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Review Article

Surgical Implications of the Potential New Tubal Pathway for Ovarian Carcinogenesis

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ABSTRACT Since 2001, many studies by different investigators have demonstrated that the fallopian tube might be at the origin of most high-grade ovarian and peritoneal serous carcinomas. Simple changes in surgical practice (ie, prophylactic bilateral salpingectomy instead of salpingo-oophorectomy) could have significant implications for death from ovarian cancer and, on the other hand, for the morbidity caused by ovariectomy (surgical menopause). In this review, we describe the new tubal carcinogenic sequence, the advantages and disadvantages of exclusive use of salpingectomy in the general population, and in cases of hereditary predisposition to ovarian cancer such as for carriers of BRCA mutation. Journal of Minimally Invasive Gynecology (2013) 20, 153–159 © 2013 AAGL. All rights reserved.

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In view of the recent descriptions of precancerous tubal lesions, most cases of pelvic serous carcinoma (ovarian and peritoneal carcinoma) may arise from the fimbriated end of the fallopian tube [1–13]. First, this finding could have important implications for the surgical management of prophylactic adnexectomy in groups presenting a genetic risk of ovarian cancer (BRCA mutation). Second, it may be an essential argument for the decision to remove the fallopian tube at the time of hysterectomy or other types of pelvic surgery where cancer is not involved and for tubal sterilization in the general population.

We'll start by describing the carcinogenic sequence in the oviduct. We'll give details of the terminology with which surgeons should be familiar from now on. Finally, we'll discuss the surgical technique for salpingectomy, once considered a simple operation that now must comply with a clearly defined procedure including pelvic washings and a meticulous histopathologic and immunohistochemical examination.

The Tubal Paradigm

The tubal theory [1–10] is based on the following finding: with the meticulous and thorough histopathologic analysis of specimens from prophylactic adnexectomy for BRCA genetic mutation, between 4% and 17% occult cancers were revealed, 57% to 100% of which were located in the distal portion of the tubes [3–8] (Table 1). These occult intraepithelial cancerous lesions are termed *serous tubal intraepithelial carcinomas* (STICs) [1–8] (Figs. 1 and 2). They are characterized by epithelial stratification, nuclear atypias with an increase in the nucleocytoplasmic ratio, loss of nuclear polarity, nuclear pleiomorphism, and loss of ciliated cells. Immunohistochemical analysis may reveal intense and diffuse expression of *p53* (up to 80% of cases), termed the *p53 signature*, and a high proliferative index (*Ki67* $>$ 40%). The overexpression of *γH2AX* (up to 90%), marker of double-strand DNA breaks, is one of the signs of genetic instability [10].

Earlier benign lesions called *serous tubal intraepithelial lesions* (STILs) or *tubal intraepithelial lesions in transition*

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Table 1

Probable tubal origin of occult cancers discovered in specimens from prophylactic salpingo-oophorectomy for BRCA mutation

	Number of cases of prophylactic salpingo-oophorectomies	Number of cancers identified in the prophylactic salpingo-oophorectomies	Tubal origin: presence of STICs
Powell et al [3]	67	7 (10%)	4 (57%)
Finch et al [4]	159	7 (4%)	6 (86%)
Callahan et al [5]	100	7 (7%)	7 (100%)
Leeper et al [6]	30	5 (17%)	3 (60%)
Medeiros et al [7]	13	5 (38%)	5 (100%)
Hirst et al [8]	45	5 (11%)	4 (80%)

(TILTs) or proliferative p53 signatures have also been reported and have been described by an overexpression of *p53*, a low proliferation index (*Ki67* between 10 and 40%) and evidence of DNA damage manifested by immunopositivity for γ*H2AX* (less than in STICs) [11–13]. These STICs and STILs are most frequently located at the fimbriated end of the fallopian tube. As we will discuss below, the question arises about whether fimbriectomy should be proposed instead of salpingectomy in prophylactic strategies.

The concept of a surrogate precursor has been more recently described and is termed *SCOUTs* (secretory cell outgrowths): these earliest benign lesions consist of a succession of at least 30 almost exclusively secretory epithelial cells, with a rather pseudostratified appearance, with a low expression of *PAX2* and *ALDH1*, to a lesser degree a low *PTEN* and *Ki67* index, and in most cases no *p53* expression [14–17]. SCOUTs are distributed throughout the fallopian tube, which finally would provide an argument in favor of salpingectomy instead of fimbriectomy. It could also argue for hysterectomy to remove the cornual tubal tissue. All these histopathologic terms (STICs, STILs, and SCOUTs) should now be familiar to clinicians and surgeons because they are and will continue to be increasingly present in pathologic reports.

Evidence supporting the fallopian tube is not only the presence of STICs and other earlier lesions in tubes (continuum of SCOUT, STIL, and STIC) but also the following facts:

The confirmed metastatic potential of STICs. The presence of STICs without invasive cancer in prophylactic salpingectomies carried out for genetic risk, and moreover STICs associated with ovarian or peritoneal cancers probably plead in favour of carcinogenesis starting from the fallopian tube [7–10].

The molecular lesional continuity between STICs, high-grade serous ovarian cancers and serous peritoneal cancers. There are especially identical molecular *p53* mutations (in order of frequency missense in about 61% of STICs, followed by frameshift, splice, and nonsense mutations) [18]. FISH analysis recently showed similar copy number changes in ovarian and synchronous fallopian tube mucosal carcinoma (3/5 cases), suggesting a monoclonal origin (either from the ovary or the fallopian tube) [19]. These results may indicate that STICs and high-grade serous ovarian or peritoneal cacrcinoma are clonally related.

Upregulated genes (*RSF-1, Cyclin E, p16, FASN, Stathmin 1, laminin γ1*) in both high-grade ovarian serous carcinoma and STICs [20–22]. Moreover, *laminin γ1* overexpression in STILs and STICs suggests a molecular relationship between these preinvasive lesions [22].

Evidence of genomic instability with short telomeres and γ*H2AX* overexpression in STICs [23]. Telomere shortening appears to take place in most human preinvasive epithelial lesions. Recent studies have also revealed activation of the DNA repair system in most early precancerous stages in human beings with a high expression of γH2AX [24–27]. Given that STICs have shorter telomeres than high-grade serous ovarian cacrcinoma and a γ*H2AX* overexpression, these results seem to prove that DNA repair

Fig. 1

STIC, hematoxilin and eosin, original magnification × 20.

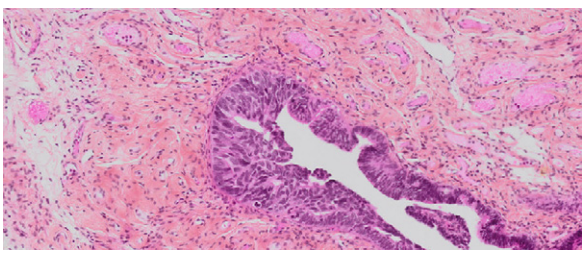

Fig. 2

STIC, immunohistochemistry and the p53 signature.