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.

Keywords: BRCA; Laparoscopy; Ovarian cancer; Ovarian dysplasia; Salpingectomy; STIC

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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 nucleocytoplasmatic 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...
(TILT) 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 γH2AX (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 carcinoma are clonally related.

Upregulated genes (RSF-1, Cyclin E, p16, FASN, Statmin 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 γH2AX 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 carcinoma and a γH2AX overexpression, these results seem to prove that DNA repair

### Table 1

<table>
<thead>
<tr>
<th>Number of cases of prophylactic salpingo-oophorectomies</th>
<th>Number of cancers identified in the prophylactic salpingo-oophorectomies</th>
<th>Tubal origin: presence of STICs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powell et al [3]</td>
<td>67</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Finch et al [4]</td>
<td>159</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Callahan et al [5]</td>
<td>100</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Leeper et al [6]</td>
<td>30</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Medeiros et al [7]</td>
<td>13</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Hirst et al [8]</td>
<td>45</td>
<td>5 (11%)</td>
</tr>
</tbody>
</table>

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Fig. 1

STIC, hematoxilin and eosin, original magnification × 20.

Fig. 2

STIC, immunohistochemistry and the p53 signature.
mechanisms are activated in these early conditions and are definitely an additional indication of genomic instability. We can also conclude that STICs are not metastases from ovarian carcinoma (different telomere lengths between STICs and ovarian cancers) but tubal precursor lesions of ovarian carcinoma.

Kast et al [28] developed an experimental model of tubal secretory cell transformation in high-grade mullerian carcinomas. The transformation and tumorigenesis were based on immortalization of primary human fallopian tube secretory epithelial cells followed by oncogene activation and xenograft-based tumorigenic assays. The high-grade mullerian carcinomas obtained were similar to high-grade serous carcinoma (same molecular and immunohistochemical profiles). There were also genomic imbalances revealed by the deletions/amplifications in array comparative genomic hybridization (array CGH) suggesting genomic instability. At last but not least, Kim et al [29] recently provided experimental evidence of the tubal origin: using a mouse model (a double KO genetic mouse in which Dicer and Pten are selectively inactivated), they showed that a high-grade serous ovarian cancer could arise from the fallopian tube. This mouse ovarian cancer demonstrated molecular similarities with human serous ovarian cancers. Moreover, removal of the fallopian tube prevented cancer initiation, whereas bilateral ovariectomy had no effect.

If the tubal carcinogenic sequence (Fig. 3) has been practically established in the tubes of patients at genetic risk, does this apply for patients with no BRCA mutation? Several series of sporadic serous ovarian cancer and primary serous peritoneal cancers have been analyzed, and STICs were only present in about 30% to 60% of cases [2,30–34] (Table 2).

In cases where STICs were absent, ovarian cancer could arise from the ovary itself. A precancerous lesion named ovarian epithelial dysplasia has been described [35–38]. Ovarian dysplasia is defined by cytologic and architectural abnormalities: surface papillomatosis, inclusion cysts, nuclear pleiomorphism, epithelial pseudostratification, and epithelial invaginations [37–39]. Evidence of ovarian dysplasia distinct from cancerous and normal ovarian epithelium has been demonstrated by use of morphometry and nuclear texture analysis [40,41].

Some other theories have been discussed such as the secondary mullerian system theory proposed by Lauchlan [42] and the unifying hypothesis proposed by Auersperg [43] in which ovarian cancer may arise from the transitional epithelium between the ovarian surface epithelium and the fimbrial epithelium of the oviduct. It is possible that the tubal pathway would be preponderant, particularly in case of associated genetic risk, whereas the ovarian and tubal pathways could coexist in sporadic ovarian cancer [39,44,45]. The models of ovarian carcinogenesis proposed would be the following [39,44,45]:

### The Tubal Carcinogenic Pathway

Appearance of p53 mutations in the oviduct mucosa, BRCA mutation (in case of genetic risk) or loss of BRCA functions (groups without any genetic risk), associated genotoxic stress. Development of epithelial tubal abnormalities (SCOUTs-STILs), clonal expansion, then evolution toward STICs, and finally extension by anatomic proximity toward the ovary by endosalpingiosis (ovarian cancer growth because of the favorable stromal microenvironment) and the peritoneum.

### The Ovarian Carcinogenic Pathway

In the ovary, at the time of ovulation, formation of cortical inclusion cysts in a hyperactive stroma, then dysplastic proliferation, and finally malignant transformation and extension by anatomic proximity toward the pelvic cavity, followed subsequently toward the upper abdomen.

### Strategy to Adopt

Reduced risk of serous ovarian cancer after tubal ligation is well known both in the general population (0.73, 95% CI 0.63–0.85) and for BRCA mutation carriers (0.43, 95% CI 0.22–0.80) [46,47]. Therefore the tubal hypothesis of ovarian cancer could lead to the following [48,49]:

In the BRCA population, is a bilateral prophylactic salpingectomy after childbearing followed later (according to menopausal status) by bilateral oophorectomy better than bilateral salpingo-oophorectomy at the same time?

Although STICs and STILs are more often found at the fimbriated end of the tube, SCOUTs can be found anywhere in the tube. Even the diagnostic significance isn’t completely

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**Table 2**

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Location</th>
<th>Tubal origin: presence of STICs</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>Ovary</td>
<td>20 (47%)</td>
</tr>
<tr>
<td>33</td>
<td>Ovary</td>
<td>20 (61%)</td>
</tr>
<tr>
<td>19</td>
<td>Peritoneum</td>
<td>9 (47%)</td>
</tr>
<tr>
<td>87</td>
<td>Ovary</td>
<td>31 (36%)</td>
</tr>
<tr>
<td>35</td>
<td>Peritoneum</td>
<td>16 (46%)</td>
</tr>
<tr>
<td>9</td>
<td>Peritoneum</td>
<td>3 (33.3%)</td>
</tr>
</tbody>
</table>
understood, SCOUTs may be an earlier precursor. When associated with p53 mutations, SCOUTs may provide the preinvasive lesions (STILs and STICs) to ovarian cancer [42]. Therefore hysterectomy or salpingectomy would be preferable to fimbriectomy.

**Hysterectomy.** Because SCOUTs are distributed throughout the fallopian tube, this could argue for hysterectomy in order to remove the cornual tubal tissue. Conversely, because there have been no reported cases of fallopian tube cancer in the cornua, why should we do a hysterectomy? We should wait to know more about the significance of SCOUTs. We can not recommend performing hysterectomy.

**Salpingectomy.** This strategy would be motivated by the distribution of SCOUTs throughout the fallopian tube and would also reduce the risk of chronic inflammation in the pelvis, which might also participate in ovarian carcinogenesis. First, the presence of Chlamydia trachomatis and mycoplasma hominis (in, respectively, 48% and 37% of cases) has indeed been established in cases of nontubal infertility, and they could play a negative role with respect to the ovary itself [50]. Human papillomavirus (HPV 16 and 18) has also been found in ovarian carcinomas although controversial [51] and could lead to genomic instability (mutation of the short arms of chromosomes 16, 19, 21, 22, and amplifications of the 20q13.2 region) [52,53]. Moreover it has been possible to detect the involvement of various inflammation mediators in ovarian carcinogenesis (cyclooxygenase-2, NO synthase, VEGF) [54]. In addition, conservation of the ovary would avoid the morbidity-mortality connected with induced menopause when ovariectomy is associated: cardiovascular, osteoporosis, and neurologic risks along with deterioration in the quality of life [49]. Nevertheless, STICs and other earlier tubal lesions are not found in 100% of prophylactic salpingectomies for BRCA mutation, depending on the series [3,4,6,8]; a certain number of ovarian cancers of hereditary nature (e.g., Lynch syndrome with mutation in the mismatch repair genes MLH1, MSH 2) could originate in the ovary itself, which would thus justify risk-reducing salpingo-ovariectomy. It is also too early yet to move directly from the results of molecular research to clinical practice, unless within the framework of a clinical research protocol [55]. In conclusion, bilateral salpingo-ovariectomy still remains recommended in populations at genetic risk.

In the general population, is it acceptable to undergo a bilateral salpingectomy instead of tubal ligation for patients who would like to have a tubal sterilization or a bilateral salpingectomy during hysterectomy for benign disease?

About 55 to 64% of women and 78% of patients over age 45 undergo prophylactic adnexectomy at the time of hysterectomy for benign disease [56,57]. Studies have established that 0.1% to 0.75% of women had development of an ovarian cancer after hysterectomy and tuboovarian conservation [58]. In the Nurses’ Health study (with long-term follow-up of 24 years), 34 of 13 035 (0.3%) women with tuboovarian conservation died of ovarian cancer [59]. Given that STICs are found in less than 61% of cases of sporadic ovarian cancer (with no BRCA mutation) [2,30–34], should there be a systematic indication for salpingectomy?

It is certainly a little too early to answer this question as yet. A recent meta-analysis showed a 34% reduction in the risk of epithelial ovarian cancer with tubal ligation [46]. Unfortunately, we do not know what reduction in risk there would be with salpingectomy instead of tubal ligation.

However, we recommend performing salpingectomy over tubal ligation. First, bilateral salpingectomy instead of tubal ligation would likely be a more effective method of contraception [60], and, second, it may reduce the risk of development of serous pelvic carcinoma in a certain number of cases [44,45].

**The Surgical Procedure**

After being considered for many years as a simple operation, salpingectomy ought to be made more standardized [61]:

The preferred approach remains minimally invasive surgery (laparoscopy or robotic surgery). The surgical procedure should be preceded by meticulous and complete inspection of the whole abdomino-pelvic cavity. Pelvic washings should take place systematically, especially in the case of patients with a BRCA mutation [62]. Of the 31 cases of STICs discovered in the context of prophylactic adnexectomy in a recent review [63], 10 gave positive cytologic study results. Certain factors could perhaps explain the low sensitivity of peritoneal cytologic study [64,65]: lack of peritoneal liquid and incomplete lavage with normal saline solution, low degree of malignant cell exfoliation, recent description of the tubal theory of ovarian cancer, and of the pathologic procedure (SEE-FIM protocol). A positive peritoneal cytologic study result means restaging in sub-class C. Although the follow-up is limited as yet, prognosis of patients with STICs appears to be improved if adjuvant chemotherapy is used [63,66]. Otherwise, we often see recurrence of the cancer (2 years after, as reported by Tone et al [67]). There were also 3 patients who had a positive cytologic study result without any STICs or ovarian carcinoma; 2 of whom received chemotherapy. It could be either an undetected peritoneal carcinoma or an occult tuboovarian carcinoma. The authors concluded that “positive cytology may be a surrogate for early undetected microinvasive disease and/or predictive marker for increased peritoneal cancer risk.”

We believe there is no advantage to fimbriectomy alone because SCOUT lesions can occur anywhere in the tube. Risk-reducing bilateral salpingo-oophorectomy for BRCA mutation significantly reduces the risk of ovarian cancer and primary peritoneal cancer (0.14, 95% confidence interval (CI) 0.04–0.89 for Domchek et al [68] and 0.21, 95% CI 0.07–0.62 for Kauf et al [69]). However, the risk is not zero, and peritoneal carcinosis has been described as late as 27 years after prophylactic surgery [70,71]. It is difficult
to understand how occult cancer can stay dormant for many years. This could be an undetected early microinvasive peritoneal carcinoma or a preinvasive peritoneal lesion. Another explanation is the persistence of tubal remnants in uterine cornual sites. In 2 pathologic studies, the length of residual tube was up to 21 mm, and the surface area was up to 117 mm² with some preserved and active tubal epithelium [72,73]. Maybe there were epithelial tubal abnormalities such as SCOUTs in the tubal remnants. Although there are no documented cases of STICs or tubal carcinoma in the uterine cornual sites, we really believe that salpingectomy must be total, right at the uterine horns. Another important point is the meticulous handling and the careful use of the bipolar electrocauclation during laparoscopy because of the real risk of diathermy-induced injury in fallopian tube that could affect detection of STICs [74].

Finally, histologic examination of the tubes should include the validated SEE-FIM protocol (Sectioning and Extensively Examining the Fimbriated End), which improves the occult tubal carcinoma detection rate by at least 17% [75]: The whole tube is fixed for a minimum duration of 4 hours to reduce the risk of deterioration of the epithelium; multiple longitudinal sections (in 4 parts) then transversal sections (every 2 to 3 mm) of the fimbrial end; and extensive histopathologic examination of the whole tube and the various fimbrial end sections.

Future Perspectives

In the near future, preinvasive lesions in fallopian tube epithelium could be identified by use of in situ and real-time optical imaging technologies. Real-time reflectance confocal microscopy is already used for the detection of preneoplastic lesions of the upper gastrointestinal tract [76]. Tomography associated with optical biopsy could even give molecular imaging of cancers in tissues at depths exceeding 200 μm [77,78].

Confocal microlaparoscopy or robotic in real time will help the surgeon in the near future to decide whether salpingectomy is needed (in case of a STIC) or not [66]. McAlpine et al [79] managed to identify STICs in a preliminary report with autofluorescence imaging with a sensitivity of 73%, a specificity of 83%, a positive predictive value of 57%, and a negative predictive value of 91%.

Conclusions

With the recent tubal hypothesis of ovarian cancer, exclusive bilateral salpingectomy as a method of risk-reducing surgical prevention seems to be very attractive. For instance, the Gynecologic Oncology of Canada recommends already bilateral salpingectomy with patients undergoing hysterectomy or requesting permanent contraception. Other studies are still needed to define the interactions between tubes and ovaries and the accurate molecular mechanisms of serous pelvic carcinogenesis [80,81].

References


