Editorial Commentary
Fallopian tube as main source for ovarian and pelvic (non-endometrial) serous carcinomas

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In 2012, it is estimated that 22,280 new cases of ovarian carcinoma will be diagnosed in the United States, with 15500 associated deaths [1]. The high case fatality rate of ovarian cancers, most of which are high-grade serous adenocarcinomas, can be attributed to the advanced stage at which most patients with this disease present, and their attendant poor prognoses at this stage [2]. Attempts at screening and early detection of ovarian cancer, using a combination of transvaginal ultrasounds, measurements of serum CA-125 and other biomarkers, have largely been unsuccessful due to their lack of sufficient specificity and sensitivity in the general population [3-5]. Prophylactic oophorectomies, which surveys shown are performed in a substantial portion of postmenopausal women [6-9], remain a subject of debate as a way a reducing the mortality of ovarian cancers. In any event, the failure of most current preventive methods is evidenced by the fact that the overall mortality for ovarian carcinoma has largely remained unchanged for several decades [10]. A logical approach to a seemingly intractable problem is to re-assess and question some fundamental assumptions, in this case the cell and organ of origin for "ovarian" or pelvic non-endometrial serous carcinomas. In this regard, the last decade has seen the emergence of a robust body of evidence that implicates the fallopian tube as the origin for most pelvic serous carcinomas that have traditionally been assumed to be of ovarian origin [11].

Several theories of ovarian carcinogenesis have been proposed over the years. Most assume the ovarian surface epithelium undergo malignant transformation. In incessant ovulation theory, a perpetual cycle of damage and repair of the ovarian surface epithelium increases the risk of malignant transformation [12]. The hormonal theory postulates that estrogen and gonadotropins cause stimulation and proliferation, and potentially malignant transformation of the ovarian surface epithelium [13]. Ovarian inclusions cysts are thought to develop from the ovarian surface epithelium, possibly after ovulation [14, 15]. Based on morphologic observations [16], the fact that inclusions are more commonly identified in the ovary contralateral to cancer-harboring ovaries [17, 18], and the extremely rare occurrence of early serous carcinomas within the inclusions [19, 20], it was assumed that after the ovarian surface epithelium invaginates into the underlying stroma to form inclusions, it undergoes mullerian metaplasia under the influence of the local stromal microenvironment [20, 21], then potentially undergoes malignant transformation resulting in carcinomas corresponding to the different cell types (serous, endometrioid, clear cell, mucinous and transitional cell). The notion that the ovarian surface epithelium is the source for ovarian serous carcinomas has endured for decades, its relatively weak evidentiary basis notwithstanding, due to the absence of a competing theory that can incorporate the available evidence into a convincing and logical framework, and/or the absence of such evidence.

It has been recognized for more than a century that serous carcinomas can be primary to the

fallopian tube [22], but the stringent guidelines that have traditionally been required to categorize a given adnexal serous carcinoma as tubal, likely resulted in an overwhelming majority of them being classified as ovarian [23-25]. The first line of evidence linking most adnexal serous carcinomas to the fallopian tube is simply observational: in risk-reducing salpingo-oophorectomy specimens performed on women at increased risk for the development of ovarian carcinomas, dysplastic, putative precancer, or intraepithelial lesions have predominantly been identified in fallopian tube, not the ovary. In one analysis of risk reducing salpingo-oophorectomy specimens from 111 BRCA mutation carriers that were pathologically processed in a systematic manner, 9.1% had occult neoplasia, including 2 patients with invasive serous fallopian tube carcinoma, 1 patient with invasive ovarian serous carcinoma, 5 patients with tubal intraepithelial carcinoma (TIC, the presumed precursor lesion for invasive high-grade serous carcinomas), and 2 patients had multifocal lesions of the ovary and TIC [26]. In a similar study by Medeiros et al [27], tubal carcinoma was identified in 5 of 13 patients; no ovarian lesions were identified. The authors also demonstrated that the fimbriated end of the fallopian tube is the preferred origin for the carcinomas [27]. Overall, the reported incidence of putative precursor or intraepithelial lesions of the fallopian tube in this setting has ranged from 6% to 50%, with tubal involvement in up to 100% [26-31]. Kindelberger et al examined 55 ovarian serous carcinomas and found that 71% involved the endosalpinx and/or had a TIC. All 5 tested TICs and their concurrent ovarian carcinomas contained identical *TP53* mutations, suggesting a common origin [32]. However, they also identified some *TP53* mutations in the fallopian tube that were absent from the ovary, which suggests that either the lesions multifocally evolved, or developed first in the tube [32]. Salvador et al [33] studied 12 cases of high-grade serous carcinoma, of which 10 cases showed either unilateral tubal mucosal involvement (7/12, 58.3%) or tubal obliteration ipsilateral to the dominant ovarian mass (3/12, 25%). Comparative analysis of chromosomal copy number changes by FISH in the tubal and synchronous ovarian lesions demonstrated similar changes in 3 cases (1 was different), providing some additional support for a common, monoclonal origin. The above observations and similar other studies [34], gave support to the proposal that TICs, which almost always were detected in the

fimbria, may be the source of high-grade serous carcinomas in both "high risk" as well as sporadic cases of ovarian serous carcinoma. Finally, the spectrum of putative and possibly non-obligate precursor lesions that have been described in the fallopian tube lends additional support to the concept that the serous neoplastic process may well begin in the fallopian tube rather than ovary [35].

Ovarian serous carcinomas are pathologically, clinically, and molecularly classifiable into high- and low-grade groups. The aforementioned studies apply predominantly to high-grade serous carcinomas. Low-grade serous carcinomas constitute only 10% of all ovarian serous carcinomas, and are recognized to evolve in a stepwise fashion from ovarian epithelial inclusions/ serous cystadenomas and serous borderline tumors [36]. This model is supported by the fact that similar mutations of the *KRAS* and *BRAF* genes are present in serous borderline tumors and in adjacent serous cystadenoma epithelium; that these mutations are shared by serous borderline tumors and low-grade but not high-grade serous carcinomas; that the majority of low-grade serous carcinomas have serous borderline areas; and the epithelial aneusomy differences in inclusion cysts between ovaries with serous borderline tumors and those without neoplastic disease [37-39]. Recently, our group evaluated the morphologic and immunophenotypic features of ovarian epithelial inclusions, ovarian surface epithelium, serous tumors (cystadenomas, borderline tumors, low-grade serous carcinomas), and distal tubal epithelium to gain some insight into the origin of low-grade serous carcinoma [40]. We found that the vast majority ovarian surface epithelium displayed a mesothelial phenotype (calretinin+/PAX8-/ tubulin-) and a low proliferative index (0.012%), while about 4% of cases displayed foci with tubal phenotype (calretinin-/PAX8+/tubulin+). Although epithelia with a tubal phenotype were only found in 4% cases, that finding did show that benign tubal epithelia are able to implant on the ovarian surface and architecturally simulate 'ovarian surface epithelium' microscopically. There were also two types of ovarian epithelial inclusions, and their proportional distributions were significantly different from those of surface epithelia. Most (78%) of the inclusions displayed a tubal phenotype and had a significantly higher proliferative index than surface epithelial, indicating that in most cases, these cell types are of different cellular line-

ages. The fact that we found more tubal-like epithelium in ovarian epithelial inclusions than in ovarian surface epithelium is a strong argument in support of the notion that most ovarian epithelial inclusions are not derived from the ovarian surface epithelium. Furthermore, if the fallopian tube-derived ovarian epithelial inclusions (78%) were truly originating from mesothelium-derived ovarian epithelial inclusions through a mullerian metaplasia, the metaplastic process must be a common event and hybrid type of ovarian epithelial inclusions should be commonly found in the ovary. However, the fact that hybrid or intermediate type of ovarian epithelial inclusions with both mesothelial and tubal phenotypes were rarely found in our practice is another strong argument that mesothelium-derived ovarian epithelial inclusions undergoing metaplasia to fallopian tube-like ovarian epithelial inclusions are unlikely. In addition, mesothelium-derived ovarian epithelial inclusions seem not able to grow through metaplasia or later on grow into a tumor mass as all these have an extremely low cellular proliferative index (similar to ovarian surface epithelium), while fallopian-derived ovarian epithelial inclusions showed comparable proliferative activity and immuophenotypes that are similar or identical to ovarian serous tumors. From these findings, we believe that the fallopian tube-derived ovarian epithelial inclusions are likely derived from tubal epithelia, and are the likely precursors of serous cystadenomas, borderline tumors and low-grade serous carcinomas.

The following model for female adnexal serous carcinogenesis is supported by the currently available evidence: Most low- and high-grade serous carcinomas likely originate from the fallopian tube. First unknown mutagenic factors (from perhaps inflammation) eventuate in the development of neoplastic lesions (TIC) in the fallopian tube, and the susceptibility to these factors may be increased in patients with DNA repair malfunctions, such as BRCA1 germline mutation carriers. Why these lesions have an increased propensity to develop in the fimbriated end is unclear. TIC lesions form papillary tufts when neoplastic epithelia grow faster than their stromal support and the constituent cells are loosely cohesive resulting in easily shedding and implanting on the surface of the ovary and the peritoneum in the absence of a mass lesion or invasive growth in the fallopian tube. This is the main carcinogenetic pathway of high-grade serous carcinoma and probably explains most

cases of "ovarian" and "peritoneal" high-grade serous carcinoma as traditionally diagnosed. Second, the normal fallopian tubal epithelium, mostly from fimbriated end, can easily implant on the ovarian surface. The latter may be related to the close spatial relationship between the ovarian surface and the tubal fimbriated end, which would allow the adjacent tubal epithelium to detach and implant in the ovarian stroma when ovulation or non-ovulation induced disruption of the ovarian surface occurs. Alternatively, adhesion of tubal epithelium on the ovarian surface may eventuate in fallopian tube derived-inclusion formation in the ovary. The acquisition of *KRAS* or *BRAF* and possibly other mutations in tubal derived inclusions and serous cystadenomas result in their transformation to serous borderline tumors and ultimately, low-grade serous carcinomas. Third, a small proportion of high-grade serous carcinomas may develop from low-grade serous carcinomas or serous borderline tumors after the acquisition of additional mutations such as *TP53* [41, 42]. The latter pathway may explain why in some high-grade serous carcinomas, there is neither evidence of tubal involvement nor TIC lesions.

A paradigm shift that results in most pelvic (non-endometrial) serous carcinomas being considered to be of fallopian tubal, rather than ovarian origination has significant clinical implications. The most important is that it introduces the possibility of prophylactic salpingectomies as a way of reducing the incidence (and mortality) of "ovarian" carcinomas. If adnexal serous carcinomas are unequivocally shown to develop almost exclusively in the fimbria, salpingectomy or fimbriaectomy alone would be sufficient to reduce the risk of pelvic serous cancer while preserving ovarian function and avoiding the negative effects associated with removal of the ovaries. Thus, simultaneous risk-reducing salpingectomies may become more widespread whenever a hysterectomy needs to be performed for benign indications and may be worth evaluating as isolated preventive procedures for women at a certain age group. It is well established that tubal ligation has a protective effect against the development of ovarian cancer [43-45]. Although the mechanisms remain unclear, with a tubal model of serous carcinogenesis, this protective risk may be explained in 3 ways: 1) For mid tubal ligation procedures, the mechanical barrier created by the ligation may prevent potentially mutagenic factors (inflammation, retro-

grade menstruation material) from reaching the distal fallopian tube 2) For distal tubal ligation procedures, removal of the spatial relationship that as previously noted, facilitates the movement of tubal epithelium to the ovary, and 3) Removal of significant segments of tubal epithelium removes potential foci of malignant transformation. Future research will define more precisely the precise sequence of ovarian serous carcinogenesis. At present, however, investigative efforts that are aimed at reducing the incidence of, and mortality from pelvic (non-endometrial) serous carcinomas should be focused on the fallopian tube, as the current state of evidence indicates that this is their site of origin in most cases. Careful and well designed clinical trials for pelvic serous carcinoma prevention by removal of fallopian tubes or their fimbriated ends are justified and should be conducted.

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