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# Why tube fimbria-end is the favorite site of carcinogenesis in hereditary ovarian cancer? A review of literature and our institution experience

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**Summary**

*Background:* Ovarian cancer (OC) is the first cause of death among gynecological malignancies. BRCA mutated women are at risk to develop an OC between 35-60% for BRCA1 and 10-27% in BRCA2 by the age of 70 years. Salpingo-oophorectomy seems to be the only technique that can reduce the risk of OC in this population. *Materials and Methods:* The authors reviewed PubMed literature about the role of STIC in fimbrial carcinogenesis and describe their 11 cases treated with a total salpingo-oophorectomy (removal of the fallopian tube comprising also the cornual site). *Results:* No case of STIC or invasive cancer were found in the cornual site of fallopian tube but only one case of STIC was found in the fimbrial end, as literature shows. *Conclusion:* In this review of the literature, the authors wanted to better understand how carcinogenesis works in the salpinges and if minimal prophylactic surgery can be a safe option.

*Key words:* Ovarian cancer; BRCA mutation; Salpingo-oophorectomy

## Introduction

Ovarian cancer (OC) is a disease with a poor prognosis and has limited options in terms of diagnosis and treatment because it often presents in an advanced stage. It is the second most common type of gynecological malignancy and the first cause of death and there is currently no effective screening test to detect this cancer in its early stage.

The lifetime risk to develop OC in BRCA positive women is about 35-60% for BRCA1 and 10-27% in BRCA2 by the age 70 years; most of these OC are sited in the tubes and accounts for approximately 0.5% of all gynecologic malignancies in the general population [1, 2].

Recent data shows that 60% of gynecological cancer due to BRCA 1 and/or BRCA 2 mutation originate from the distal part of tubes and then spreads to ovaries and peritoneum. In particular ovarian screening is the predominant problem in hereditary syndrome for ovarian and breast cancer.

The scientific field is still debating if it is time to stop OC screening in particular in BRCA 1 and BRCA2 positive population because all studies, regarding ovarian surveillance in this population, has failed to demonstrate its efficacy [3]. The only recognized technique that is able to prevent and reduce the risk of OC is bilateral salpingo-oophorectomy.

In this review, the authors discuss the various hypotheses regarding ovarian etiology and pathogenesis and the epidemiology of OC, including hormonal and inflammatory factors that influence OC risk.

Approximately 6% of BRCA1 and 2% of BRCA2 carriers who undergo prophylactic salpingo-oophorectomy will be found to have an occult carcinoma if the ovaries and tubes are rigorously examined. The majority of these cancer originates in the terminal site called fimbria. Normal fallopian tube consists primarily of two types of epithelial cells, ciliated and secretory. The serous tubal intraepithelial lesions (STIL) and serous tubal intraepithelial carcinomas (STIC) in ovarian epithelial tumors propose their pathogenetic association with a certain histotype of the ovarian tumor. STICs are associated with only serous carcinomas of peritoneal, ovarian, or endometrial origin, and not with any other non-serous lesions. The occult carcinoma is a lesion limited to the epithelium of the fallopian tube, and the histologic diagnostic criteria of STIC is described with very restrictive criteria as below:

"A discretely different population of malignant cells replacing the normal tubal epithelium, disorganized growth pattern and lack of cell polarity without ciliated cells, in malignant cells, elevated nuclear-to-cytoplasm ratio with more rounded nuclei, marked nuclear pleomorphism with prominent nucleoli, and a high mitotic index and sometimes abnormal mitotic [4]. The mass is found in the fallopian tube, the tumor's histological appearance must reflect features of the tubal epithelium, the ovaries and uterus have to be normal or contain less tumor than the fallopian tube does, and a tran-

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sition from benign to malignant epithelium has to be apparent". According to these strict criteria, tubal carcinoma is very rare and accounts for only 0.3% of malignant gynecologic tumors. For this reason the Sectioning and Extensively Examining the Fimbriated End (SEE-FIM) protocol was elaborated, and thanks to this accurate resolution of the fimbriae, more occult neoplasia in this site was discovered. It has to be performed at the time of histopathologic analyses and it permits a correct visualization of all fimbriae [5, 6].

Rabban *et al.* demonstrated that using a rigorous surgical protocol with a meticulous pathologic review at the time of risk-reducing salpingo-oophorectomy (RRSO) yielded an overall detection rate of 9.1% for occult carcinoma in BRCA positive women and lowered the rate of primary peritoneal carcinoma after RRSO. STICs are detected in 50-60% of cases of sporadic pelvic high-grade serous carcinomas (HGSCs) (ovarian, tubal, or "primary" peritoneal carcinomas) [7, 8].

The SEE-FIM protocol has changed the way to look into the fimbriae in BRCA 1 and BRCA 2 associated cancer. To answer the question why only the fimbria is a site of carcinogenesis the authors report Hong-Xia Li *et al.*'s words:

"First, the fimbria is the closest portion to the ovarian surface. If there is a definite relationship between the tube and ovarian carcinogenesis, the portion of the tube closest to the ovarian surface deserves the most attention. Second, the fimbria is an area of epithelial-to-mesothelial transition and may differ in biology by its juxtaposition to the peritoneal cavity. Third, the fimbria contains a larger surface area than the more proximal tube does, and thorough exposure of this area is facilitated by longitudinal sectioning of the infundibulum and the fimbria" [9].

Koc *et al.* showed that among 495 cases, 110 cases had malignant lesions, and among them, STIC was located at the fimbrial end in 12 cases. STIC role is not yet well established and it is no clear if STIC is the precursor of OC or just an associated OC lesion [10].

Clinical and pathological findings of prophylactic salpingo-oophorectomies in BRCA 1 and BRCA2 carriers shows that almost 4-6% of occult cancers are detected thanks to this procedure and occult cancers are more frequent in women carrying a BRCA 1 mutation and occult carcinoma is four times greater in women older than 50 years [11-13].

The role of chemotherapy to treat an isolated STIC is not yet well known and there are no guidelines, so individual treatment depend on clinicians. The study by Patrono *et al.* shows that 11 patients with STIC discovered at the time of RRSO were treated with chemotherapy and three of them, BRCA mutated despite this, developed a peritoneal carcinoma (4.5%) after a medium follow up of 43-72 months [14]. Some data show that at the time of RRSO perhaps some tumor cells could have been spread to peritoneum, however another point of view shows a different theory. This theory demonstrates that two events, first STIC and peritoneal cancer, are not linked: they are two separate events due to constitutive cells mutations in BRCA patients. Other studies demonstrate the same theory that "primary peritoneal carcinoma" is probably derived from occult HGSC in the fallopian tube.

STIC can involve the tube in a second moment or HGSC is implantation of normal fimbrial epithelium on the denuded ovarian surface at the site of rupture when ovulation occurs. Literature speculates that this tubal epithelium can result in the formation of a cortical inclusion cyst (CICs) that can then undergo malignant transformation. Thus, serous tumors may develop from inclusion cysts, as has been previously proposed, but by a process of implantation of tubal (Müllerian-type) tissue rather than by a process of metaplasia from ovarian surface epithelium (OSE, mesothelial). Due to these theories, it is very difficult to answer the question whether STIC in BRCA mutated ovarian cancer is or not the primary cause of OC [15].

If we analyze BRCA 1 and BRCA2 germline mutations and we want to understand why cancers in patients with this predisposition are most frequent in ovaries, breasts, prostate, pancreatic, and other sites, we still do not know why. Perhaps there is and hormonal drive and in particular for tubal and OC, a homeostatic hormonal alteration seems to be involved. This theory can help understand why ovarian screening made via pelvic and transvaginal ultrasound plus CA125 serum dosage performed on the assumption that enlarged ovaries is an early manifestation of cancer, has failed. As a consequence, the identification of women at risk for the disease is based primarily on clinical grounds, with family history being the most important risk factor and then other factors which modify gene penetrance are involved in the carcinogenic process.

The causes of epithelial OC are poorly understood, but reproductive hormones are thought to be involved in the etiology. For a long time the 'incessant' and 'gonadotropin' hypotheses have been promoted in relation to carcinogenesis, both hypotheses find support in OC epidemiology, and recent progress in molecular biology adds to the understanding of possible etiological mechanisms.

Another hypothesis is focused on the retrograde transport of contaminants or carcinogens through the fallopian tubes. It is important to establish if the same risk factors can be apply to the various histological types of OC, because in particular, the mucinous ovarian tumours seem to present with different risk factors and genetic etiology.

In the light of the data presented, the question is if sporadic *vs.* inherited ovarian tumors carry distinct risk profiles. As the hypotheses above do not explain all of the results derived from OC epidemiology, there is a need to test additional hypotheses to possibly define preventive programs and to come closer to the cause of OC [16].

Recently Hansen *et al.* published a paper in which explains that uncontrolled growth in tumours cannot be explained solely by aberrations in cancer cells themselves. To

fully understand the biological behavior of tumors, it is essential to understand the microenvironment in which cancer cells exist, and how they manipulate the surrounding stroma to promote the malignant phenotype. Those conclusions can show that to carry a mutation in BRCA 1 and BRCA2 genes is not enough to develop a cancer, but external exposure is needed to complete the process. The fimbrial end is part of the tube where there is more exposure to peritoneal fluid and its components, potential carcinogens, and it might be the explanation why this is a site for carcinogenesis and development of STIC [17-22].

A recent paper by Wang *et al.* showed that in high risk women, there is a dramatic increase of secretory cells in fallpian tubes. Secretory cell expansion is more prevalent than secretory cell outgrowth in both fimbriae and ampulla tubal segments and it is significantly associated with serous neoplasia ($p < 0.001$). This could be a potential sensitive biomarker for early serous carcinogenesis within the fallopian tube. The study also supports a relationship between serous neoplasia and increased secretory to ciliated cell ratios, and the relationship between frequency of secretory cell expansion within the fallopian tube and increasing age and-more significantly-presence of high-risk factors or coexisting serous cancers [23]. For this reason during the inflammatory process of ovulation, potentially an oncogenic factor can be released in the fimbrial end.

Large epidemiological studies have confirmed the protective role of oral contraceptives, pregnancies, and lactation which suppress ovulation [24]. Another study by Malmberg *et al.* shows that no differences in tubal injury or inflammation were seen when comparing the sporadic serous cancer group and the control group or within the hereditary group. STIC and invasive cancer were seen more often in the older patients than in the younger patients ($p = 0.528$) and no correlation with chronic tubal injury or inflammation was identified [25].

The role of STIC in ovarian carcinogenesis, inflammatory injuries, and hormonal microenviroment are still not clear and they cannot be considerate as cause of ovarian cancer.

The recent paper by Tomasetti *et al.* shows that the role of environmental factors in cancer development and inherited factors either of which can directly increase the mutation rate and vary widely among individuals and across populations [26].

Primary prevention is the best way to reduce cancer deaths, but the recognition of a third contributor shows that not all cancers can be prevented by avoiding environmental risk factors, secondary prevention as early detection, and surgery can also be lifesaving.

Despite all these theories nowadays we still do not know how ovarian and tube carcinogenesis develop and we still do not know why in BRCA mutations' carriers carcinogenesis in gynecological cancer originates often in the fimbrial ends even if BRCA mutation is a constitutive mutation and for this reason all cells carry these mutations.

Because of these theories and because fimbria is constituted by three sites: end, wall of the oviduct, and hostium, the present authors wanted to analyze if all the three sites could be sites of carcinogenesis, and because during the standard surgery technique of salpingectomy. the hostium of the tube is left in the uterus and in this manner, total primary prevention surgery is performed.

The present authors would like to remove all the fimbriae with the hostium and analyze all the epithelium to evaluate if it copuld be a site of cancer. To answer to this question, they performed a prospected small one-center local study of 11 patients who underwent RRSO with total anatomical removal of tubes [27].

## Materials and Methods

The present authors hypothesized that women affected by BRCA 1 and BRCA 2 mutations could be at risk to develop OC originating from the oviduct wall or from the hostium of the tubes. The present study aimed to prospectively evaluate the entire salpinges with the pathological review after the application of the SEE-FIM protocol .

The authors proposed to include 11 BRCA positive patients (four were BRCA 1, six BRCA 2 carriers, and one variant of uncertain significance (VUS) in a family with three cases of OC) aged 40 or older who were candidates for RRSO and submitted to surgery between 2011 and 2016. After genetic confirmation of BRCA 1 or BRCA 2 mutation and a multidisciplinary validation, all consecutive patients were offered modified RRSO after submission of informed consent. All patients were prospectively followed up and evaluated before surgery, after surgery. and then once a year.

Table 1 resumes the characteristics of the patients, their BRCA mutation status, medical history, menopausal status, and previous breast cancer. Data were collected from patients records.

Usually, during laparotomic RRSO, the procedure includes the ligature of the fallopian tubes and the utero-ovarian ligament, which are then dissected. In a second step, the gynecologist performs a double bound and then section of the infundibulus. During laparoscopic surgery, the infundibulus and the utero-ovarian ligament with the emergence of the fallopian tubes are dissected by diathermocoagulation.

Table 1. — Characteristics of study patients.

| Pts. | BRCA status | Age (yrs) | Previous breast cancer | Anatomo-pathology |
|---|---|---|---|---|
| 1 | 2 | 55 | No | Negative |
| 2 | 1 | 43 | Yes | TIC p53+ |
| 3 | 1 | 43 | Yes | Negative |
| 4 | 2 | 42 | Yes | Negative |
| 5 | 1 | 42 | Yes | Negative |
| 6 | 1 | 44 | Yes bil | Negative |
| 7 | 2 | 45 | Yes | Negative |
| 8 | Variant of uncertain significance class3 | 45 | Yes | Negative |
| 9 | 2 | 65 | No | Negative |
| 10 | 2 | 45 | Yes | Negative |
| 11 | 2 | 58 | Yes | Negative |

Even, during the standard surgical laparotomic procedure for RRSO, the uterine corna is left behind the residual fallopian tubes. In this particular case the present authors performed the resection of both ovaries and fallopian tubes in toto, with the cyst after peritoneal washing. The fallopian tubes were resected until the intramural site dissectioned the uterine cornua where the hostium is sited. The surgical specimens were placed in a large bag which was removed through an intra-abdominal incision with Trocar clamps and scissors. During the surgical procedure of this case, the gynecologist performed the anatomical isolation of both fallopian tubes with the section of the intramural site. The steps of surgery procedures included: 1) isolation of pelvic infundibulus prior identification of ureter, 2) diathermocoagulation of pelvic-infundibulum and uterus-ovarian ligament to reduce mesosalpinx vascular flow, 3) isolation and dissection of mesosalpinx, 4) removal of the total tube with the intramural portion by endobag, 5) pressure points, and 6) removal of the ovaries.

## Results

Only one patient of 11 who underwent total salpingo-oophorectomy was found with a STIC in the fimbrial end. The present study reflects the incidence of STIC as literature shows, and it is about 10%. The mainstay of prophylactic surgery is the removal of ovaries and total fallopian tubes up to the cornua. This surgical technique was safe and all patients experienced one night of hospitalization without any complication.

## Discussion

Fallopian tubes carcinoma is one of the recent of BRCA syndromes hallmark. Nowadays there are still some open questions, as for example how and when to treat an isolated STIC. Opportunistic salpingectomy with postponed ovariectomy now seems to be the last challenge.

Some studies have shown a risk reduction of OC in women with bilateral prophylactic salpingectomy. The prevalence of salpingectomy at the time of hysterectomy has increased significantly in the last years; one of the reasons is the close relationship between serous OC and STIC. Removal of the fallopian tubes with ovarian preservation has been suggested as a reasonable strategy after childbearing in women at high risk, to be followed by bilateral oophorectomy at a later date [28]. Some studies in which bilateral salpingectomy was performed for benign disease showed that this procedure was safe and ovarian function did not seem to be compromised. The study by Falconer *et al.* shows a statistically significantly lower risk for OC among women with previous salpingectomy (HR = 0.65, 95% CI = 0.52 to 0.81) when compared with the unexposed population [29]. The study by Kwon *et al.* instead shows that salpingectomy followed by delayed oophorectomy could be an acceptable alternative for those unwilling to undergo bilateral-oophorectomy; however Delarius *et al.* showed that long-term endocrine effects of salpingectomy alone are still unknown, but ovarian preservation does not seem to affect in vitro fertilization response rates [30-32].

A Committee Opinion published in Gynecological Oncology in 2015 showed that prophylactic salpingectomy may offer clinicians the opportunity to prevent OC in their patients. Randomized controlled trials are needed to support the validity of this approach to reduce the incidence of OC [33].

The rule of STIC in the carcinogenesis of ovarian/tube cancer is still not clear and the dualistic hypothesis of OC carcinogenesis is still debated. Early diagnosis of OC options with CA125 serum dosage and pelvic ultrasound is still questionable. The only technique that demonstrated to be effective is prophylactic salpingo-oophorectomy (RRSO).

## Conclusion

The authors report their Institutional experience of 11 women treated with modified RRSO (removal of the fallopian tube included the cornual site) to show that the total removal of potential carcinogenesis sites can be safe and feasible. They did not find any STIC or invasive cancer in the cornual sites, therefore the cornua site should be removed only when salpingectomy alone is performed as NCCN guidelines reports [34]. There are no reasons to remove only the fallopian tube without ovaries out of a clinical trials and we are still waiting for the first results of the safety of this procedure. This is the reason why we require the results of randomized studies to show if prophylactic salpingectomy alone, can be a safe options for BRCA positive women who want to decrease their risk of OC.

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