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Review

Precursors to pelvic serous carcinoma and their clinical implications

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ABSTRACT

Pelvic serous carcinoma has traditionally been viewed as a rapidly evolving malignancy, due principally to its late stage at diagnosis and tendency for poor outcome, both in the endometrium and the upper genital tract. Recently, studies of women with BRCA1 or BRCA2 mutations (BRCA+) undergoing risk reducing salpingo-oophorectomy have highlighted the distal fallopian tube as a common (80%) site of tumor origin and additional studies of unselected women with pelvic serous carcinoma have demonstrated that serous tubal intraepithelial carcinoma may precede a significant percentage of these tumors. This review examines the serous carcinogenic spectrum in the fallopian tube, highlighting recent evidence that these tumors may follow a defined precursor that has been present for a prolonged interval. The data supporting a candidate precursor, the implications of these findings for early detection and prevention of pelvic serous carcinoma and the caveats, are discussed.

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Introduction

The majority of epithelial cancers, whether they arise in the lung, colon, stomach, pancreas, uterus, ovary, cervix or other sites, arise via a sequence of events that progressively evolve into a malignant phenotype. In most cases, this pathway begins in a biologically normal epithelium, which, for a period of time, is vulnerable to intervention (or spontaneous resolution) relative to later stages of the neoplastic continuum. A classic example is the cervix, where infection by oncogenic human papillomaviruses initiates as a precancerous lesion (CIN). Interruption of this process by colposcopic exam and lesion ablation prevents cervical cancer. Similarly, immunization with viral-like particles that duplicate the antigenic determinants of these cancer-related HPV types prevents CIN from developing. Hence, cervical cancer is prevented by blocking the development of the earliest phase of tumor development [1]. If by analogy, cancer is viewed as a forest fire, the precursor is a lit match. The vaccine effectively prevents the match from being struck or extinguishes it before it can ignite the forest fire.

Prevention of ovarian carcinoma, the most common of which is serous carcinoma, has been complicated by factors that are not present in the cervical cancer model. First, the ovary is not sufficiently accessible to permit frequent inspection. Second, serous carcinomas of the ovary typically spread early in their *clinical* course, and third, the source of the tumor – by analogy the place and mechanism by which the match is struck – has until recently been a mystery. Ovarian cancer accounts for approximately 3% of malignancies in women but is the leading cause of death from gynecologic cancers with an estimated 15,280 deaths in 2007 [2]. The lifetime risk of developing an ovarian cancer is much higher for women with hereditary mutations in BRCA1

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or BRCA2 [3]. Because serous carcinoma is usually discovered at a late clinical stage after spreading to the ovarian surface and peritoneum, it has a poor outcome.

Recent molecular studies have suggested that epithelial ovarian malignancies can be divided into two groups based on shared genetic mutations and observed progression from precursor lesions [4,5]. The type I tumors show mutations in a variety of pathways including mismatch repair genes, BRAF, KRAS, Beta-catenin, and PTEN. This family includes clear cell, endometrioid, mucinous, and low-grade serous carcinomas as well as the borderline (serous, mucinous, endometrioid) tumors. Type I tumors seem to evolve in a stepwise fashion from cortical inclusion cysts and endometriosis to borderline tumors to invasive malignancies. Low-grade serous carcinomas, for instance, are more likely to have mutations in BRAF and KRAS similar to their borderline mucinous and endometrioid counterparts. Conversely, high-grade serous carcinomas (type II tumors) commonly show mutations in p53 and are usually not found in association with adjacent borderline serous tumors. High-grade serous malignancies are usually discovered at an advanced stage, which has made identification of a precursor lesion elusive in the past due to the extensive tumor distribution when detected.

The BRCA+ model and serous tubal intraepithelial carcinoma (STIC)

Historically, primary fallopian tube malignancies have been considered rare relative to conventional ovarian carcinomas, approximately one fiftieth as common [6,7]. Part of this disparity was attributed to the stringent criteria for the diagnosis of a primary tubal malignancy. Criteria include the presence of a mass lesion in the fallopian tube that contrasts with other candidate sites, such as the ovaries and the presence of an intraepithelial component, identical to serous intraepithelial carcinoma of the uterus. Until recently, the fallopian tube received little notice as a significant source of serous carcinomas, given that the estimated incidence is 0.41 per 100,000 [8]. In the population carrying BRCA1 or BRCA2 mutations (BRCA+), most symptomatic serous carcinomas are designated as ovarian in origin according to the traditional method of primary site assignment mentioned above. Examination of prophylactically removed fallopian tubes and ovaries, however, has shown that a large number of early serous carcinomas involve the fallopian tube, either as an invasive or intraepithelial carcinoma. Between 57 and 100% of these cases have exhibited involvement of the fimbriated end of the fallopian tube (Table 1) [9–12]. These observations have increasingly focused attention to the fallopian tube as the source of a pathway to high grade serous malignancies.

Table 1
This table illustrates the proportion of cases with a possible tubal origin in women with BRCA1 or BRCA2 heritable mutations (BRCA+) undergoing prophylactic salpingo-oophorectomies (upper) and symptomatic women with ovarian cancer (lower)

Author	Subjects	Number	Tumor (%)	Possible tubal origin[a]
Prophylactic salpingo-oophorectomies from asymptomatic women				
Powell et al. [9]	BRCA+	67	7 (10)	4 (57)
Finch et al. [10]	BRCA+	159	7 (4)	6 (86)
Callahan et al. [11]	BRCA+	100	7 (7)	7 (100)
Leeper et al. [12]	BRCA+	30	5 (17)	3 (60)
Unselected women with a clinical diagnosis of serous ovarian or peritoneal carcinoma				
Kindelberger et al. [14]	Ovarian serous CA	43	All	20 (47)
Carlson et al. [15]	Peritoneal serous CA	19	All	9 (47)
Roh et al. [17]	Ovarian serous CA	87	All	31 (36)

All have undergone as complete examination of the fallopian tubes as possible.
BRCA+, BRCA1 or BRCA2 mutation-positive.
[a] Possible tubal origin based on the presence of serous tubal intraepithelial carcinoma.

In the fallopian tube model, serous tubal intraepithelial carcinoma (STIC) is the earliest morphologic manifestation of serous carcinoma. STICs are composed of secretory cells showing significant atypia, such as loss of nuclear polarity, prominent nucleoli, and increased nuclear to cytoplasmic ratio. By immunohistochemistry, STICs are usually positive for p53 and should show an increased proliferation ratio (MIB-1) as compared to the background tubal epithelium [13].

Tubal intraepithelial carcinomas, ovarian and peritoneal serous cancer

The association of STIC with BRCA+ status has strongly endorsed the concept that this entity is the more common early malignancy in women with this genetic risk factor. This association raised the obvious question of whether pelvic serous malignancies without a documented history of BRCA+ could be linked to the distal fallopian tube. Three recent studies have supported this pathway as an explanation for a significant proportion of pelvic serous carcinomas, including many fulfilling the criteria for either ovarian or primary peritoneal serous carcinomas. Kindelberger et al. showed that 47% of tumors classified as serous ovarian carcinomas co-existed with a STIC [14]. Carlson et al. similarly showed that complete examination of the fallopian tubes in women with primary peritoneal serous carcinomas disclosed a STIC in 47% [15]. In both studies, p53 mutation analysis in the STICs and remote tumors disclosed the same mutations, genetically linking the two. Moreover, a recent study from another group that examined paired STICs and remote tumors supported a genetic link between the two by examining anomalies in chromosomal number [16]. A fourth study by Roh et al. computed a slightly lower frequency of STIC in ovarian carcinomas (36%; Table 1) [17].

The concept that STIC – when present – represents the earliest phase of pelvic serous carcinoma is still controversial; an alternative explanation would be spread from an ovarian or peritoneal primary to the endosalpinx. This is an interesting controversy in as much as the presence of STIC is *required* to validate the diagnosis of primary fallopian tube carcinoma in more traditional classification schemes. Irrespective of how one views the pathogenetic significance of STIC, it is the earliest known malignant alteration in most BRCA+ women. Moreover, STIC has also been shown to correlate inversely with another parameter used to estimate site of origin, which is the presence (or absence) of a dominant ovarian mass. A dominant mass is frequently found in endometrioid adenocarcinomas of the ovary, which are presumed to arise in endometriosis. As would be expected, endosalpingeal involvement by these tumors is uncommon and tubal intraepithelial carcinoma rare. A recent report showed a significant inverse relationship between a dominant ovarian mass, defined as a two-fold greater difference in the greatest dimension of the ovarian tumors, and both endosalpingeal involvement and STIC [17]. Importantly, the majority of pelvic serous carcinomas, approximately two-thirds, were not associated with a dominant mass and approximately one half had a STIC. Although a tumor mass that predominates in one ovary, particularly a serous carcinoma, does not guarantee origin in that organ (spread from contiguous disease in the tube or peritoneum cannot always be excluded), such associations do support both an ovarian and tubal origin, the latter much more relevant to the serous subset of tumors.

A prevailing issue that arises in the discussion of STIC and its role as a source of pelvic serous carcinoma is the possibility that STIC is caused by implantation of neoplastic epithelium from another site. The evidence against this is as follows:

1. STIC is uncommon in the setting of advanced uterine papillary serous carcinoma (UPSC). One study catalogued the distribution of serous carcinoma in the upper genital tract from a group of these women [18]. Although they noted extensive involvement of the