New Insights Into the Pathogenesis of Serous Ovarian Cancer and Its Clinical Impact

Keren Levanon, Christopher Crum, and Ronny Drapkin

ABSTRACT

There are only a handful of concepts concerning cancer and carcinogenesis that are currently beyond dispute. One such dogma is the adenoma-carcinoma sequence and that a multistep accumulation of genetic alterations is required for transformation from a benign to a neoplastic tissue. The inevitable derivative of this dogma is that every invasive carcinoma is in fact a missed in situ tumor, and furthermore, a late evolutionary stage in the sequence of development from a precursor lesion. Until fairly recently, high-grade serous ovarian carcinoma seemed to be one of the only known deviants of these concepts. In this article, we discuss the emergence of the fallopian tube fimbria as a field of origin for high-grade serous carcinomas and present a binary model of ovarian cancer pathogenesis that takes into consideration prior epidemiologic, morphologic, and genetic data. With the rise of the fallopian tube secretory epithelial cell as a cell of origin for high-grade pelvic serous carcinomas, the need to develop tools and model systems to characterize the biology and physiology of this cell is recognized.

INTRODUCTION

The body of literature on the involvement of oncogenes and tumor suppressors in the pathogenesis of many epithelial tumors has grown tremendously over the past two decades. Despite the diversity of aberrant pathways, it is now possible to begin to sketch out common themes for many epithelial cancers and their precursor lesions. For instance, recent studies demonstrate that in most epithelial tumors, one of the earliest identifiable changes in precursor lesions is the activation of the DNA damage repair (DDR) machinery and nuclear accumulation of p53 as recently reviewed by Halazonetis et al.1 In this model, the DDR pathway is activated by replicative stress and is considered a barrier to malignant transformation by inducing cell cycle arrest, senescence,2 and apoptosis.3

Most epithelial tumors also follow the adenoma-carcinoma sequence4 scheme whereby a normal epithelial cell undergoes genetic alterations of increasing complexity resulting in a morphologic evolution toward a state that is phenotypically consistent with a tumor cell.4 This pathway has been described in most epithelial tumors including colorectal carcinoma, where this sequence was first described by Jackman and Mayo in 1951,1 breast, thyroid, prostate, bladder,5 gastric, esophageal, pancreatic, cervical, endometrial, head and neck squamous cell carcinoma, skin,6 and non–small-cell lung carcinoma.6 A subset of low-grade adenocarcinomas of the ovary, specifically endometrioid and mucinous tumors, also follow a similar sequence.7 Therefore, the two models of epithelial carcinogenesis, the DDR pathway and the adenoma-carcinoma pathway, are active in most cancers studied. However, high-grade serous ovarian carcinomas (HGSOC), which typically emerge in the absence of recognizable pre-existing conditions, have been one important exception. In fact, the reproducible identification of a precursor and preinvasive lesion for this tumor has eluded clinicians and scientists for decades.

The apparent defiance of serous carcinomas to conform to the adenoma-carcinoma or DDR models is likely linked to the propensity of this tumor to spread early in its course. The dramatically rapid spread of this malignancy in the pelvis makes early-stage detection a highly rare event, and even in such cases finding a clear spectrum of continuous development from hyperproliferative to neoplastic tissue requires deliberate rigorous pathologic examination. Is it possible that serous ovarian carcinoma is indeed a fundamentally different entity, with exceptional biologic behavior, or have we been looking in the wrong place all along?
Recent molecular understanding correlated well with what was known by oncologists and pathologists for a long time: high-grade serous tumors differ from all other ovarian carcinomas in terms of their development, prognosis, pathologic findings, and underlying genetic alterations. This leads to the classification of ovarian cancers into type 1 tumors which are low grade and slowly developing (including endometrioid, mucinous and low grade serous); and type 2 tumors which are rapidly progressing high-grade serous carcinomas. Expression profiling studies have shown that high-grade tumors cluster separately from low-grade carcinomas and borderline tumors. Moreover, the former is associated strongly with TP53 mutations, whereas the latter are associated with mutations in \textit{KRAF}, \textit{BRAF}, \textit{PTEN}, and \textit{CTNNB1/\beta-catenin}.

The serous subtype of ovarian carcinoma accounts for approximately 60% to 80% of ovarian cancer cases and is by far the most aggressive histology. Fewer than 25% of the cases are detected at an early stage (stages I and II), a statistic which reflects grimly on the survival figures. Nearly 22,500 women are diagnosed with ovarian cancer every year in the United States alone, with approximately 200,000 new cases worldwide, and more than 50% die of this disease. High-grade serous carcinoma involves the surface of the ovary, often bilaterally, and the peritoneal membranes, with rapid onset of carcinomatosis, a fact that restricts the surgical options to debulking only. Despite the introduction of taxanes to the therapeutic protocols and the prolonged survival with intraperitoneal chemotherapy administration, there has been little progress in improving cure rates, a parameter that is still solely dependent on the disease stage at time of presentation. Certain targeted therapeutics have advanced into clinical trials in the past few years, but most of them have met with little success.

Several germ-line mutations and copy number variations that harbor increased risk for HGSOC have been reported, \textit{BRCA1} and \textit{BRCA2} being the most prevalent ones, accounting for 5% to 10% of the cases with up to 54% lifetime risk. Women recognized to have \textit{BRCA} mutations are currently treated with risk-reducing (prophylactic) excision of the adnexa (bilateral salpingo-oophorectomy [BSO]). This practice, which targets healthy women, has provided most of the emerging data in the study of early serous carcinomas, as will be discussed later.

The ongoing debate about the cell of origin of pelvic serous carcinomas (defined as tumors of serous histology arising in the ovary, fallopian tube, or peritoneum) was previously comprehensively reviewed by Piek et al. and from a pathologic point of view by Crum et al. An updated review of the genetic pathways to ovarian carcinogenesis, including the serous subtype was recently published by Landen et al. This review aims to confront the traditional models for serous carcinogenesis with accumulating data about the fallopian tube being the site-of-origin of a large proportion of high-grade pelvic serous carcinomas. We will focus on the proposed precursor lesions, and show that they comply with the established models of epithelial carcinogenesis. We will discuss the need to develop experimental model systems to study this epithelium and will raise questions, both clinical and biologic, that for the first time can actually be addressed as the fog surrounding the origin of this disease begins to clear.

The single layer of ovarian surface epithelium (OSE) constitutes less than 1% of the total ovarian mass, yet more than 90% of ovarian cancers are described as epithelial in origin. The OSE cells are uncommitted mesothelial cells that express both epithelial and mesenchymal markers. However, human OSE normally does not express certain markers of ovarian carcinomas such as E-cadherin, CA-125, and human epididymis protein 4 (HE4).

The OSE has endured as the field of origin for ovarian cancers since the dawn of the incessant ovulation hypothesis, coined by Fathalla in 1971. This hypothesis focuses on the OSE because of its exposure to repeated trauma and repair processes with every ovulatory cycle. It combines observations about spontaneous ovarian cancer in animals, specifically hyperovulated hens and epidemiological data about risk factors in humans, and hypothesizes that the greater the total number of lifetime ovulatory cycles the greater the risk for derangement of the repair mechanism of the OSE, leading to ovarian carcinoma. Over the years this model was expanded to account for the contribution of inflammation to ovarian carcinogenesis. In this scenario, normal ovulation is seen as an inflammatory response, involving cellular infiltration as well as cytokines’ and chemokines’ release. The main mediators are nitric oxide, prostaglandins, IL-1β, IL-6, IL-8, tumor necrosis factor-α, and neutrophil elastase. Presumably these factors may induce DNA damage in OSE cells, which along with the tissue repair processes proposed by Fathalla may result in neoplastic transformation.

Two other hypotheses relate to the hormone responsiveness of the OSE, which expresses receptors for gonadotrophin-releasing hormone, luteinizing hormone, follicle-stimulating hormone, estrogen, androgen, and progesterone. The gonadotrophin hypothesis suggests that the exposure to excessive hormone concentrations may be an independent facilitator of malignant transformation of the OSE. High gonadotrophin levels are characteristic in menopause, the polycystic ovary syndrome, infertility treatments or low parity and in women that do not use oral contraceptives, all of which are established risk factors for ovarian cancer. The hormone stimulation hypothesis regards elevated androgens as a predisposing factor, while progesterone it is a protective factor. It reconciles observations about increased risk in polycystic ovary syndrome, and protection conferred by gestation and oral contraception. It is likely that a combination of various aspects of these models contribute to the transformation of the OSE and the development of ovarian carcinomas.

There is strong evidence that many of the tumors of borderline malignancy and low-grade carcinomas of the ovary arise from cortical inclusion cysts (CICs) within the ovarian parenchyma underlying the OSE. These benign cysts are composed of Mullerian epithelium that closely resembles the fallopian tube. One proposed origin of CICs is invaginations of OSE into the stroma of the ovary as a result of ovulation and aging, with acquisition of a Mullerian epithelial phenotype through metaplasia. Another possible source is shedding of tubal epithelium (endosalpingiosis). Irrespective of the mechanism, CICs are lined with Mullerian epithelium that is exposed to the ovarian cortical stromal milieu. Presumably, as a result of hormone exposure and wound remodeling that occurs in...
### Table 1. Involvement of the FT in Patients With Invasive Pelvic Carcinomas and in High-Risk Population Undergoing Prophylactic BSO

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>BRCA Mutations Status</th>
<th>Pelvic Carcinoma</th>
<th>Involvement of FT</th>
<th>Extensive Sectioning</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic carcinoma</td>
<td></td>
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<td></td>
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<tr>
<td>Agoff et al70</td>
<td>7</td>
<td>4/7 57</td>
<td>7 100</td>
<td>5/7 71</td>
<td>+</td>
<td>Diagnosis of two FT malignancies required peritoneal lavage</td>
</tr>
<tr>
<td>Piek et al71</td>
<td>50</td>
<td>NA</td>
<td>50/50 100</td>
<td>3/50 6</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kindelberger et al72</td>
<td>55</td>
<td>NA</td>
<td>55/55 100</td>
<td>41/55 75</td>
<td>+</td>
<td>93% of TICs occurred in the fimbria</td>
</tr>
<tr>
<td>Carlson et al73</td>
<td>45</td>
<td>NA</td>
<td>45/45 100</td>
<td>28/45 62</td>
<td>±</td>
<td>26 cases had incomplete pathologic examination and the rate of tubal involvement was 50%, while the next 19 cases, which underwent extensive sectioning had tubal involvement rate of 79%</td>
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<td>High-risk prophylactic BSO v general population</td>
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<tr>
<td>Carcangiu et al74</td>
<td>26 high-risk v</td>
<td>BRCA1, 22 85</td>
<td>2/26 7.7</td>
<td>2/2 100</td>
<td>NA</td>
<td></td>
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<tr>
<td></td>
<td>49 control BSOs</td>
<td>BRCA, 24 15</td>
<td></td>
<td></td>
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<tr>
<td>Medeiros et al75</td>
<td>13 v 13 control BSO</td>
<td>NA</td>
<td>5/13 38</td>
<td>5/5 100</td>
<td>+</td>
<td>4/5 (80%) of cases involved the fimbria</td>
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<td>High-risk prophylactic BSO</td>
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<tr>
<td>Lu et al76</td>
<td>50</td>
<td>NA</td>
<td>4/50 8</td>
<td>0/4</td>
<td>+ (37/50 cases)</td>
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<tr>
<td>Kauff et al77</td>
<td>98</td>
<td>BRCA1, 56 57</td>
<td>0 0</td>
<td>0</td>
<td>–</td>
<td>One case of primary peritoneal carcinoma 16.3 months after BSO</td>
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<td></td>
<td></td>
<td>BRCA2, 42 43</td>
<td></td>
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<tr>
<td>Leeper et al78</td>
<td>30</td>
<td>BRCA1, 19 63.5</td>
<td>5/30 16.6</td>
<td>3/5 60</td>
<td>+</td>
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<td></td>
<td></td>
<td>BRCA2, 4 13.5</td>
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<td>No mutation detected, 7</td>
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<tr>
<td>Colgan et al79</td>
<td>60</td>
<td>BRCA1, 64 64</td>
<td>5/60 8</td>
<td>2/5 40</td>
<td>+</td>
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<td></td>
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<td>BRCA2, 7</td>
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<td></td>
<td></td>
<td>Both BRCA1/2, 1 1</td>
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<td></td>
<td></td>
<td>Not specified, 28</td>
<td></td>
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<tr>
<td>Olivier et al81</td>
<td>90</td>
<td>BRCA1, 58 64</td>
<td>5/90 5.5</td>
<td>3/5 60</td>
<td>+</td>
<td>Three additional cases of primary peritoneal cancer detected in follow-up; 38 additional high-risk patients underwent only prophylactic oophorectomy—no malignancies found</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2, 7</td>
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<td></td>
<td></td>
<td>Both BRCA1/2, 1 1</td>
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<td>Not specified, 28</td>
<td></td>
<td></td>
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<tr>
<td>Powell et al82</td>
<td>67</td>
<td>BRCA1, 43 64</td>
<td>7/41 17</td>
<td>4/7 57</td>
<td>+ (41/67 cases)</td>
<td>No abnormalities detected in 25 standard protocol cases; two additional cases of primary peritoneal cancer detected in follow-up</td>
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<tr>
<td></td>
<td></td>
<td>BRCA2, 24 36</td>
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<tr>
<td>Meeuwissen et al83</td>
<td>133</td>
<td>BRCA1/2, 86 65</td>
<td>1/133 0.75</td>
<td>1/1 100</td>
<td>–</td>
<td>One additional case of primary peritoneal cancer detected in follow-up</td>
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<td></td>
<td></td>
<td>Unknown, 47 35</td>
<td></td>
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<tr>
<td>Lamb et al84</td>
<td>113</td>
<td>BRCA1, 40 35</td>
<td>7/113 6.2</td>
<td>5/7 71</td>
<td>+</td>
<td>One of the two cases of malignancies that did not involve the FT was diagnosed as ovarian borderline adenofibroma with epithelial cytological atypia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2, 22 19</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Not tested or no mutation, 45</td>
<td></td>
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<tr>
<td>Finch et al85</td>
<td>159</td>
<td>BRCA1, 94 59</td>
<td>7/159 4.4</td>
<td>6/7 85</td>
<td>+</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2, 65 41</td>
<td></td>
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<tr>
<td>Callahan et al86</td>
<td>122</td>
<td>BRCA1, 60 49</td>
<td>7/122 5.7</td>
<td>7/7 100</td>
<td>+</td>
<td>6/7 (85%) of findings occurred in the fimbria, 1/7 involved the ampulla</td>
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<tr>
<td></td>
<td></td>
<td>BRCA2, 60 49</td>
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<td></td>
<td>Not specified, 2</td>
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</table>

Abbreviations: FT, fallopian tube; BSO, bilateral salpingo-oophorectomy; TIC, tubal intraepithelial carcinoma; NA, not available.
response to ovulation, these cells are rendered susceptible to neoplastic transformation and in some cases give rise to mucinous, endometrioid and low-grade serous carcinomas (Fig 1).59-52 CICs often occur adjacent to benign epithelial tumors, suggesting lineage continuity. Many of the endometrioid and mucinous carcinomas are associated with these benign tumors, a convincing link between CICs and these malignancies. In contrast to these tumors, a morphologic continuum from OSE to HGSOC has not been mapped and there has been scant evidence for the existence of a precursor lesion in the OSE or the CICs. Moreover, the majority of ovarian carcinomas (serous, mucinous, and endometrioid) seem to bear little resemblance to their proposed cell of origin (the OSE), recapitulating the histological features of Müllerian epithelia of the fallopian tube, cervix, and endometrium, respectively.53,54

Several studies have extensively examined the epithelium of ovaries removed as part of risk-reducing BSO procedures. Their findings have not established a consistent relationship between CICs and serous carcinomas. While some groups reported an increase in the number of inclusion cysts, metaplastic changes in these cysts, and cellular abnormalities55-57 others publications disputed these findings.58-62 The most recent study by Folkins et al, examining the largest cohort reported thus far, extensively studied 75 cases of prophylactic BSO from women who were BRCA1/2 mutation positive. Only one case harbored a questionable precursor lesion on the OSE, characterized by p53 staining.63 These observations raise the following questions: is the origin of HGSOC fundamentally different from other ovarian carcinomas? Is there a serous carcinogenic sequence? If so, where does this sequence occur?

Extraterine serous carcinoma is presumed to arise in three different locations in the female pelvis: the ovary (serous ovarian carcinoma), the endosalpinx (serous fallopian tube carcinoma [FTSC]), and on the peritoneal surface (primary peritoneal serous carcinoma). The assignment of tumor origin by pathologists has been predicated on pathologic criteria that focus on the location of the bulk of the disease. Because most serous carcinomas present as large ovarian masses, ovarian cases outnumber the other two by about a 50:1 ratio. The only site with a recognizable “early” carcinoma is the fallopian tube. A diagnosis of FTSC requires that four criteria be met:64-66 the main tumor is in the fallopian tube and arises from the endosalpinx, histology matches the tubal phenotype, if the tubal wall is invaded there has to be an evident transition between normal and malignant tubal epithelium, and the fallopian tube should contain more tumor than the ovary or endometrium. It is noteworthy that tumors meeting these criteria are uncommon, such that FTSC is decidedly a rare diagnosis. This is in part due to two facts. The first is that tumors presenting as large tubal masses are uncommon. The second is that pathologists do not customarily examine the entire fallopian tube in cases of pelvic serous carcinoma, but rather only a perfunctory section of the central fallopian tube. In retrospect, it is this practice that delayed the appreciation of the role of the distal fallopian tube—the fimbria—in serous carcinogenesis.

The aforementioned facts notwithstanding, the role of the fallopian tube in serous carcinogenesis was not ignored. Although the reported average annual incidence of FTSC in the United States is believed to be 0.3 per 100,000 women per year (compared with 16 per 100,000 per year in ovarian cancer),67 some investigators appreciated that BRCA1 and BRCA2 germ-line mutations confer an increased risk for FTSC. In a prospective study of 381 BRCA1 mutation carriers, Brose et al reported a 120-fold increased risk of fallopian tube cancer compared with the general population.68 Bannatyne and Russell69 commented that rigorous sectioning is essential to detect early tubal carcinomas. They anticipated finding tubal intraepithelial carcinoma (TIC) in 5% to 10% of serous ovarian cancer cases and suggested this phenomenon signified multifocal serous neoplasia. A reassessment of the incidence and the prognostic and clinicopathological features of this malignancy became possible with the widespread practice of prophylactic BSO for management of patients with familial high risk. In contrast to the standard pathologic sampling of the ampullary region of the fallopian tube in ovarian cancer cases, the more extensive complete sectioning of the tube highlighted the relative abundance of lesions specifically in the fimbria. Table 1 summarizes the results of published studies looking at the incidence of fallopian tube intraepithelial or invasive carcinoma in patients with the diagnosis of pelvic serous carcinoma or in patients undergoing risk-reducing BSO.

What have emerged from this data are two realizations. First, although the majority of serous carcinomas in symptomatic women with BRCA 1/2 mutations are attributed to the ovary, a majority of
early serous malignancies (TICs) detected in risk-reducing BSOs of healthy women are localized to the distal fallopian tube. Second, in women with pelvic serous carcinoma whose \textit{BRCA} status is unknown, TICs can be detected in approximately 50% of cases. Moreover, analysis of \textit{TP53} mutations in the TICs and the adjacent bulky carcinomas in these cases invariably reveal shared mutations, further supporting an origin in the distal fallopian tube.\textsuperscript{72}

The conclusions from these works are that the initial modified criteria by Hu et al\textsuperscript{64-66} for the diagnosis of FTSC detects only a portion of FTSCs and that the fallopian tube is a major site of origin for pelvic serous cancer irrespective of \textit{BRCA} status.

\textbf{MISSING PRECURSOR LESION}

The classical adenoma-carcinoma sequence model not only outlines the transition from an intraepithelial to an invasive lesion, but also highlights the latent precursor phase, that may or may not eventually progress to a neoplasm. In the distal fallopian tube, TICs cannot be considered precursor lesions, as they are widely viewed as frank malignancies that will eventually spread if not detected. What has been missing in the serous carcinogenesis sequence has been a bonafide precursor with limited potential of progressing to malignancy. Thus, the question has been whether one could find the precursor that preceded TIC and its lethal consequence, pelvic serous carcinoma.

Piek et al\textsuperscript{87} were the first to describe dysplastic changes in the fallopian tubes of 12 patients with familial high risk for ovarian cancer undergoing prophylactic BSO, and 13 control cases without increased risk. The dysplastic regions were pure secretory cell segments and displayed a higher proliferative index (demonstrated by positive Ki-67 staining). However, only one of these lesions displayed increase nuclear p53 staining.\textsuperscript{87} Carcangiu et al reported atypical hyperplastic lesions in two of 22 (9%) prophylactically resected fallopian tubes of \textit{BRCA1} mutation carriers.\textsuperscript{74} These studies, however, did not identify a discrete entity that was associated with the most common genetic defect of HGSOC—\textit{TP53} mutations. Resolving the earliest step in the \textit{TP53} mutation pathway was needed to bring forward a novel precursor to pelvic serous cancer.

The mentioned studies focused on the secretory epithelial cells of the fallopian tube (FTSECs). While the normal fallopian tube epithelium is a mixture of ciliated and secretory cells, the TIC and the invasive FTSC as well as HGSOC are comprised of only secretory cells. Using a protocol for sectioning and extensively examining the fallopian tube fimbria, termed the SEE-FIM protocol,\textsuperscript{75} Lee et al\textsuperscript{88} detected discrete segments of secretory cells with strong nuclear p53 immunostaining in benign-appearing tubal mucosa, which were termed p53 signatures. Interestingly, the p53 signatures displayed evidence for genome-wide DNA damage (as measured by positive immunohistochemical staining for phosphorylated histone H2A.X), a finding common to other epithelial precursors described by Bartkova et al\textsuperscript{5} and Gorgoulis et al.\textsuperscript{6} \textit{TP53} gene mutations were reliably detected in eight of 14 p53 signatures tested (57%).\textsuperscript{88} Figure 2 shows the histological characteristics of the spectrum of carcinogenic changes in the fallopian tube epithelium, ranging from normal to p53 signature, TIC, and invasive HGSOC.

The same group compared 41 \textit{BRCA} mutation carriers versus 58 cases undergoing BSO for benign indications and 17 patients with TICs. The p53 signatures occurred in 37% and 33% of fallopian tubes of these cases, respectively. Approximately 80% were detected in the fimbria. In fallopian tubes harboring TICs, p53 signatures were detected in 53% of the cases. Occasionally direct continuity was detected.\textsuperscript{89} Rarely p53-positive foci with features intermediate between p53 signatures and TICs were identified. These transition lesions, like the
Dysplasias previously reported by Piek et al, have an increased proliferation index (represented by high Ki-67/MiB1 scores) compared with p53 signatures but less so than TICs. No similar findings were found on the surface of ovaries removed in risk-reducing BSOs or for other benign indications.

In summary, the findings from these recent studies reveal a spectrum of visible epithelial alterations that offer a plausible serous carcinogenic model with three stages: the p53 signature, the in situ carcinoma (TIC), and the invasive carcinoma. All of the components of this spectrum share the following features with frankly malignant serous carcinoma: secretory-cell phenotype, evidence of genome-wide DNA damage, TP53 gene mutations, and a predominant fimbrial localization (Figs 3 and 4). The p53 signature precursors are similarly prevalent in women with familial high risk for ovarian cancer and in the general population. One mystery that remains to be unraveled is why the fallopian tube is invariably linked to BRCA1- and BRCA2-associated malignancies and to only one half of HGSOC in the general population. Conceivably, BRCA mutation carriers are either more susceptible to the aberrations in the pathways that lead to fallopian tube transformation, or conversely, less susceptible to transformation associated with CICs. Deciphering the answer to this question requires a thorough understanding of the carcinogenic pathways involving the two sites of origin.

**FTSEC: THE PRIME SUSPECT EMERGES**

Identification of the field of origin of serous carcinogenesis, immediately positions the FTSEC in the spotlight as being the cell of origin. The current knowledge about the normal biology of the fallopian tube is very limited, and most of the data originates from the discipline of assisted reproduction. As previously mentioned, the normal epithelium of the fallopian tube is comprised of two cell types: ciliated and secretory. The ciliated cells of the fallopian tube play a major role in the transport of the ovum, the sperm cells, and the zygote. Several markers uniquely distinguish the ciliated cells from the FTSEC: LhS28 (marks 9/H11001 ciliary basal bodies), CDKN1A/p21/WAF (cell cycle–related protein), and Foxj1 (transcription marker expressed during ciliogenesis).

The secretory cells secrete mucus that slows the progression of the spermatozoa through the fallopian tube, preserves their viability, and facilitates their appropriate capacitation and activation. Markers reported to be exclusively of the FTSEC subpopulation include: human milk fat globule 2, Bcl-2 (mitochondrial suppressor of apoptosis), and Pax-8 (transcription factor, regulator of thyroid, and urogenital tract development).

![Fig 3. High-grade serous carcinogenic sequence. The spectrum of fallopian tube (FT) epithelial transformation ranges from normal epithelium, through p53 signature, an intraepithelial, and eventually, an invasive carcinoma. Exfoliation into the peritoneal cavity is an early event. This model suggests that all types of pelvic serous tumors are the same entity, the majority of which originate from the FT fimbria. TIC, tubal intraepithelial carcinoma.](image-url)

![Fig 4. An integrated model of high-grade serous carcinogenesis. This model integrates the data about the stepwise development of serous carcinoma in the fimbria of the fallopian tube (FT) and in the ovarian surface epithelium (OSE) --derived cortical inclusion cysts (CICs). The hormone stimulation and the inflammatory mediators involved in ovulation are believed to have similar carcinogenic effect in both pathways.](image-url)
The ability to conduct in-depth studies of the cell of origin, beyond the descriptive histopathological research described earlier, depends on adequate in vitro culture systems. Several studies reported culturing human fallopian tube epithelial cells. However, these culture systems fail to present us with the proper tools to investigate the complexity of the carcinogenic process since, in these systems, the cells senesce and dedifferentiate after a short time in culture. Specifically, the enigmatically exclusive transformation of the FTSEC which spawns the serous tumors in a setting of a mixed cell population warrants insight. One report, by Kervanciouglu et al, highlights the fundamental advantage of polarized epithelial culture in recapitulating the in vivo tissue biology. With a similar approach in mind our group developed a fallopian tube epithelium culture system based on previous experience with polarized airway epithelium cultures. We are now able to mimic the normal histology of the fallopian tube fimbria epithelium, with ex vivo cocultures of ciliated and secretory cells. Furthermore, this model system mimics the in vivo profile of the two cell populations with regards to some of the immunomarkers mentioned earlier, and can be, for the first time, utilized to more closely examine serous carcinogenesis (Levanon and Drapkin, unpublished). With the identification of the FTSEC as a cell of origin for serous cancers and the emergence of in vitro culture systems, the time is now ripe to ask questions and apply well-established investigational approaches to the problem of pelvic serous carcinoma.

**IMPLICATIONS AND FUTURE DIRECTIONS**

The standard of care for pelvic serous carcinomas has not become integrated into the era of targeted therapy. The lack of insight into mechanisms of serous carcinogenesis reflects our inability to utilize the newer biologic therapies. It is tempting to speculate that an unprecedented rate of progress is now possible because the fundamental hurdle of identifying the correct field of origin and precursor lesion has been resolved. Clinical issues that must be addressed include the following points.

Should prophylactic surgery be limited to the fallopian tubes, or can one or both ovaries be spared in BRCA mutations carriers? Currently there is no data to support or reject such a practice. It carries an obvious decrease in early menopause–related morbidity and an improvement in quality of life, including preservation of fertility, but evidence supporting this approach is still limited in terms of the number of prospectively accrued cases. Irrespective of this, the pathologic practice for assessing BSO specimens from high-risk cases should number of prospectively accrued cases. Irrespective of this, the pathologic practice for assessing BSO specimens from high-risk cases should...
unpublished). Similar culture systems can be used to probe the relation between cumulative lifetime ovulation cycles and the risk for HGSOC. Does periodic exposure of the FTSEC to hormonal and inflammatory mediators of ovulation participate in the carcinogenesis of this cell type? If so, one can imagine future studies aimed at moderating the risk of some of these insults in high-risk individuals.

The genetic aberrations responsible for the adenoma-carcinoma sequence of HGSOC can now be better described. We can now shed some light on the endogenous and exogenous risk factors for pelvic serous carcinomas. One possible question may be why is it that the incidence of precursors in BRCA1 and BRCA2 mutation carriers is similar to the general population, but the risk for cancer is significantly increased. A retrospective genetic epidemiological study enrolling patients who underwent prophylactic BSO and were diagnosed as having precursor lesions but not invasive cancer compared with HGSOC patients may help shed light, though the cohort size is still small.

Finally, it is the hope that with the evolution of molecular imaging (reviewed by Weissleder), translation of the above noted genomic and phenotypic studies on serous precursor lesions, will result in the development of new imaging modality or probes that will make early detection a reality.

Role of the Fallopian Tube in Ovarian Cancer

Last but not least, perhaps it is time to refine the nomenclature and ascribe the credit to the true organ of origin. Naming the tumor pelvic serous carcinoma rather than ovarian serous carcinoma may not only be a matter of semantics, but hopefully the first step toward its eradication.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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