IN THE SPOTLIGHT

Culprit or Bystander? The Role of the Fallopian Tube in “Ovarian” High-Grade Serous Carcinoma

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Summary: The concurrence of intraepithelial high-grade neoplasia in the fallopian tube with metastatic implants has been taken as evidence of a tubal origin for high-grade serous pelvic carcinomas. In the current issue, Eckert and colleagues perform detailed genomic phylogenetic analyses and demonstrate that some cases of high-grade serous intraepithelial tubal neoplasia are metastatic implants and not precursor lesions. Cancer Discov; 6(12):1309–11. ©2016 AACR.

See related article by Eckert and colleagues, p. 1342 (7).

“Ovarian” (pelvic) carcinomas comprise a heterogeneous group of neoplasms, which may be unique among solid tumors in the lack of consensus about the organ or origin. Traditionally, nonuterine pelvic carcinomas have been labeled as ovarian, fallopian tube (FT), or primary peritoneal based on arbitrary assignations based on the volume of disease identified at different sites and the presumption that the ovary is the most common site of origin. For example, Gynecologic Oncology Group (GOG) criteria specify the ovary as the primary site of disease for any nonuterine high-grade serous carcinoma (HGSC) involving multiple intra-abdominal organs with at least 0.5 cm of ovarian stromal involvement. Similarly, if both the ovary and FT have bulky neoplasm, the primary site is labeled ovary unless there is a clear transition from intraepithelial neoplasm to invasive carcinoma in the FT. However, no such transition is required to label nonuterine HGSC as ovarian primary, and a similar precursor intraepithelial neoplasm of the ovary has yet to be identified. The increased use of neoadjuvant chemotherapy, which affects disease distribution, further increases the difficulty of determining the site of origin. Understanding the origin and the path of progression of these aggressive carcinomas directly bears on strategies for risk assessment, early detection, and prevention.

The ovary is primarily composed of stroma with a smaller fraction consisting of germ cells and ovarian surface epithelium, which is derived from primordial mesothelium. Pelvic nonuterine carcinomas can be broken down into a number of distinct histologic subtypes, including serous, clear cell, endometrioid, mucinous, and those with mixed features. Each of these subtypes is associated with distinct molecular pathways and may arise from different organs and cells of origin. For example, clear cell and endometrioid carcinomas probably arise in endometriosis and share characteristic alterations in PTEN, PIK3CA, and ARID1A. Serous carcinomas are divided into low-grade and high-grade carcinomas. HGSC is the most common form of nonuterine pelvic carcinoma, representing approximately 70% of cases, and is characterized by near-universal mutations in TP53, genomic instability, and defects in DNA repair, particularly homologous recombination repair. Pelvic HGSC usually presents with metastatic and bulky multifocal disease, making the organ of origin difficult to determine.

It was recognized in the early 1980s that HGSC could be multifocal and coexist with intraepithelial neoplasia in the FT, and Bannatyne and Russell recommended more careful pathologic evaluation of the entire FT in cases with HGSC (1). But it was the uptake of preventive surgeries in the late 1990s for genetic risk of “ovarian” carcinoma conferred by inherited mutations in BRCA1 and BRCA2 (BRCA1/2) that provided a new window into the origin of HGSC (2, 3). Occult neoplasms identified at risk-reducing surgery in BRCA1/2 mutation carriers are almost always located in the FT and not the ovary, including both microscopic invasive HGSC and high-grade intraepithelial neoplasia (also termed serous tubal intraepithelial carcinoma [STIC]). The predominance of the FT as the site of these early neoplasms led to the tubal hypothesis: that the FT is the origin of nonuterine pelvic HGSC. The practice of complete serial sectioning of the FTs became standard of care for risk-reducing surgeries in high-risk women, a practice essential to the identification of microscopic neoplasia in the FT (2, 3). The tubal origin of HGSC was further supported by a series of studies that identified frequent occult tubal involvement in advanced-stage pelvic HGSC if careful serial sectioning of the FT was performed (4). However, these studies showed an association between neoplastic lesions in the FT and elsewhere, without proving the site of origin. The relative role of the FT in sporadic HGSC may also have been confused by not distinguishing sporadic from inherited pelvic HGSC in most studies.

Nevertheless, the paradigm shift toward a tubal origin of nonuterine HGSC was so complete that the tubal hypothesis was featured by Dr. Oz in 2009 and discussed widely on blogs. High-risk women wondered why they needed to remove their ovaries and suffer the consequences of surgical menopause if the real culprit was the FT. The clinical implications are great; risk-reducing salpingo-oophorectomy reduces mortality of BRCA1/2 mutation carriers (5). The safety for high-risk women...
of retaining the ovaries is unknown, and a randomized trial comparing bilateral salpingectomy to salpingo-oophorectomy would be unethical. For women at normal risk of “ovarian” cancer, some experts have suggested that bilateral salpingectomy should be the preferred method of female sterilization and should be performed with every hysterectomy when ovaries are retained (called opportunistic salpingectomy; ref. 6).

The study by Eckert and colleagues provides new insights into this thorny problem (7). The diminutive size of STIC lesions in the FT provides challenges for detailed molecular characterization. Nevertheless, the authors isolated neoplastic cells using laser-capture microdissection and applied whole-exome sequencing to STIC paired with metastatic deposits from the same patient. They then used phylogenetic analyses to postulate the primary site. Among eight women with STIC and multifocal HGSC, mutational profiling identified the STIC as the precursor lesion in half. But notably, in at least two cases, the STIC appeared to be a metastatic implant. They experimentally supported the plausibility of intramucosal spread to the FT by demonstrating that HGSC spheroids can implant into the epithelium of ex vivo FT explants and attain a similar appearance to STIC (Fig. 4E of ref. 7).

The potential for intramucosal metastatic implants is not unique to this scenario, as it is a well-documented finding in bronchial epithelium from lung carcinomas and even in FT epithelium from nongynecologic sources (8, 9). Previous evidence for the possibility of metastatic spread to the FT from HGSC came from the observation of multifocal STIC present in some advanced HGSC cases and the presence of STIC in some cases of uterine serous carcinomas.

These findings call into question previous assumptions that the finding of synchronous STIC and metastatic HGSC implicates the FT as the organ of origin. The best evidence for a FT origin for HGSC remains the location of the early microscopic cancers identified in women with increased genetic risk. When only microscopic cancer is identified, FTs are serially sectioned, and cases with multifocal disease or elevated serum CA125 (implying macroscopic disease) are excluded, the FT is the location in 90% of HGSC in BRCA1/2 mutation carriers. The role of the FT in sporadic HGSC is less well defined. Eckert and colleagues evaluated only cases without BRCA1/2 mutations and provide some answers. In half of the cases, STIC was the presumed precursor lesion, so the FT remains the likely origin for many sporadic “ovarian” HGSCs. But these cases were specifically chosen because they had identifiable STIC, and many women with sporadic ovarian and peritoneal HGSC have no such identifiable lesions. Therefore, the fraction of unselected sporadic HGSCs that have an FT origin remains unknown. Larger phylogenetic studies of HGSC genotyped for inherited risk are needed to answer this question. These data will be critical in understanding the efficacy of opportunistic salpingectomy in reducing cancer risk.

The origin of HGSC that is labeled primary peritoneal carcinoma is another interesting mystery on which the work by Eckert and colleagues sheds light and raises important questions. In BRCA1/2 mutation carriers who have undergone bilateral salpingo-oophorectomy, the majority of primary peritoneal carcinomas occur in the first 5 years after risk-reducing surgery with only rare cases reported after that (10). These data suggest that an occult FT or ovarian carcinoma missed at
time of risk-reducing surgery might be the actual source of the majority of “primary peritoneal” carcinomas in women with BRCA1/2 mutations. The omentum is typically the anatomic site of bulkiest tumor in “primary peritoneal” carcinoma. In the two cases in which the STIC was secondary to metastatic spread, Eckert and colleagues identified the omentum as the most “basal” of the sampled tumor sites (7). In women without cancer, the omentum is a common site of endosalpingiosis, non-neoplastic FT-like epithelium occurring outside the FT. Possibly, endosalpingiosis in the omentum was the site of origin, though endosalpingiosis is more often associated with low-grade serous neoplasms. Alternatively, the primary site may not have been sampled for these 2 patients, and the omentum represented an early site of metastasis with further metastasis occurring from the omentum to FT mucosa.

Understanding the origin of pelvic carcinomas is critically important for optimizing cancer prevention strategies at both the individual and population levels. In studying the origin of HGSC, it remains important to separate cases driven by germline mutations in BRCA1/2 or other ovarian cancer susceptibility genes from sporadic carcinomas. Eckert and colleagues have made a seminal contribution to our understanding by providing genomic and experimental data supporting the ability of at least some sporadic HGSC to secondarily implant into the FT mucosa (Fig. 1). We congratulate the authors and look forward to further revelations on the molecular progression of pelvic HGSC.

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