Lessons from BRCA:
The distal fallopian tube is a source of surface “ovarian” cancer

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Introduction
Ovarian epithelial cancer is diagnosed in approximately 25,000 women yearly in the United States, accounting for approximately 12,500 deaths. These tumors typically afflict women near or post menopause and peak in the sixth and seventh decades of life. Women with a hereditary predisposition (including those with mutations in the BRCA 1 or 2 genes) develop the disease on average a decade earlier, and management of this group centers on removal of the fallopian tubes and ovaries prior to the age of risk for cancer onset. Based on recent data, this “age of risk” initiates at 39-40 years of age.

Ovarian cancer has traditionally been presumed to arise in the ovarian surface epithelium (OSE) or in derived ovarian cortical epithelial inclusions, which exhibit the morphologic features of reproductive tract (mullerian) epithelium. These mullerian inclusions are not present at birth, but are acquired during reproductive life. Three possible mechanisms for their development include epithelium from the distal fallopian tube (endosalpingiosis) by exfoliation or tubal-ovarian adhesions, transformation of the ovarian surface mesothelium to a mullerian epithelium, and implantation of cells from the endometrium via retrograde menstruation (endometriosis). The malignancies that presumably arise from these epithelia fall into two general groups with respect to presentation and behavior. The first consists of adenocarcinomas with mucinous or endometrioid differentiation. These tumors are usually identified in the substance of the ovary and often, confined to one or more cysts (intra-cystic), consistent with an origin in these mullerian cysts or their endometriotic variants. The second group consists of serous carcinomas, which are so-called because of a resemblance to fallopian tube epithelium in their benign counterparts. These tumors are typically discovered on the ovarian surface, although a smaller percentage probably arises within the substance of the ovary. Because serous carcinomas are discovered on the ovarian surface, they often involve the fallopian tubes, mesentery and omentum. Because of the latter, serous carcinomas of the ovary are the most lethal form of epithelial ovarian cancer.

The aggressive nature of serous carcinoma is explained also by its pathogenesis. Endometrioid and mucinous carcinomas arise in a step-wise fashion, often in the presence of a benign tumor, such as endometriotic cyst, or a mucinous cystadenoma. This gradual process of malignant transformation occurs within the substance of the ovary and does not usually extend beyond the ovary until late in its course. In contrast, serous
cancer appears to arise quickly via mutations in the p53 tumor suppressor gene. This property, coupled with their propensity to involve the ovarian surface, makes these tumors difficult if not impossible to detect prior to spread.

Although the OSE/mullerian inclusion theory is the most enduring, and will explain some ovarian tumors, it has not satisfactorily resolved the origin of serous carcinomas. Only a few prior pathologic studies have attempted to identify early ovarian serous carcinomas. In one study, 14 small serous carcinomas were identified in the ovarian cortex from a large consultation experience. However, a precursor lesion per se was not illustrated. Another study of ovaries prophylactically removed from women at risk for ovarian cancer did not identify a precursor lesion in the ovarian cortex.

The fallopian tube

Quietly emerging parallel to the OSE theory of serous carcinogenesis has been the realization that the fallopian tube is also a source for serous carcinoma. Beginning in 1995, investigators began identifying early serous carcinomas of the fallopian tube in prophylactic salpingo-oophorectomies from women with BRCA mutations (BRCA+). This finding necessitated a shift in thinking, with emphasis on removing both tubes and ovaries from these patients. Since then, early serous carcinoma has been diagnosed in the fallopian tubes of approximately 5% of BRCA+ patients undergoing prophylactic bilateral salpingo-oophorectomy. Depending on the study, from 40 to 100% of tumors discovered in these patients were located in the tubes. In some of these cases, the carcinomas were detected sufficiently early that they were confined to the epithelium (tubal intraepithelial carcinoma).

The relatively high frequency of early tubal carcinoma in prophylactic salpingo-oophorectomy specimens contrasts sharply with the reported frequency of tubal carcinomas. Primary tubal carcinomas are rare, likely due to the criteria imposed for their distinction from ovarian cancers. Primary tubal carcinomas must show a precursor lesion; exhibit the bulk of the tumor inside the tube, and extra-tubal tumor must be smaller and largely confined to the ovarian surface when present. Classic primary tubal carcinomas – those that fulfill the requirements for the diagnosis - thus typically present as a fusiform expansion in the center of the fallopian tube.

The fimbria in BRCA+ associated early serous carcinomas

Although it is conceivable that BRCA+ women are more prone to fallopian tube carcinomas than those without a family history, we hypothesized that the discrepancy between frequency of this tumor in the general population and BRCA+ women might be resolved by the site of origin in the tube. Because central tubal carcinomas are rare, we elected to study the fimbriated end of the tube on the premise that it was the most susceptible to neoplastic transformation. In part using a protocol for sectioning and extensively examining the fimbrial end (SEE-FIM) we analyzed a series of prophylactic salpingo-oophorectomies from BRCA+ women. In five of five cases, the tumors arose within (4 cases) or just proximal to the fimbriated end (one case). Medeiros et al summarize this in poster 117. In a larger study examining the location(s) of serous carcinomas in the tube, both sporadic and BRCA+ tumors predominated in the distal tube. The natural question in the face of this information is whether the distal fallopian tube explains sporadic surface ovarian serous carcinomas.
Ovarian surface serous carcinoma and the fimbria

Because a significant proportion of early serous carcinomas diagnosed in BRCA+ women initiate as intraepithelial carcinomas in the fimbria, we addressed the second hypothesis that non-familial serous carcinomas involving the ovaries and peritoneum originate in the distal fallopian tube. This is presented in the abstract by Kindelberger et al. This hypothesis had not been addressed previously because the fallopian tubes are not routinely examined in toto in cases of ovarian cancer.

In a study of 42 completely evaluated specimens, three fourths (31) also had involvement of the inner lining of the tube. Of twenty-five cases classified as primary ovarian serous carcinoma, 20 (80%) contained preinvasive intraepithelial carcinoma. Of the one-fourth that did not exhibit involvement of the tubal mucosa, most contained a feature (such as a co-existing benign ovarian tumor) that would suggest origin in the ovary, similar to endometrioid and mucinous tumors. Based on these statistics, it is conceivable that nearly three out of four serous “ovarian” carcinomas arise in the inner lining of the distal fallopian tube.

In fulfilling the hypothesis that most familial and sporadic serous carcinomas are arising in the distal tube, we have been able to resolve many of the observations listed as points one through six above. It explains the high rate of surface involvement of both ovaries due to proximity to the fimbria, provides for a morphologically recognizable preinvasive carcinoma (intraepithelial carcinoma) that is capable of metastasizing by exfoliation without undergoing replacement of the tube, explains why most tumors originating in the fimbria are not appreciated as primary carcinomas, and why centrally placed tumors that replace most of the tube are so rare, simply because the ampulla is an uncommon site of origin. Additional support for the tube as an origin for serous carcinomas has been addressed in prior studies, including those showing that the gene expression profile of serous neoplasia closely resembles that of the normal fallopian tube.

“p53 signatures”: both pitfall and promise

In our efforts to detect early serous carcinomas in BRCA+ women, we employed a commonly used immunohistochemical stain for p53. p53 protein is over-accumulated in serous carcinoma, registering as a strongly positive intranuclear signal. We found that early serous carcinomas of the tube also stained strongly, a property that facilitated its detection in difficult cases. However, a significant pitfall in interpretation stems from the fact that occasionally foci of benign-appearing mucosa also stain strongly for this marker. We termed these foci “p53 signatures”. Because of this we routinely employ both MIB-1 (a proliferative marker) and p53 immunostaining as adjuncts to histopathologic evaluation when discriminating neoplastic from non-neoplastic p53 positive epithelium.

Although a potential pitfall in the interpretation of early fallopian tube neoplasia, “p53 signatures” may hold considerable promise. As discussed in poster 113 by Lee et al, p53 signatures are not a random event. We have found that these signatures are most commonly present in the distal tube and predominate in a specific cell type (secretory) that is the presumed cell of origin for tubal serous carcinoma. Currently, studies are in progress to determine if p53 signatures exhibit other properties that fulfill the requirement of an “early” precursor to serous carcinoma.
A paradox explained

The rarity of fallopian tube carcinoma can now be explained by the fact that the conditions that permit a large tubal tumor require an origin in the center of the tube, which is distinctly uncommon. Conversely, tumors arising on the fimbria will by definition be more likely to exfoliate to the ovarian and peritoneal surfaces. Thus the latter are less likely to be appreciated as primary tubal cancers because they will not fulfill the definition of tubal cancer (ie the tube hosts the largest tumor mass). The site of origin in the fimbria may be missed with limited sectioning, and the bulk of the tumor will be on the ovaries or peritoneum. Whether all high grades serous carcinomas ultimately coming from the fallopian tube – either directly or indirectly via an interval of endosalpingiosis – remains to be confirmed, but is a viable concept.

Implications to the field

If the above observations are validated by larger studies, it is likely that three-fourths of pelvic serous carcinomas will not be prevented by early detection. However, these discoveries raise considerable hope for strategies designed to reduce the risk of precursor development and/or remove the epithelium that is most susceptible to early serous carcinoma. To this end, greater knowledge of how risk-lowering variables such as oral contraceptive therapy impact on the tubal epithelium is essential; perchance other drugs exist that are more effective. The fimbria shares similarities with the ovarian cortex, one of which is a susceptibility to adenofibromas (See Bossuyt et al, poster 114). Ultimately a greater knowledge of the fimbrial “transformation zone” may spawn an entirely new list of tools for preventing the most lethal of “ovarian” carcinomas.

10 Finch A, Shaw P, Rosen B, Murphy J, Narod SA, Colgan TJ. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol Oncol. 2005 Aug 30;
