface epithelium or Müllerian inclusions, fallopian tube mucosa, and Müllerian epithelium elsewhere in the peritoneal cavity [15]. A widely accepted theory was that HGSC arises from Müllerian metaplasia of the ovarian surface epithelium or subcortical epithelial inclusions and that it develops as a function of genotoxic stimuli introduced to this epithelium during the reproductive years [16]. This model can explain some forms of ovarian cancer, although an ovarian precursor to HGSC has not been demonstrated, and the theory has not been universally accepted. At one time, the diagnostic criteria of primary tubal serous carcinoma were relatively restrictive: the mass had to lie in the fallopian tube, the tumor’s histological appearance had to reflect features of the tubal epithelium, the ovaries and uterus had to be normal or contain less tumor than the fallopian tube did, and a transition from benign to malignant epithelium had to be apparent [17]. According to these strict criteria, tubal carcinoma is very rare and accounts for only 0.3% of malignant gynecologic tumors. Coexisting intraepithelial carcinoma is a prerequisite for a diagnosis of primary tubal carcinoma, but it is rarely reported in serous carcinomas directly attributed to the ovary or peritoneum [16, 18], perhaps because it is difficult to identify the anatomic structure in HGSCs classified as ovarian or peritoneal primaries (due to the large mass or diffusely spread pattern). It is likely that some tubal lesions may be missed due to limited sampling.

Accumulating evidence suggests that the distal fallopian tube is a primary site of the origin of primary ovarian or pelvic carcinoma. For this reason, STIC is considered a potential precursor lesion of pelvic HGSC. STICs are detected in more than half of cases of sporadic pelvic HGSCs (ovarian, tubal, and “primary” peritoneal) [9, 10] and in approximately 10-15% of fallopian tubes prophylactically removed from women at high risk of developing ovarian cancer because of BRCA mutations [4-8]. Kindelberger et al [13] reported that tumors classified as primary ovarian serous carcinomas often involve the endosalpinx (30/42, 71%), and that many of these tumors (20/42, 48%) contain STICs. Przybycin et al [10] studied 45 cases of consecutive pelvic carcinomas and identified STICs in 59% of HGSCs but not in any of the other subtypes; among these HGSCs, all
would have been classified as ovarian or peritoneal in origin according to conventional criteria on the basis of disease distribution (i.e., sufficient ovarian tumor or extensive peritoneal tumor). In a study of 300 consecutive gynecologic cases performed by Tang et al [1], the frequency of detected STICs differed by the type of malignancies: 6/32 (19%) of ovarian serous carcinomas, 4/28 (14%) of endometrial serous carcinomas, and 2/7 (28%) of peritoneal serous carcinomas. No STICs were identified among non-gynecologic malignancies, benign conditions, or other types of malignancies of the ovaries, endometrium, or cervix. The results from this study indicated that STICs were associated with only serous carcinomas of peritoneal, ovarian, or endometrial origin and not with any other non-serous lesions such as endometrioid, clear cell, or mucinous carcinomas [1]. Thus, STIC may be the earliest morphologically recognizable form of pelvic HGSC, and the fallopian tube may be the origination site of many pelvic HGSCs.

In cases with concordant STICs and ovarian HGSCs, identical TP53 mutation in both STICs and the associated ovarian neoplasms has been demonstrated, indicating that the two lesions are clonally related [19, 20]. STICs and HGSCs also have in common some up-regulated oncogene products, such as cyclin E1, fatty acid synthase, and Rsf-1, which provide molecular evidence about the correlation between these carcinomas [21]. Moreover, STICs have been found to contain relatively shorter telomeres than normal-appearing fallopian tube epithelium (FTE) do, as occurs in precursor lesions of other cancer types [22]. These findings and the presence of STICs in prophylactic salpingectomy specimens in the absence of carcinoma are among the most important pieces of evidence that argue against the view that STIC represents lateral extension or metastasis from adjacent HGSC.

Kim et al [23] provided an in vivo progression model of HGSC that began with lesions in the fallopian tube and then spread to the ovaries, ultimately leading to widespread peritoneal metastases and death. In that study, they used a double-knockout genetic mouse model in which Dicer, an essential gene for microRNA synthesis [24], and PTEN, a key negative regulator of the PI3K-Akt signaling pathway [25], were selectively inactivated throughout the Müllerian tract. All the animals eventually developed fallopian tube serous carcinomas that spread to the ovaries and metastasized throughout the peritoneal cavity to cause death. No ovarian cancer developed if the oviduct had been removed at an early age, indicating that surgical removal of the oviduct might prevent cancer from developing in the ipsilateral ovary. In addition to the clinical resemblance to human serous cancers, these fallopian tube cancers in the mouse model highly expressed genes known to be up-regulated in human serous ovarian cancers, thereby demonstrating molecular similarities [23].

In summary, STIC is a new model for studying ovarian and pelvic HGSCs [7]. Because HGSC represents approximately 70% of all ovarian cancers and accounts for the vast majority of deaths from this disease, this model has profound implications for disease prevention and early detection.

Fallopian tube sampling for STIC

Accurate diagnosis of STIC has important management implication not only for specimens from prophylactic removal but also for patients with existing gynecologic malignancies. Comprehensive examination of the fallopian tubes is critical to maximize the identification of possible STIC lesions. In the past, randomly sections obtained provide not enough information because of lack of representative. Embedded the fimbria alone can detect most lesions but not all STICs.

To solve the problem about limitation of previous sampling, Lee et al [26] developed a protocol for sectioning and extensively examining the fimbriated end (SEE-FIM) to maximize the proportion of the fallopian tube mucosa that is accessible for microscopic examination. In this protocol, the ampullary portion is sectioned at 2- to 3-mm intervals and the infundibulum is amputated and sectioned longitudinally to maximize exposure of the fimbrial mucosa. The latter procedure increases the longitudinal surface area of the fimbria that is examined by approximately 60% versus conventional serial cross-sectioning. The SEE-FIM protocol emphasizes the importance of sampling of fimbria. First, the fimbria is the closest portion to the ovarian surface. If there is a definite relationship between the tube and ovarian carcinogen-
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esis, the portion of the tube closest to the ovarian surface deserves the most attention. Second, the fimbria is an area of epithelial-to-mesothelial transition and may differ in biology by its juxtaposition to the peritoneal cavity. Third, the fimbria contains a larger surface area than the more proximal tube does, and thorough exposure of this area is facilitated by longitudinal sectioning of the infundibulum and the fimbria.

Even so, Mahe et al [27] also point out that SEE-FIM as described was only about 75% effective in detecting fimbrial or tubal lesion upon further resectioning of the samples. For the cases with ovarian serous carcinoma who received neoadjuvant chemotherapy, multiple deeper sections should be examined if the initial hematoxylin and eosin (H&E) sections are negative.

Diagnostic problem of STIC

It is crucial to identify potential lesions from fallopian tubes, especially for patients who undergo prophylactic salpingo-oophorectomy because of a high risk of developing cancer (due to a family history of ovarian cancer, or germline mutations of BRCA1/2). With the use of the SEE-FIM protocol and immunohistochemistry, a variety of lesions ranging from benign to malignant have been encountered, representing a continuous spectrum of disease. Among these lesions, three in particular need to be taken into consideration. The first lesion is secretory cell outgrowth (SCOUT), an entity first described by Crum et al [28], which contains a discrete expansion of at least 30 epithelial cells of secretory type (BCL2 positive, p73 negative). This lesion shares aberrant expression of some markers (PAX2 loss), but do not overexpress p53 [29]. Another is the p53 signature, which has normal-appearing tubal epithelium without atypia, overexpressed p53 and a low Ki-67 proliferation index [20]. The last is serous tubal intraepithelial lesions (STIL), which display cyto-logic atypia but fall short of STIC; the nature of this lesion and its relationship to STIC have not been clearly established [5, 30-32].

The existence of such borderline lesions mentioned above (p53 signature, SCOUT, STIL) has posed additional considerable challenge in the diagnosis and differential diagnosis of STIC, and therefore reproducible diagnostic criteria for these types of lesions are required. The current diagnosis of STIC depends mainly on morphologic features and lacks reproducibility. This problem was highlighted in a morphology-based study by Carlson et al [33], who demonstrated that this diagnosis is not optimally reproducible on the basis of only histologic assessment, even among experienced gynecologic pathologists [33, 34]. This issue has serious implications for both clinical management and research.

To address this problem, Visvanathan and Vang [34, 35] developed a diagnostic algorithm by combining morphologic features and immunohistochemically determined expression levels of p53 and Ki-67, thereby substantially improving the reproducibility of diagnosis among pathologists, not only for experienced gynecologic pathologists but also for trainees. In their algorithm, the histologic features are evaluated first, and a morphology-only diagnosis of unequivocal, suspicious, or not suspicious for STIC is established. Then, for histologically atypical lesions (unequivocal or suspicious for STIC), immunostains are used in areas that correspond to the atypical focus. If the focus shows at least 75% of cells with moderate-to-strong expression or a 0% (completely negative) labeling index, p53 expression is interpreted as positive. Ki-67 expression is considered low when less than 10% of cells show staining and high when 10% or more show staining. Finally, the lesion is categorized as STIC (Figure 1, left column), STIL, p53 signature (Figure 1, middle column), or normal/reactive. Overall consensus (between at least four of six pathologists) in these four categories was achieved for 76% of the lesions assessed using this method [35]. Combining the diagnoses into two categories (STIC versus non-STIC) resulted in an overall consensus of 93%, which greatly improved the diagnostic reproducibility for tubal mucosal lesions and may be very useful in standardizing their classification.

STIC and HGSC biomarkers

In light of the lack of reliable criteria and reproducibility of using morphology to identify STICs, molecular studies are required to confirm the role of STIC as a precursor lesion. Identifying molecules that are up-regulated in STIC is meaningful, not only for providing biomarkers to assist in the diagnosis of STIC but also for
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our further understanding of the pathogenesis of HGSC.

p53

One of the most important useful markers for STIC is p53. It is well known that TP53 mutations play a critical role in the development of several human cancers [36, 37], including ovarian HGSCs, for which they occur in more than 95% of cases [38, 39]. Crum et al proposed a sequential model of HGSC: progression from a precursor with the p53 signature to STIC and thence to invasive carcinoma [7, 20, 26, 40]. TP53 mutations, which have been recorded for the majority of known STICs, likely represent one of the earliest events in initiating pelvic HGSCs [41]. Kuhn et al [19] undertook a mutational analysis of pelvic HGSCs with concurrent STICs which showed that somatic TP53 mutations were detectable in all 29 HGSCs and that identical mutations were detected in 27 of 29 pairs of STICs and concurrent HGSCs. These results support the idea of a clonal relationship between STICs and pelvic HGSCs. Moreover, the authors found that strong diffuse staining correlated with a missense TP53 mutation, complete absence of staining correlated with null TP53 mutations, and weak and patchy staining generally corresponded to wild-type TP53. Overall, this p53 staining pattern yielded a sensitivity of 87% and a specificity of 100% in detecting TP53 missense mutations, demonstrating the utility of p53 immunostaining as a surrogate for TP53 mutation in the histologic diagnosis of STIC [19]. Other researchers have correlated p53 protein expression with TP53 mutation in ovarian HSGC, indicating that
immunohistochemical staining patterns of p53 can serve as a marker for TP53 mutations in ovarian carcinoma as well [42-44].

However, the p53 immunostaining pattern does not always correlate with TP53 mutations. In fact, although an intense and diffuse p53 immunostaining pattern correlates with nonsense TP53 mutations, approximately 40% of STICs are p53 negative due to frameshift, nonsense, or splicing junction mutations of TP53 [19]. In addition, negative staining for p53 could be mistakenly interpreted as an absence of a TP53 mutation. Mutational analysis, which necessitates laser capture microdissection, would be a better approach, although it is not feasible in routine pathology practice. Piek et al [32] described the dysplastic change in fallopian tubes of pure secretory cell segments with a high proliferation index, but only 12.5% of the cells were immunoreactive for p53, suggesting that the p53 signature is a useful but not sensitive marker. Identification of other molecular markers for detecting precursor lesions is desirable.

Laminins

Laminins are extracellular matrix glycoproteins composed of three types of chains, α, β, and γ. Five α, four β, and three γ chains have been identified; their combination results in the 16 known heterotrimeric laminin isoforms. Laminins have been described in a wide variety of biological and pathologic processes, including tissue development, tumor cell invasion, and metastasis [45-48].

In another study by Kuhn et al [49], HGSC and normal FTE transcriptomes were compared by applying RNA sequencing and reverse transcription-polymerase chain reaction. The results showed that LAMC1, which codes for lamininγ1, is upregulated in HGSC as compared with normal FTE. Further immunohistochemical analysis of 32 cases with concurrent HGSC and STIC revealed that lamininγ1 immunostaining intensity was significantly higher in STICs and HGSCs than in adjacent FTE in all cases. In addition, the staining pattern was different between normal tissue and malignancies: lamininγ1 immunoreactivity in normal FTE was predominantly localized in the basement membrane or on the apical surface of ciliated cells, whereas in STIC and HGSC, lamininγ1 staining was diffuse and intense throughout the cytoplasm (involving both membrane and cytoplasm). This pattern suggested a similar mechanism of altered lamininγ1 production is operative in both lesions. More important, strong lamininγ1 staining was detected in all 13 STICs that lacked p53 immunoreactivity because of null mutations [49]. Thus, overexpression of lamininγ1 and a distinct staining pattern in STIC could serve as a useful supplementary biomarker, especially for STICs that are negative for p53 and have a low Ki-67 labeling index.

The similarity of lamininγ1 expression in STIC and HGSC suggests that upregulation of lamininγ1 may alter the microenvironment of premalignant and malignant tubal epithelial cells, conferring a competitive growth advantage and leading to tumor progression. The detailed mechanisms by which lamininγ1 facilitates tumor progression remain to be determined, but the expression of this protein might contribute to the detachment, protection from anoikis (detachment-induced cell death), and dissemination of STIC cells to ovaries and peritoneal surfaces. Moreover, adhesion of cancer cells to the peritoneal mesothelium is a key step in the malignant progression of this disease. Accordingly, upregulation of lamininγ1 may play an important role in tumor spread by promoting adherence of STIC cells to peritoneal surfaces, as mesothelial cells express abundant laminin receptors such as α3β1 integrin [50-52].

HMGA2

High-mobility group AT-hook 2 (HMGA2), a non-histone nuclear binding protein, has an important role in regulating cell growth and differentiation [53, 54]. It is also an oncofetal protein, overexpressed in embryonic tissue and many malignant neoplasms [54], including ovarian cancer [55-57], but rarely in normal adult tissues [58, 59]. HMGA2 overexpression has been associated with tumor growth [60], differentiation [56, 61], metastasis [62], unfavorable outcome, and resistance to treatment [63-65]. Silencing of HMGA2 expression in ovarian cancer cells has a therapeutic effect on ovarian cancer growth [55]. HMGA2 overexpression is an early genetic event in animal models of RAS-induced ovarian cancer [55, 56].

HMGA2 is weakly and occasionally moderately immunoreactive in normal FTE, exclusively
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locating in ciliated cells and not in secretory cells [59]. Wei et al. [66] examined HMGA2 and p53 expression in HGSCs and STICs by immunohistochemistry, which revealed that tumor cells in more than two thirds of STIC patients were immunoreactive for HMGA2, p53, or both but that only a small proportion were negative for either HMGA2 or p53. The rate of HMGA2-positive STIC (75%) was slightly higher than that of p53-positive STIC (71%). The rate of HMGA2 positivity (87.5%) was slightly higher than that of p53 positivity (75.0%) in the invasive carcinoma component with STICs. But by using both HMGA2 and p53, 92% of STICs could be detected [66]. Thus, HMGA2 could be a valuable marker complementary to p53 in detecting precursor or early serous carcinoma arising from the fallopian tube. This study established a link between HMGA2 and HGSC tumorigenesis and provided a possible tool for diagnosis of early ovarian cancer. Just like the terminology of “p53 signature”, they defined the HMGA2 signature with criteria similar to those of the p53 signature previously described [67]: the presence of moderate-to-strong immunoreactivity for HMGA2 in more than 20 consecutive secretory cells in the fallopian tube showing no more than moderate cytologic atypia and no intraepithelial proliferation (Figure 1, right column).

Summary

Increasing evidence points to STIC as a likely precursor for some HGSCs; however, it is important to note that not all cases of HGSC are associated with STIC [1], and other possibilities may explain the origin of pelvic HGSCs. Jarboe et al. [68] put forward a novel hypothesis that noninvasive, genetically related serous carcinomas coexist in both the tube and endometrium, suggesting that another possible origin of serous ovarian cancer may be found in the uterus. Another study [69] found that the stem cell niche of the hilum ovarian surface epithelium showed increased transformation potential after inactivation of tumour suppressor genes Trp53 and Rb1, whose pathways were altered frequently in high-grade serous carcinomas. So, in conclusion, the direct evidence regarding STIC as the precursor of HGSC is still tantalizing. Further molecular genetic studies are required to address this important question.

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Disclosure of conflict of interest

None.

Abbreviations

HGSC, high grade serous carcinoma; STIC, serous tubal intraepithelial carcinoma; FTE, fallopian tube epithelium; SCOUT, secretory cell outgrowths; STIL, serous tubal intraepithelial lesion; HMGA2, high-mobility group AT-hook 2.

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