



The fallopian tube: a change in the paradigm of the ovarian carcinogenesis

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Epithelial ovarian cancer is the most severe gynecological cancers, with a low five-year survival, estimated at 35% at any stage (1). A true “silent killer” due to a late diagnosis almost always beyond all therapeutic resources, however, it has a good prognosis, when discovered at an early stage (stage IA at 90% and 70% at stage II) (1,2). Until the early 2000s, various theories on ovarian carcinogenesis were proposed, which focused on the ovary itself and its superficial epithelium with complex functional roles endowed with plastic properties and differentiation (3). Since 2001, new theories based on immunohistochemical and molecular studies have demonstrated the dominant role of the fallopian tube in the genesis of ovarian cancer (1,2).

The tubal theory started from the following observation: the meticulous and detailed histopathological analysis of the prophylactic annexations for BRCA 1 or 2 mutation revealed up to 10% of occult tumors, from 57% to 100% of these were located in the distal portion of the tubes. These lesions were called «serous tubal intraepithelial carcinoma» or STIC. Several series of sporadic ovarian tumors (without BRCA mutation) were further analyzed and the presence of abnormalities of the tubes with STIC was found in almost 50% of cases that suggest a tubal origin in most ovarian cancers (4,5). Immunohistochemistry showed a significant, early and predominant marker (expression between 80% and 92%) from TP53, called “p53 signature”: a sequence of at least 12 cells associated with high positivity of the p53 marker, the Ki67 proliferation marker and the rupture marker double-strand doubleH2AX (1,2). The ovarian

carcinogenesis model would consist in the appearance of dysplastic tubal anomalies, p53 mutations, associated with genotoxic stress (mainly at the level of secretory tubal cells), then clonal expansion, and therefore the evolution towards STIC and finally the metastatic extension by contiguity towards the ovary and the peritoneum. If the study of samples of prophylactic adnexectomies has effectively found the presence of tubal dysplasia and the p53 molecular signature (abnormalities detected early in the tubes in the pre-cancerous state), the chronology of the various events is much more complex to demonstrate in late and non-late stages and it's not sure that the tubal abnormalities associated with ovarian cancer are the first to appear. However, these data underscore the importance of salpingectomy associated with prophylactic ovariectomy, but also of salpingectomies called opportunistic during benign hysterectomy and finally complete anatomopathological analysis of ovaries and fallopian tubes.

The article by Samimi *et al.* (6) described the paradigm shift in the histopathological analysis of the fallopian tubes in US laboratory practices thanks to these new discoveries. Previously, the tube underwent a macroscopic examination and a random cut with microscopic analysis. After the description of tubal precancerous lesions, an exhaustive histopathological analysis of the tubes should be necessary. Some authors have proposed a complete and meticulous fallopian tube analysis protocol that poses greater emphasis on the fimbria (the main localization of STICs). This is the SEE-FIM protocol (Sectioning and Extensively Examining

the Fimbriated End) (7,8):

- ❖ Fixation of the entire tube for a minimum of 4 hours to reduce the risk of damage to the tubal epithelium;
- ❖ Multiple longitudinal sections (in four parts) and then cross-sections (every 2 or 3 mm) of the fimbria;
- ❖ Comprehensive histopathological analysis of the entire tuba and of the different sections of the fimbria.

This technique would improve the detection rate of occult carcinoma by 17% (8). The best knowledge of ovarian carcinogenesis with the tubal origin and its spread among surgeons, oncologists and pathologists necessarily should lead to focus on the fallopian tubes. Several questions remain unresolved to date:

- (I) Do all the ovarian cancers come from the fallopian tube? For the high-grade serous subtype (the most common), the majority would have a tubal origin but it is possible that a minority has a purely ovarian origin. For endometrioid subtypes and clear cells, the tuba would serve as a channel for atypical and precancerous endometrium cells: salpingectomy could stop this tubal reflux and prevent the development of these tumors (1,2).
- (II) In the population with genetic risk (BRCA mutation, Lynch syndrome), could we propose prophylactic salpingectomies with ovarian preservation? Which would have the advantage of avoiding an induced menopause and its related complications such as osteoporosis and cardiovascular type? The protection may be not complete if the origin of some tumors is not tubal. Various strategies have been proposed such as the execution of a prophylactic salpingectomy followed a few years later by a complementary ovariectomy (9). This strategy would have the advantage of providing complete cancer prevention, with a better quality of life (delaying the surgical menopause), but what would be the ideal period for ovariectomy?
- (III) In the general population, should the so-called opportunistic salpingectomies be performed during benign hysterectomy or on the occasion of a tubal ligation? the morbidity and mortality of this surgical procedure is very low for operations performed in laparoscopy or laparotomy, but it is not negligible in the case of vaginal surgery (10,11). The impact of salpingectomy on the ovarian

reserve and, finally, the onset of the menopause has been the subject of numerous studies that seem to find no particular ovarian risk (12).

Little by little, research is progressing. Who would have imagined 20 years ago that ovarian cancer would have been the only one to have an origin external to itself? In a relative short time we should have the results of numerous studies that will help us to know how to treat the fallopian tube in an optimal and relevant way.

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