The role of the fallopian tube in ovarian serous carcinogenesis: biologic mechanisms and clinical impacts

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Abstract: Epithelial ovarian tumors, especially serous carcinomas, are a topic of frequent study due to their high prevalence and devastating prognosis. Much of the recent advancements have centered on the newly characterized precursor lesions in the fallopian tube. Although high-grade and low-grade serous carcinomas have distinct molecular pathogenesis and cellular carcinogenetic pathways, a common precursor cell, the fallopian tube secretory cell, has been identified. The classification of serous cancers, cellular precursor lesions and carcinogenesis is discussed in detail in this review, focusing on the role of the fallopian tube in the development of neoplasia. The development of prophylactic measures is also described, with particular emphasis on ovary-sparing salpingectomies for the prevention of ovarian serous cancer. Studies on the topic of tubal contribution of ovarian serous cancer development were identified for this review by searching the English language literature in the PubMed database, including publications from our own group. This was followed by a review of bibliographies from articles found through the search. Commentary from authors on the topic and clinical impact is also provided.

Keywords: Fallopian tube, tubal secretory cells, high-grade serous carcinoma, low-grade serous carcinoma, ovarian cancer

Introduction

Ovarian cancer is the fifth most common cause of cancer in women, diagnosed 25,000 times per year in the United States and 225,500 per year worldwide [1-3]. The average lifetime risk for developing ovarian cancer is between 1.4% and 1.7% for women without germ-line mutations, while patients with BRCA1 and BRCA2 mutations have a 56% and 27% lifetime risk, respectively [4, 5]. Although accounting for only 3% of cancer diagnoses, ovarian cancer is the most lethal gynecologic cancer in developed countries due to rapid extraovarian spread [2, 6-10].

Among ovarian cancers, the epithelial serous type are the most frequently encountered, representing 60% of all tumors [11]. Despite much headway in discovering the origin, classification and behavior of serous cancers, the 5-year survival rate of 20-30% has not changed in over 50 years [1, 12, 13]. Furthermore, the prototypical ovarian tumor that arises in BRCA+ individuals is the lethal high-grade serous carcinoma (HG-SC) [14]. Therefore, effective screening, diagnosis and treatment of serous ovarian cancer are of great importance.

It is the lack of effective screening, advanced stage at diagnosis, paucity of symptoms and limited advanced stage treatment options that make ovarian cancers one of the most deadly cancers in the world [2, 4, 6, 7, 15]. Prognosis is dismal, with 75% of cases presenting in advanced stages with a median overall survival of only 15-23 months [5, 16, 17]. Late presentation and early extra-ovarian spread often
necessitates aggressive surgical debulking procedures in addition to chemotherapy [16]. Even after treatment with surgery and/or chemotherapy, which can have a response rate of up to 70%, the relapse rate is very high and patients often do not have very prolonged tumor-free interval. Screening, in general, is extremely problematic as the ovary is physically not accessible to frequent examination and tumor markers have lacked specificity [18]. For these reasons, ovarian cancer is a topic of extensive research and study.

In this review, we discuss the classification of serous ovarian cancers, cellular origin, molecular signatures and carcinogenesis. The role of the fallopian tube as the primary precursor site is highlighted. We also investigate the possible screening modalities in the context of recent advancements for both BRCA affected and unaffected individuals. We conclude with future promises and limitations of these modalities and further aims of research.

Dualistic model of ovarian epithelial cancer

Serous ovarian cancers are classified as either Type 1 (low-grade) or Type 2 (high-grade) tumors [8, 13]. The proposition of this two-tier grading system was adopted for routine use after it was found that tumors with grade 2 nuclei behave genetically and clinically similar to a tumor with grade 3 nuclei, with similar mutations and metastatic potential [19]. Histologically, it was observed that 60% of low-grade serous carcinomas (LG-SC) were associated with a tumor of low malignant potential, while only 2% of HG-SC had the same association, suggesting that HG-SC develop from an independent pathogenic process [20]. Furthermore, LG-SC and HG-SC have discrete genetic alterations and divergent clinical courses [21]. The organization of the system is based mostly on nuclear features with mitotic activity being a secondary component [19, 20].

Tumors classified as Type 1 include low-grade serous, endometrioid, clear cell, mucinous and Brenner carcinomas [2, 16, 18, 22]. The most common clinicopathologic features of Type 1 cancer is that they develop in a stepwise fashion and the majority are associated with benign and borderline developmental stages. LG-SC likely begins with ovarian epithelial inclusions (OEI) forming cortical inclusion cysts (CIC) that progress systematically to serous cystadenoma, serous borderline tumor including micro-papillary formation, and then to invasive carcinoma [2, 18, 23]. They generally present while still in a non-metastatic stage and evolve slowly [24]. Genetically, they are characterized by several mutations including those involved in cell signaling such as KRAS, BRAF, ERBB2, PTEN, CTNNB1, PIK3CA, ARID1A, PPP2R1A [2, 22]. Mismatch repair genes KRAS and BRAF mutations are the most common and are present in 65% of cases. Alterations in Beta-catenin and PTEN are also frequent [13, 18, 24]. In contrast to the Type 2 tumors, Type 1 tumors are generally not associated with TP53 mutations and do not harbor the large amount of chromosomal instability that Type 2 tumors exhibit [25].

Type 2 tumors, including HG-SC, high-grade endometrioid carcinomas, carcinosarcoma (malignant mixed mesodermal tumors) and undifferentiated carcinomas, have a very different genetic profile and clinical course [13]. In contrast to type I tumors, these tumors are characterized by a distinct lack of KRAS and BRAF but very frequently contain TP53 mutations and florid genetic instability [2]. TP53 mutations occur in up to 80-90% of cases and they also display a very high MIB-1 proliferation index of 50-75% [19, 24]. Of distinct clinical importance, BRCA1 and BRCA2 mutations are associated with high-grade serous tumors and have proven to be a very effective model for the study of these tumors. The behavioral pattern of these tumors, however, is indistinguishable between BRCA and non-BRCA patients and is prototypically rapidly developing with involvement of the ovarian surface [23].

Theories of pathogenesis and cellular origin of ovarian serous cancers

Incessant ovulation theory

The incessant ovulation theory of the development of ovarian serous tumors, originally described by Fathalla in 1971 [26], illustrated a process in which inflammation was the catalyst for the cellular transformation. In this model, post-ovulation adhesion leads to the development of surface epithelial invaginations, which can then become an OEI, also referred to as a CIC. These epithelial lined cysts then undergo an assumed Müllerian “metaplasia” through an unknown mechanism and after a series of
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Events at the molecular level, become malignant. Support of this theory lies in the protective role of pregnancy, breastfeeding and oral contraceptive usage, all of which inhibit ovulation [24]. However, this theory is incongruent to the more widely accepted theory that serous ovarian cancers probably arise from the fallopian tube, and not the ovarian surface epithelium (OSE). Evidence in opposition to ovarian epithelial carcinoma (OEC) deriving from OSE includes the observation that HOXA and PAX8, which are very prominent in OECs, are not present in OSE but are frequently expressed in the fallopian tube [2, 27-29]. Furthermore, the ovaries are derived from mesodermal epithelium on the gonadal ridge, separate from the Müllerian ducts that give rise to the cervix, endometrium and fallopian tubes [13]. Although Müllerian metaplasia is fundamental to this theory it is unlikely considering that a precursor lesion of OEC has not been identified in the ovary. In the absence of a defined precursor lesion, other theories have surfaced.

Müllerian theory

In 1972, Lauchlan proposed an alternate theory to the pathogenesis of serous cancers [30]. His theory described the formation of a “secondary Müllerian system”, where tissues within the genital tract could, directly or indirectly through metaplasia, give rise to the phenotypically Müllerian tumors such as serous, endometrioid and clear cell [2]. These tumors would be derived from one of several places. 1) Invasion of the OSE during post-ovulation repair is facilitated by open wounds following ovulation or by peri-ovarian adhesions resulting in an OEI [31]. 2) The development of a “secondary Müllerian system”, a process where cells from the fallopian tube come into contact with the ovarian surface and form a “Müllerian-mesothelial” junction, similar to the transformation zone in the cervix. This site could potentially be a vulnerable point to initiate malignant transformation [32]. The cells from the fallopian tube are then incorporated onto the ovary via exfoliation of cells or tubal-ovarian adhesions, which represents the process of endosalpingiosis [33, 34]. 3) Retrograde menstruation causing the implantation of cells upon the ovarian surface, commonly known as endometriosis [1, 23]. Although Dr. Lauchlan’s secondary Müllerian system theory does not perfectly explain the current understanding of the ovarian serous carcinogenesis, historically it provided an outstanding illustration that ovarian epithelial cancers are actually Müllerian derived [2].

Fallopian tube theory

With much evidence and ongoing studies, the fallopian tube has emerged as the probable site of ovarian serous tumors for high-grade lesions and now low-grade lesions. Doran et al. [35] was the first to note the fallopian tube as a possible origin in 1896 but his theory was disregarded until Piek et al. [36, 37] again described the fallopian tube as a possible suspect [16, 38]. The topic was fully revived after the work of Crum et al. [23, 39, 40] showed that serous carcinoma precursor lesions in BRCA patients were mostly located in the fimbriated ends of the fallopian tube [38, 41]. In fact, studies have shown that the most distal fimbriated end of the fallopian tube is the preferred site, irrespective of BRCA mutations, for early tumor growth and that 70% of serous carcinomas involve the endosalpinx [23]. In a study examining serous, clear cell, endometrioid and mucinous tumors, only serous tumors were related to cancerous lesions in the fallopian tube [42].

Numerous other studies have been conducted naming the fallopian tube as the newly discovered precursor site. Medeiros et al. used the Sectioning and Extensively Examining the Fimbriated End (SEE-FIM) protocol in thirteen BRCA+ women undergoing bilateral salpingo-oophorectomies and identified five cases of carcinoma within the fallopian tube and no ovarian carcinomas [34]. Diniz et al. also reported that the fallopian tube was involved in 70% of the cases they examined with 17% having a definitive fallopian tube origin and a further 29% having lesions that were highly suspicious for origin in the fallopian tube [5]. This work was consistent with the work by Kindelberger et al., who conducted a similar study using the SEE-FIM protocol showing that the fallopian tube is now a credible origin of serous carcinomas [43]. Similar reports have been published by Cass et al., Finch et al. and Leeper et al. [44-47]. Even in a study using double-knockout mice by Kim et al., it was shown that by deleting Dicer and PTEN genes, the mice developed very aggressive fallopian tube cancers, which consistently spread to the ovary before metastasizing rapidly throughout the abdominal cavity eventually resulting in death. These tumors were shown to express many genes that are
known to be up regulated in ovarian serous cancers [48]. Further evidence is provided in molecular studies showing mutations in TP53, PTEN and PAX2, which are all present in tubal intraepithelial carcinomas [49]. The predilection for cancer to arise in this remote location is unknown. However, it could simply be that the abundant surface area of fimbriated mucosa provides a much larger proportion of cells than any other structure, making it statistically more probable that damage to cellular DNA and subsequent neoplastic growth would arise here [34].

An emerging theory from the efforts of Seidman et al. suggests that the instead of the fimbriated end, it is the tubal-peritoneal fimbrial junction (TPJ) that could be the origin of the neoplastic cells [50]. Their group notes that epithelial/mesothelial junctions such as those in the cervical, gastrointestinal and anorectal areas are well known perpetrators of dysplastic change. Upon microscopic examination of the fallopian tubes, they found that 20% of cases demonstrated transitional metaplasia. However, these so called “junctional theories” for OECs development are currently hypothetical and are difficult to prove.

High-grade serous carcinoma

HG-SC constitutes over 90% of the serous carcinomas in the dualistic model. These tumors behave in a much more aggressive manner than their low-grade counterparts but are more susceptible to platinum-based chemotherapy [51]. The origin of these tumors has recently come into debate, and the fallopian tube has been labeled as a probable source of cells that would eventually evolve into this deadly cancer. The role of the fallopian tube and HG-SC precursors, such as p53 signatures, serous tubal intraepithelial carcinoma (STIC) lesions, secretory cell outgrowths (SCOUT) and secretory cell expansions (SCE) is discussed here, as well as the role of the BRCA gene in carcinogenesis.

Serous tubal intraepithelial carcinoma

Initially, research on the origin of ovarian cancer was primarily focused on the OSE as the expected source of neoplasia. As attention shifted towards the fallopian tube as a site of origin, the description the STIC lesion emerged as a viable precursor lesion for an unknown percentage of HG-SCs. Eventually, the observation that at least 70% of sporadic HG-SC contained a STIC was compelling evidence that STIC was indeed the precursor lesion for HG-SC and not a focus of metastasis from an ovarian serous cancer [13].

The STIC is now considered a precursor or non-invasive counterpart to HG-SC in the fallopian tube theory in patients with and without a BRCA mutation [2]. They are defined as secretory fallopian tube cells that exhibit striking cellular atypia (loss of nuclear polarity, prominent nucleoli, and increased N:C ratio), positive p53 immunohistochemistry staining in 80-92% of cases, and a very high proliferative index with a MIB-1 of > 40% [19]. STICs are present in 4-17% (some report 5-7% [52]) of prophylactic salpingo-oophorectomies of BRCA cases and are located in the distal portion of the tubes 57-100% of the time [24, 41]. Several studies have shown that examination of the fallopian tube in patients with serous carcinomas revealed a STIC located simultaneously in the fallopian tube 47% of the time, with reproducible results by Crum et al., Carlson et al. and Kindelberger et al. [18, 23, 41, 43]. Other studies reported a wide range of association rates, such as by Przybycin et al. (59%), Gao et al. (92%), Tang et al. (19%) and Roh et al. (36%) [53-56]. Furthermore, RSF-1, Cyclin E, p16, FASN and Statmin 1 were found to be upregulated in STICs and are also commonly overexpressed in HG-SC [24].

The tubal theory involving STICs does have some limitations. First, only about half of HG-SC has a STIC present at the time of diagnosis, even after extensive sectioning of the tube [41]. It is also possible that during ovulation, normal fallopian tube cells detach, implant on the ovary, and become an OEI (endosalpingiosis), which may then become a HG-SC [13]. Lastly, there have been instances of HG-SC arising from LG-SC in about 5% of cases [57, 58]. However, in the case of OEI formation, the tubal cells were still the originating cell of the neoplastic process [8]. Moreover, the lack of STIC in some cases could be due to an iatrogenic process such as damage to the tissue before sectioning, not sectioning the fimbria properly or lack of experience of the reading pathologist [24, 52]. Nevertheless, the abundance of evidence supporting STICs as the precursor lesion leads to the conclusion that the majority, if not
all, HG-SC have their origins in the fallopian tube secretory cells.

**p53 signatures**

The p53 signature has likewise emerged as a latent precancerous lesion to HG-SC and possesses several characteristics that identify them as such: fimbrial location, TP53 mutations, H2AX mutations (DNA damage) and cellular specificity (secretory cells) [41]. p53 signatures are foci of benign looking mucosa in the distal fallopian tube that show p53 immunoreactivity in at least 12 secretory cells with little remaining ciliated cells and have a low proliferative index (MIB-1 < 20%) [9, 23]. The work by Lee et al. was integral in describing these lesions with their observation that p53 signatures were equally as common in BRCA+ (37%) and BRCA- (33%) women, suggesting that the p53 signature is a not directly associated with this germline mutation. However, these p53 signatures were found to be more frequent and multifocal in women with STIC lesions, where they resided concurrently in the fimbria 80-100% of the time [9]. P53 signatures and STICs share several homologous features. They are both located in the fimbria in > 80% of cases, stain for p53 and H2AX, exhibit identical TP53 mutations when they occur simultaneously and preferentially involve the secretory cell [2, 44]. An intermediate lesion between p53 signatures and STICs has also been described, termed serous Tubal Intraepithelial Lesions in Transition (TILTs) or Tubal Epithelial Dysplasia, highlighting that these lesions lie on some sort of continuum [24, 59]. The p53 signature is extremely common, rarely progresses to malignancy, and is not sufficient to bring about a neoplastic transformation in the majority scenarios [18, 31]. Instead, the p53 signature should be viewed as a latent pre-cancer lesion and one of the “building blocks”, which under optimal circumstances and further genetic mutations, is a necessary step in bringing about the disease [2, 33].

**Secretory cell outgrowths and secretory cell expansion**

A SCOUT consists of 30 or more secretory epithelial cells that may be pseudostratified in appearance and are morphologically distinct from the surrounding mix of secretory and ciliated cell population [60]. Phenotypically, they are BCL2+ and p73- with low PAX2 and semilow PTEN and MIB-1 expression with essentially no TP53 mutations. Their significance lies in the observation that they are found more frequently in the presence of a serous carcinoma and that the number of SCOUT lesions increases with patient age. SCOUTs are a distinct entity from the benign precursor lesion, the p53 signature. However, it is possible to consider a p53 signature as a p53 positive SCOUT that has different size requirements [2]. Other features that differentiate a SCOUT form a p53 signature, besides the conspicuous lack of TP53 mutations, are that SCOUT lesions are PAX2 negative and that SCOUTs have a wider distribution between fimbrial and proximal areas of the fallopian tube [60].

Yet, a causal relationship between SCOUTs and HG-SC is missing and recent studies by our own group have highlighted the secretory cell expansion (SCE) as a more sensitive biomarker for serous neoplasia. We defined SCEs as a linear stretch of more than 10 secretory cells without interrupting ciliated cells in the tubal mucosa. By definition, a SCOUT lesion is a type of SCE. The secretory to ciliated ratio (S/C) is central to this concept, and was found to be increased in patients with strong risk factors for serous carcinoma and increased with increasing patient age, similar to SCOUTs. SCEs and SCOUTs were also more frequently identified in tubal segments of high-risk patients and those with serous carcinoma compared to controls. However, SCEs were more prevalent in both high-risk and carcinoma groups in comparison to SCOUTs and also found to be more sensitive in the association with serous neoplasia. In the future, molecular studies of SCEs for use as a biomarker may have a better chance of leading to early detection of serious cancers [61].

**Molecular aberrations**

HG-SC displays an incredible amount of genetic mutations and genomic instability. Although TP53, BRCA1 and BRCA2 are the most common offenders, other genes including NF1, FAT3, CSMD3, GABRA6, CDK12 and RB1 are noted to be commonly mutated [2]. TP53 mutations have been recognized in 96.7% of HG-SC cases, with p53 dysfunction reaching 100% of cases [62]. This change in TP53 has been noted as the earliest change to occur in the formation of HG-SC and to be a necessary modification [9, 41, 43, 59, 63]. Yet, despite its cen-
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The BRCA gene plays a considerable role in the development of HG-SC. The mutation is inherited in an autosomal recessive fashion, and both mutated genes are necessary for the increased risk of carcinoma development [2]. The BRCA1 and BRCA2 genes denote a 30-70% chance of developing HG-SC by the age of 70 and 22% of diagnosed HG-SC have BRCA mutations [64, 65]. BRCA gene mutations have an intimate relationship with TP53 mutations in the process of carcinogenesis. Studies have shown that while BRCA mutations are observed in STICs, they are not observed in all p53 signatures [66]. Conversely, all BRCA+ cancers contain a heavy p53 immunostaining [66]. These observations indicate that while BRCA mutations are not necessary for the formation of p53 signatures and TP53 mutations, BRCA positive lesions must contain p53 dysfunction in order to progress to neoplasia.

Other genetic changes include amplifications and deletions of cyclin E1, AKT2, Notch3, PIK3CA, c-Myc, RB1, CDKN2A/B, CDK12, CSMD1, CSMD3, DOCK4, NF1, FAT3, GABRA6 [65, 67-69]. These tumors also have a high level of allelic imbalance and DNA copy number changes, especially when compared to Type 1 tumors [8, 67, 70]. Some of these genes may have prognostic significance, and one study showed high expression of CASP3, XIAP, NFKB1, FAS and GSK3B correlated with a better clinical prognosis [71]. However, definitive utility of these genes in clinical practice remains to be seen.

Low grade serous carcinomas

LG-SCs account for only 10% of all serous carcinomas. They are a rare important subtype of this class of tumors [51]. They are thought to evolve in a stepwise fashion, progressing from ovarian epithelial inclusions (< 1 cm) or serous cystadenomas (> 1 cm) to serous borderline tumors and then to invasive carcinomas [72-74]. Evidence for this process is extensive. First, there are many examples of clear histologic transition from cystadenoma to borderline tumors and similar mutations in KRAS and BRAF are present throughout this continuum [2, 75, 76]. Second, the majority of LG-SCs are associated with borderline lesions and examples of invasive borderline tumors markedly resemble LG-SC [20, 75, 77-79]. This is especially apparent in cases of serous borderline tumor of micropapillary in appearance, which have histological features identical to those of LG-SC [80, 81].

Origin of the ovarian epithelial inclusion

The question that remains is whether the origin of OEI is from the OSE or actually from the fallopian tube. Our group was the first to propose the fallopian tube as the source of the OEI, with the secretory cells being the principle player. Tubal type epithelium was found only 4% of the time on OSE and 78% of the time in OEI, lending evidence to the theory of endosalpingiosis and identifying the fallopian tube as the source of the OEI cells. Furthermore, another study by our group demonstrated that “tubal-type” genetic markers (calretinin-/PAX8+) were found within OEIs 78% of the time and mesothelial type genetic markers (calretinin+/PAX8-) only 22% of the time, making the fallopian tube 3.54 times more likely to be the origin of the OEI cells [82].

There is ample data to discount the OSE as the source of OEIs. As touched on above, the vast majority of OSE have a distinct genetic phenotype, most consistent with mesothelial type (calretinin+/PAX8-/tubulin-) and very low proliferation while only 4% of cases have shown a tubal phenotype (calretinin-/PAX8+/tubulin+). This low rate of tubal-phenotype cells on the OSE likely accounts for benign tubal epithelial cells that have implanted on the ovary directly from the fallopian tube. Additionally, the low proliferative rate of mesothelium-derived OEIs (similar to OSE) is opposite from what is seen in tubal-derived OEIs, which have proliferation rates comparable to serous tumors. It has been suggested that the fallopian-type cells arose from Müllerian metaplasia and originally had a mesothelial phenotype. However, if this was the case, then a hybrid of tubal and mesothelial OEIs should be relatively common when in reality, these hybrids are rarely found.

Molecular aberrations

Three genes, KRAS, BRAF and ERBB2, play a unique role in the molecular carcinogenesis of
LG-SC. These genes have proven to be mutually exclusive, and more than 61-68% of LG-SC harbor mutations in these three genes [83, 84]. Moreover, mutations in these genes have been detected in cystadenomas as well as in nodal endosalpingiosis. Both lesions are morphologically benign, denoting that they are probably early events [76].

KRAS mutations were found in 35% of LG-SCs in one study, and 33% of borderline tumors. BRAF mutations were also found in equally high proportions, reaching 30% of LG-SC and 28% of borderline lesions. A mutation in either BRAF or KRAS was found in 68% of micropapillary serous carcinomas and 61% of borderline tumors [83]. Similarly, the gene for HER2/neu, denoted as ERBB2, is mutated in 9% of tumors. This gene activates an upstream regulator of KRAS, and is therefore involved in the same pathway [86]. From these studies, it seems that BRAF and KRAS are both necessary and early mutations in the molecular carcinogenesis of LG-SC. Whether or not these two genes are sufficient in of themselves to facilitate a neoplastic process is yet to be determined. This knowledge could lead to important clinical implications, as the detection of BRAF or KRAS in cystadenomas by molecular assays could imply a higher risk of progression to carcinogenesis and therefore, more aggressive prophylactic measures may be required [76].

A multitude of other chromosomal and genetic abnormalities are found in LG-SC, but not to the extent that is seen in HG-SC [2]. Chromosomes 1p, 5q, 8p, 18q, 22q and Xp demonstrated allelic imbalances in a gene profiling analysis. The genetic instability was observed to increase as the tumor progressed from borderline to carcinoma [70, 87].

Mechanisms of carcinogenesis

The mechanism by which tumor cells undergo metaplastic change and implant on the ovarian surface to form ovarian serous tumors is complicated and may derive from several distinct pathways. It is known that both LG-SC and HG-SC arise from the secretory cells, but their divergent mechanisms of carcinogenesis are characterized here.

Initially in the development of HG-SC, DNA damage secondary to a toxic stimulus accumulates in the secretory cells of the fallopian tube. The DNA damage can be due to changes associated with ovulation, which would affect both the ovarian surface and the fallopian tube [43]. Evidence for this was seen in a study done by Levanon et al., who showed that secretory cells of the fallopian tube, when compared to nearby ciliated cells, show a distinct response to DNA damage and a limited ability to resolve the damage [88]. The continual addition of chromosomal abnormalities and genetic instability along with the early mutation of the TP53 gene results in a clonal proliferation of p53 signatures. Subsequently, only a small population of these “p53 signature” cells will develop yet another chromosomal insult, such as a BRCA mutation, to transform that particular lesion into a STIC. STICs are friable and easily shed onto the ovarian mucosa, creating foci that can transform into HG-SC [2, 25].

Rarely, some HG-SC may develop directly from LG-SC after additional genetic mutations are acquired, such as TP53, but this does not seem to be a very common occurrence in LG-SC [2, 82]. Another possibility is that some OEIs from the fallopian tube, which would generally lead to LG-SC, develop instead into HG-SC in women with BRCA mutations [89]. These instances are examples of why there remains to be occasions of HG-SC development in the setting of no tubal involvement.

In the case of LG-SC, the mechanism in which the fallopian tube cells become implanted on the ovarian surface can happen in one of two ways. The first theory is that since the distance between the two is very small, and several mechanisms can lead to the disruption of the fallopian tube cells (i.e. ovulation), the cells can simply detach and reattach to the ovarian surface [13]. The second theory involves the fallopian tube actually becoming adherent to the ovarian surface, and the transfer of cells occurring through this means [83, 85, 90-92]. Stromal growth surrounding the implant can eventually lead to the formation of an OEI. OEIs and cystadenomas that develop KRAS or BRAF mutations then progress systematically to borderline and ultimately, LG-SC lesions.

Overall, the cellular and molecular mechanisms of LG-SC development remain unclear. We believe that the critical issue here is to determine the fundamental differences between the...
secretory and ciliated cells on the molecular level. The experiments designed to answer this question are currently being carried out in our laboratories.

Clinical implications

As it has now been established that the fallopian tube is largely responsible for the vast majority of serous cancers of the ovary, attention has turned to the clinical implications of this knowledge. As discussed, the prognosis of ovarian cancer in the advanced stage is dismal the cure rate has not significantly increased in the past few years [53]. Treatment is complicated and ineffective, often relying on bulk-reducing surgeries and chemotherapy to which LG-SC is particularly resistant [51, 85]. Further complicating management is the disappointing lack of reliable screening modalities, as the use of CA-125 has resulted in the same rate of advanced stage cancer diagnoses as unscreened populations [2]. Therefore, efforts are now being made to explore the utility of detecting STICs as precursor lesions and the value of prophylactic salpingectomies as a fertility-sparing prophylactic measure for BRCA+ patients. Yet, all of these efforts depend largely on the single, still unanswered question of what proportion of HG-SC originates from the fallopian tube.

Prophylactic salpingectomies

The practice of bilateral prophylactic salpingectomies has been recently considered as a means of prophylaxis against cases of BRCA+ serious ovarian carcinoma. The oviduct does not contribute physiologically after an oophorectomy and its presence after such a procedure does not alter the female hormonal profile. If the tubal theory is accepted as true, and most cancers arise from the fallopian tube, a salpingectomy would be a sufficient means to negate that risk while preserving reproductive capability [2]. In fact, some groups quote that even with the most conservative estimates, over 3000 cases could be prevented each year by utilizing prophylactic surgery [53]. It is already known that prophylactic salpingo-oophorectomies results in a cancer-free rate in 96% of patients, compared to only 69% of those under close surveillance [23]. This poses the questions, would a salpingectomy be sufficient to prevent cancer in all patients? The consensus thus far is that it would not. Based upon the observation that some HG-SC may arise from foci of endosalpingiosis within the ovary or a minor component of residual Müllerian tissue, a small percentage of HG-SC may continue to evolve even after salpingectomy.

This does bring a very important point into discussion, as described in a case study by Lorusso et al., who reported a patient with BRCA positivity who developed HG-SC after a bilateral salpingo-oophorectomy from a small foci of fimbriated tissue that was left behind. Although salpingectomies may not be the answer for BRCA+ ovarian cancer prevention, extra care should be taken to ensure that the tube is always removed in its entirety [93]. The tube should also be sectioned and submitted extensively, using the SEE-FIM protocol [33]. This protocol involves submitting the tube in toto in 2-3 mm ampullary sections and longitudinally sectioned fibriated mucosa which will increase the detection of carcinoma by 17% as STICS are quite small and can be missed by representative sectioning [24, 94]. The authors of the protocol also recommend the utilization of p53 and MIB-1 immunohistochemical staining for difficult cases, and routine collaboration with gynecologic pathologists [33]. Limitations of the SEE-FIM protocol were described in the study discussed earlier by Seidman et al., who stated that the sections taken in this protocol amputate the fimbriated end right at the region of the TPJ, which may confound the role of TPJ in ovarian serous cancer study [95].

Overall, we believe that the majority, if not all, ovarian HG-SCs could be prevented by performing bilateral salpingectomy. However, LG-SC may continue to develop if endosalpingiosis has occurred prior to the salpingectomy. There is hope for success in this field in the future, and results of prophylactic ovary-saving salpingectomy clinical trials by the Gynecologic Oncology Group are expected to be available in the near future [96-98].

Detection of sTICs as an early precursor lesion

The presence of a STIC in the absence of further disease designates a Stage 0 lesion with low rate of spread, low recurrence and excellent prognosis [41]. By detecting this lesion early in its development, it is reasonable to theorize that many deaths could be prevented [99]. In spite of that, many questions regarding
the utility of the STIC lesion as a diagnostic marker remain. First, a definitive cure needs to exist when a STIC lesion is detected. Second, STIC lesions will need to have a significant interval period prior to progression to HG-SC to allow sufficient time for detection. Third, the means of detection must be simple, cost effective and non-invasive, possibly involving biomarkers. Yet, in what specimen should the biomarkers be tested? Are they specific enough to detect microscopic foci of proliferating cells? And lastly, is there a way to interrupt p53 signature and halt the entire process before it even begins [18].

**Cytologic detection of cancerous cells**

A recent study from Otsuka et al. discussed the utility of cytologic samples from the endometrial cavity or the vaginal in detecting HG-SC [100]. They found that 5 patients that did not show any sign of disease on imaging did demonstrate malignant cells in endometrial aspirates. Vaginal detection was found in only one patient. Three of those patients were found to have an early HG-SC but the other two patients did not demonstrate any sign of a tumor. Although cytologic examination for tubal serous cancer has shown to have diagnostic value, the effectiveness of this method for routine use requires further investigation.

Considering the great potential of tubal cytology for early detection of ovarian serous cancers, our lab has recently started to develop a tubal cytology method that aims at setting up a normal standard for tubal cells with respect to different patient conditions. We sincerely hope that tubal cytology may prove to be a successful means of early ovarian cancer detection.

**Conclusion**

After many decades of ignorance, the fallopian tube is now regarded as the precursor site for ovarian serous cancer carcinogenesis. Furthermore, the secretory cells of the fallopian tube have emerged as the most likely origin of serous tumor cells with ample cellular and genetic data to support this theory. The development of biomarkers and other modalities to detect early pre-cancerous lesions are currently under investigation. As an alternative to current practice of prophylactic salpingo-oophorectomy, a more favorable prophylactic means in preventing ovarian serous carcinoma, especially in BRCA+ patients, may be prophylactic salpingectomy. However, this promising mode of prophylaxis will not be formally instituted until satisfactory results from cellular and molecular studies focusing on the oviduct and large-scale clinical trials are obtained.

**Abbreviations**

HG-SC, High Grade Serous Carcinoma; LG-SC, Low Grade Serous Carcinoma; OEC, Ovarian Epithelial Inclusion; CIC, Cortical Inclusion Cyst; OSE, Ovarian Surface Epithelium; OES, Ovarian Epithelial Carcinoma; TPJ, Tubal Peritoneal Junction; SCOUT, Secretory Cell Outgrowths; STIC, Serous Tubal Intraepithelial Carcinoma; TILT, Tubal Intraepithelial Lesions in Transition; SCE, Secretory Cell Expansion; SEE-FIM, Sectioning and Extensively Examining the Fimbriated End.

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