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Molecular catastrophe, the peritoneal cavity and ovarian cancer prevention

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Running title: Origin and prevention of high-grade serous carcinoma

Abstract

The current theory of carcinogenesis for the deadliest of "ovarian" cancers - high-grade serous carcinoma (HGSC) - holds that the malignancy develops first in the fallopian tube and spreads to the ovaries, peritoneum and/or regional lymph nodes. This is based primarily on the observation of early forms of serous neoplasia (serous tubular intraepithelial lesions (STILs), and serous tubular intraepithelial carcinomas (STICS)) in the fimbria of women undergoing risk reduction surgery. However, these lesions are uncommon in the general population, confer a low risk (5%) of HGSC following their removal in at-risk women with germ-line *BRCA1/2* mutations and require 4 or more years to recur as intraperitoneal HGSC. These features suggest that isolated STILs and STICs behave as precursors with uncertain cancer risk rather than carcinomas. Their evolution to HGSC after escape from the tube could proceed step-wise with multiple biologic events; however, it is unclear whether immediately adjacent HGSCs in the setting of advanced disease evolved in the same fashion. The latter scenario could also be explained by a "catastrophic" model in which STICs suddenly develop with invasive and metastatic potential, overwhelming or obscuring the site of origin. Moreover, a similar model might explain the sudden emergence of HGSC in the peritoneal cavity following escape of precursor cells years before. Long term follow-up data from opportunistic or prophylactic salpingectomy should shed light on where malignant transformation occurs, as well as the time-line from precursor to metastatic HGSC.

Keywords: ovary; high-grade serous carcinoma; prevention; fallopian tube; primary peritoneal carcinoma; chromothripsis **editors note: these sre slightly different from the portal keywords**

The tubal theory of ovarian carcinogenesis

Extrauterine high grade serous cancer is a disease that underscores the importance of tumor origin to management and prevention [1]. Over 90% of tumors present at Stage II or higher, screening efforts have been unfruitful, and only 20% of women survive 10 years [1-3].

With genetic screening and risk reducing salpingo-oophorectomy (RRSO), early HGSCs with *TP53* mutations have been reported in the fallopian tubes of asymptomatic vulnerable women with germ-line *BRCA1/2* mutations ($BRCA^m$) [4-14]. A pathologic dissection protocol ("SEE-FIM") introduced in 2005 focused on the distal fallopian tube (fimbria), and a range of serous cancer precursors (serous tubular intraepithelial lesions, STIL) and serous tubular intraepithelial carcinomas (STIC) with *TP53* mutations have been described (Figures 1A-C) [15-17]. Approximately 5% of $BRCA^m$ RRSOs contain a STIC and of these about 5% will eventually be followed by disseminated HGSC [18-20]. Both the distal fallopian tube and endometrial lining have now been shown to harbor possible precursors with *TP53* mutations (Figure 2) [21-23].

Based on literature review, from 11% to 60% (mean 31%) of HGSCs are associated with a STIC [24]. With STIC as the cornerstone in early HGSC development, models have been constructed with a "window of opportunity" to intercept these early malignancies at a curable stage [25].

Incidental *versus* symptomatic STIC

STIC is generally defined as a stratified depolarized population of atypical proliferating non-ciliated cells. The term implies an intramucosal malignancy. However, most STICS found incidentally are not followed by a subsequent intraperitoneal HGSC. If HGSC does occur, based on a small number of cases reported, it usually emerges 4-7 years later [18, 18,26, 27]. Contrasted with the rapid growth rate of most established HGSCs leading to short recurrence intervals, most isolated STICs seem to function more as precursors - akin to STILs - than intramucosal carcinomas that can readily metastasize. For the purpose

of this review these precursors are combined under the term serous tubal intraepithelial neoplasia (STIN), implying an intraepithelial neoplasm with a risk - albeit low - of a HGSC outcome. Given the long recurrence interval, one can argue that HGSC following the discovery of such lesions occurred after a form of "precursor escape". This model fits into the concept of primary peritoneal carcinomas, which could have an ultimate origin in a tubal precursor [28-30].

STIC is much less commonly found in women presenting with *advanced* HGSC (averaging 31%) [24]. Explanations include simple inundation of the STIC by tumor overgrowth, precursor escape, or rapid development of a STIC with instant metastatic potential.

The conundrum of tumor origin

The challenges faced in resolving the origin of all HGSCs can be appreciated from examination of the surgical specimen. Table 1 is a summary of pathology reports from 387 consecutively diagnosed HGSCs from specimens reportedly containing both fallopian tubes, removed at Brigham and Women's Hospital between 2015 and 2020. Review of the cases was performed under institutional board approval. All cases were processed using the SEE-FIM protocol. Cases were categorized with attention to the fallopian tubes, both of which were removed: 1) presence of STIC, 2) endosalpingeal involvement (any fimbrial involvement was included), 3) one or more tubes not found or obliterated, 4) serosal or paratubal involvement only, and 5) no tumor identified. These data are from reports only, and interpretation is limited somewhat by the prior administration of chemotherapy, which might lower the frequency of STIC; however, a minority of cases showed a marked chemotherapeutic response (cases with no remaining tumor were not included).

From the two columns at the left, 17.5% of cases likely arose in the tube based on the presence of STIC. From the two columns at the right, 20.6% of cases did not exhibit involvement of the endosalpinx, in which case the cancer likely initiated away from the tubal mucosa. The middle three columns are a

"mixed bag". Endo-salpingeal involvement or complete obliteration of the tube could signify overgrowth by a primary tubal carcinoma or metastatic disease. Either way, this process implies rapid growth and contrasts with the isolated "STIC" that behaves as an indolent precursor with a low risk of subsequent metastatic HGSC. The data thus support the role of three phenomena in the genesis of HGSC; 1) an initiating event characterized by a *TP53* mutation in the upper female genital tract; 2) Malignant transformation of the cells, either in the tube or following precursor escape; 3) and possibly, *rapid* transformation and dissemination beginning either in the tube, ovarian surface or the peritoneal cavity [31, 32]. What remains is a high percentage of cases presenting with high-stage HGSC without a clear-cut early cancer in the tubal mucosa.

The case for sudden catastrophic genomic events

A current model of HGSC formation is through gradual genetic evolution (Figures 3A and 4A). Comparing intraepithelial (*i.e*. STIC) and invasive serous carcinomas, phylogenetic analyses based on single nucleotide variants (SNVs) and copy number variants (CNVs) derived from whole exome sequencing (WES) describe a window of ~6.5 years between development of a STIC and initiation of HGSC [25, 33]. Once the precursors find their way to the ovary, the progression appears to be clinically rapid, as less than 5% of HGSCs are confined to the ovary at diagnosis [34], and based on phylogenetic analyses, metastases rapidly follow HGSC formation within an average window of ~2 years. This current model thus describes the STIC-HGSC transition as a major bottleneck in clinical progression, which appears to be eventually overcome through gradual accumulation of SNVs and CNVs (Figures 3A and 4A). One well-established example of such a carcinogenic sequence is the Vogelstein model of colorectal carcinogenesis, which involves mutations in the *APC* and *KRAS* genes, followed by loss of the tumour suppressor genes, *SMAD4*, and *TP53*, sequentially leading to the formation of adenomas and ultimately carcinoma [35]. This is perhaps the best demonstration of the gradual pathogenesis model, with the windows between adenoma-carcinoma being estimated at 5-15 years. However, in contrast to colorectal carcinoma, the number of

genetic events definitively linked to serous carcinogenesis is low. It is understood that *TP53* mutation and the resulting p53 dysfunction are crucial truncal events [36, 37]. Other genetic events impacting the RB/p16/CDK4 pathway, such as *RB* promoter methylation and/or *RB* gene copy loss are also frequent if not universal [38,39]. *CCNE1* amplification, based on its well-established prognostic significance, could accelerate disease progression [40, 41], but no other genetic events have been identified as either sufficient or necessary for HGSC formation. Perhaps reflecting this, some murine models of HGSC often resort to combinations of genetic lesions (such as *Dicer-Pten* double-knockout) rarely seen in human HGSCs, however this limits their value as models for this disease [42, 43].

An alternative to the gradual model is one involving rapid, catastrophic genomic events. Chromothripsis, which, briefly, is thought to entail shattering, followed by subsequent, sometimes seemingly random, re-assembly of one or few chromosome(s) [44], has been reported detectable in about 60% of ovarian HGSCs [45]. In some cancers, *e.g.* glioblastoma, these catastrophic events have been associated with amplification of *bona fide* oncogenes, such as *MYC*, where *MYC* overexpression alone does not appear to be sufficient to induce catastrophic events [46], arguing that chromothripsis may be an important truncal event, driving carcinogenesis. Pertinent to HGSC, chromothripsis is generally common in cancers associated with p53 dysfunction, including liposarcoma (where p53 dysfunction is induced by *MDM2* copy gain), pediatric medulloblastoma in Li-Fraumeni patients (where p53 dysfunction is associated with germline *TP53* mutations), and HGSC (where p53 dysfunction is associated with somatic *TP53* mutations) [47]. Although several different working definitions exist for chromothripsis, one identifiable finding is alternating gains and losses occurring in a single region [44]. Thus, at least some of the genomic complexity in HGSCs could be explained by a single catastrophic genomic event rather than as a gradual accumulation of CNVs. Arguably, such catastrophic events would be difficult to incorporate into phylogenetic analyses, creating a different molecular timeline relative to the gradual model (Figures 3B, 3C and 4B and 4C).

Hypothesis and Prevention

The impact of bilateral salpingo-oophorectomy (BSO) on subsequent ovarian cancer (a reduction in cases of approximately 15-fold vs controls) is well established, both in the general population and in $BRCA^m$ women [48]. Retrospective studies have estimated a risk reduction for bilateral salpingectomy as well, albeit less so than BSO [49]. The promise of prophylactic or opportunistic salpingectomy is palpable. The most plausible early examples of HGSC (STICs) are found in the fallopian tubes from $BRCA^m$ women; however, only a fraction will metastasize, suggesting that *incidental* isolated STICs are best viewed as intraepithelial neoplasms of uncertain malignant/recurrent potential. This scenario contrasts to the more than 90% of women with HGSC who present with disseminated disease, and on average about 30% will harbor a recognizable STIC, most of which are unmistakably malignant. These facts argue for a dualistic pathway including a relatively rapid onset of metastatic HGSC originating in the tube or peritoneal cavity. The relative contributions of malignant transformation occurring in the tube *versus* the peritoneal cavity remain to be determined. However, estimates will be feasible in the context of data emerging following opportunistic or prophylactic salpingectomy. It is unlikely that salpingectomy will completely eliminate the risk of HGSC. However, a dramatic reduction in cancer incidence following these procedures will argue for a model with rapid cancer development in which metastatic spread occurs from an established tubal HGSC. A less striking reduction in HGSC incidence would favor a model of precursor escape or an alternate site of tumor initiation. Addressing the latter might necessitate attention to removal of the tubes and the peritoneal milieu where precursor cells with future malignant potential could be left behind. Resolving the role of each scenario will require long-term follow-up studies to account for the potential delays inherent in the time required for transition from precursor to malignancy.

List of abbreviations

(BRCA^{m}) *BRCA1/2* mutation; BSO, bilateral salpingo-oophorectomy; CNV, copy number variant; HGSC, high-grade serous carcinoma; RRSO, risk reducing salpingo-oophorectomy; STIC, serous tubular intraepithelial carcinoma; STIL serous tubular intraepithelial lesion; STIN, serous tubal intraepithelial neoplasia; SNV, single nucleotide variant; WES, whole exome sequencing

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Author contributions:

Conception and writing of manuscript (CPC, JYY, DC, TRS, WX), collection and confirmation of human tissue and cytologic diagnoses (EG, XQ, JM, NH), molecular analysis (AM, JYY, WX). All authors read and approved the final manuscript for publication.

Table 1. Breakdown of 387 consecutive HGSC cases by pattern of fallopian tube involvement in the pathology report

STIC identified (17.5%)		**STIC *not* identified (82.5%)**				
		Endosalpingeal involvement		**One or more tubes not identified**	**Serosal involvement only**	**No tumor identified**
Unilateral	**Bilateral**	**Unilateral**	**Bilateral**			

15.2%	**2.3%**	**30.0%**	**15.2%**	**16.5%**	**7.2%**	**13.4%**

Figure legends

Figure 1. *Serous cancer precursors in the fallopian tube containing TP53 mutations*. (A), (C) and (E) show H&E images, including p53 signature (A) and serous tubal intraepithelial lesion (C). (E) shows a serous tubal intraepithelial carcinoma for comparison. Panels (B), (D) and (F) display diffuse nuclear staining for p53, in keeping with a *TP53* mutation.

Figure 2. *Evidence of TP53 mutations in histologically benign-appearing endometrial lining epithelial cells.* (A) shows H&E stained section and (B) shows strong staining for p53 indicating the presence of a *TP53* mutation.

Figure 3. *Three models of HGSC pathogenesis*. (A) "Gradual" model of HGSC formation, with sequential accumulation of mutations. (B) and (C) show two potential routes in the "Catastrophic" models of HGSC formation, with early *TP53* mutation, ultimately leading to genomic catastrophe (e.g. chromothripsis). In (B), the catastrophic event happens *in situ* (i.e. in the intraepithelial fallopian tubal lesion), leading to the formation of identifiable STIC. In (C), the precursor escapes into the peritoneum, prior to the catastrophic genomic event, which occurs later in the peritoneal cavity. In both (B) and (C), genomic catastrophe is either lethal to the precursor cells or carcinogenic, and thus carcinogenic progression is stochastic over time, arising from a selected precursor cell.

Figure 4. *Cartoon of mucosal epithelium corresponding to the models in Figure 3*. (A) A gradual step-wise sequence including normal, precursor, non-metastasizing STIC and metastasizing STIC. (B) A catastrophic model in which a metastasizing STIC emerges rapidly from normal mucosa or an early precursor. (C) A

precursor escape model in which cells with TP53 mutations escape the tube and become metastatic-capable later in the peritoneal cavity. STICs in such instances could be metastatic deposits.

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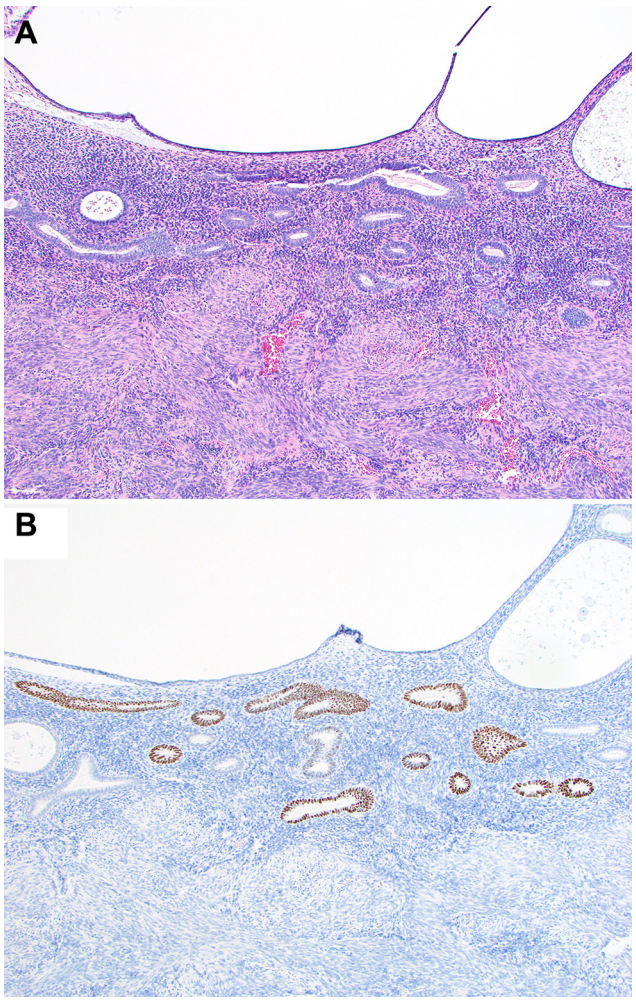

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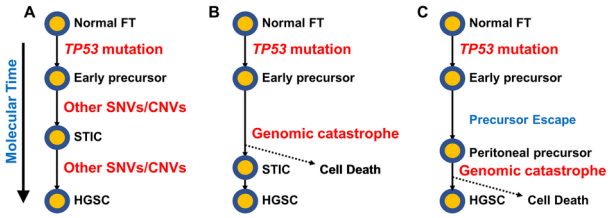

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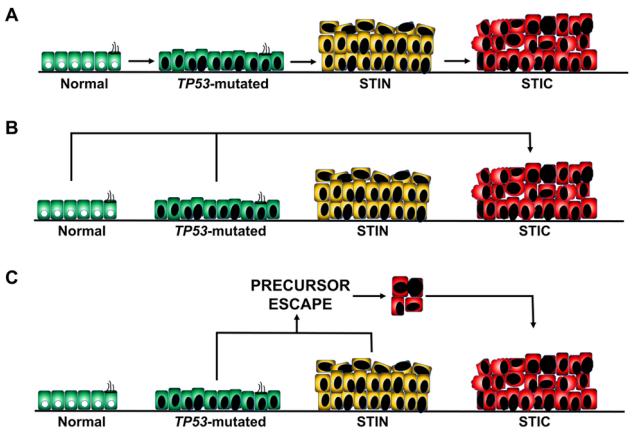

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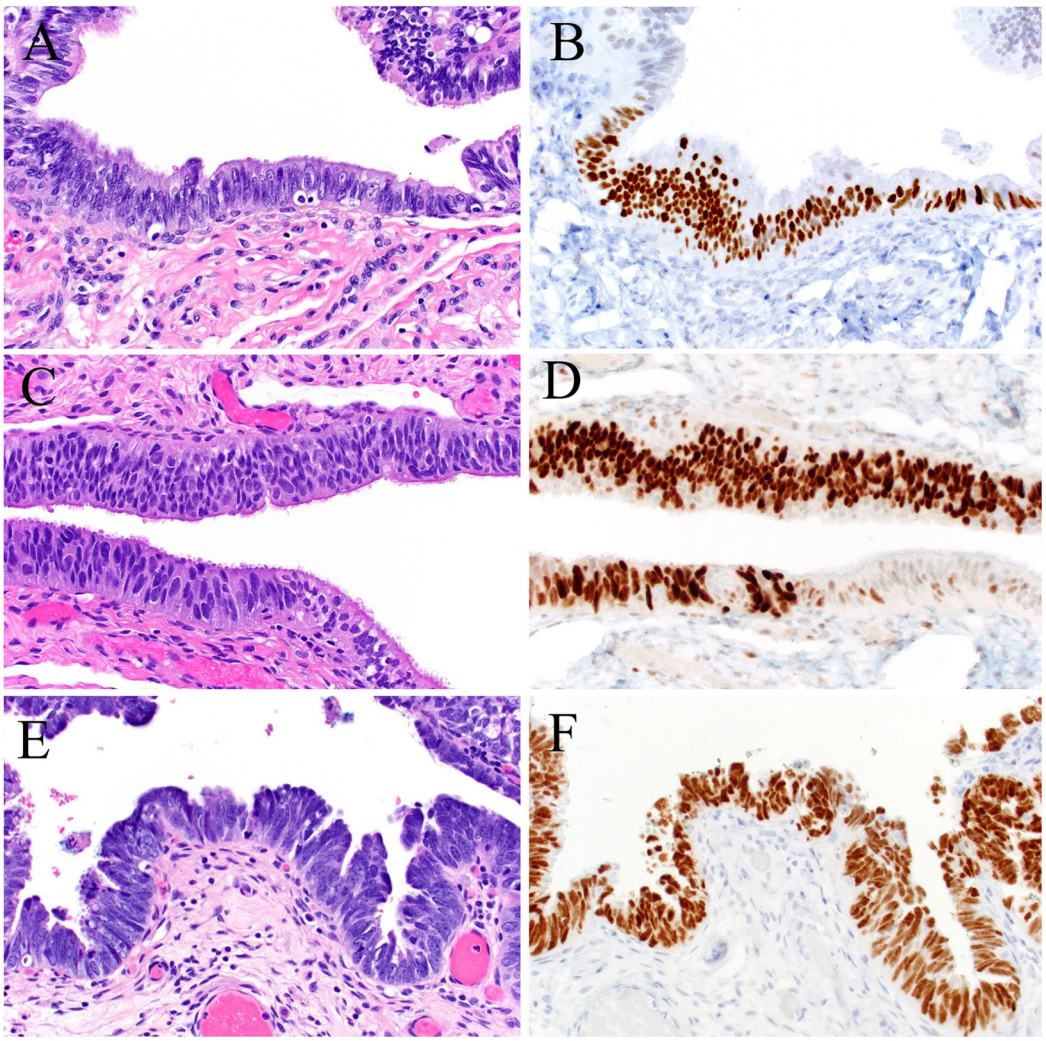

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