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From the Ovary to the Fallopian Tube: A History of Ovarian Carcinogenesis

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1. Introduction

Because of the poor prognosis for ovarian cancer due to the fact it is most often diagnosed late at an advanced stage, screening and early detection could likely reduce the mortality rate. Epithelial ovarian cancer represents 90% of all ovarian cancers [1, 2]. Initially divided into a double-pathway, epithelial subtypes are in fact distinct diseases with specific characteristics and molecular signatures (see tables 1 and 2) [3, 4]. Recent persuasive data support the idea that high grade serous carcinoma (HGSC) may arise from the Fallopian tube epithelium whereas endometrioid and clear cell cancers could arise from atypical endometriosis through the Fallopian tube. Opportunistic salpingectomy could reduce both HGSC, and endometriosis-associated ovarian cancers (EAO) (i.e. endometrioid and clear cell cancers).

	Type 1	Type 2
Molecular signatures	BRAF, KRAS, PTEN, b catenin	TP53
Genomic instability	low	high
Frequency	20%	80%
Precursors	adenoma/ borderline tumors, endometriosis	de novo
Prognosis	stage 1, slow evolution	> stage 1, fast evolution
Histological sub-types	low grade serous, endometrioid, mucinous, clear cell carcinoma	high-grade serous, non-differentiated carcinoma, carcinosarcoma

Table 1. Diagram of double-pathway oncogenesis [2]

	Low grade serous	Clear cell	Endometrioid	Mucinous	High grade serous
Molecular signatures	BRAF KRAS HER2	ARID1A HNF 1B PI3KCA PTEN	ARID1A PTEN B-catenine KRAS	KRAS HER2	TP53 BRCA
Genomic instability	low	low	low	low	high
Frequency	5%	10%	10%	3%	70%
Precursors	Borderline serous	Endometriosis Adenofibroma	Endometriosis Adenofibroma	Sequence: Adenoma/ Borderline	-Fallopian tube (STIC) -Ovary (dysplasia)
Prognosis	Favourable	Intermediate	Favourable	Favourable	Poor
Initial response to platinum salt chemotherapy	Intermediate (20-30%)	Chemoresistance (15%)	Good	Chemoresistance (15-20%)	Good (80%)
Potential therapeutic targets	BRAF inhibitors MEK inhibitors	PI3K inhibitors	mTOR inhibitors	MEK inhibitors	PARP inhibitors Cell cycle inhibitors

Table 2. Diagram of quintuple-pathway oncogenesis [3, 4]. This classification shows the clinico-pathological differences along with potential therapeutic targets for each histological sub-type. An advantage of this new classification is that it describes the heterogeneous nature of ovarian cancer.

We propose to discuss the origin of HGSC and EAOc cancers and the potential clinical implications.

2. High-grade serous ovarian cancer (see figure 1)

At this point it seems appropriate to recall the anatomy and embryology involved in order to clarify the close relationship and interaction between Fallopian tube and ovary. During embryonic development, the coelomic epithelium gives rise to the peritoneum and ovarian surface epithelium (OSE). The Mullerian duct develops as an invagination of the coelomic epithelium in direct continuity of the OSE. So the OSE and Fallopian tube share the same origin. Moreover, there is a direct histological connection between the epithelium of the fimbria and the OSE [6] (see figure 1). As we will show below, all these various elements suggest that we should no longer use the term ovarian cancer, but rather tubo-ovarian cancer.

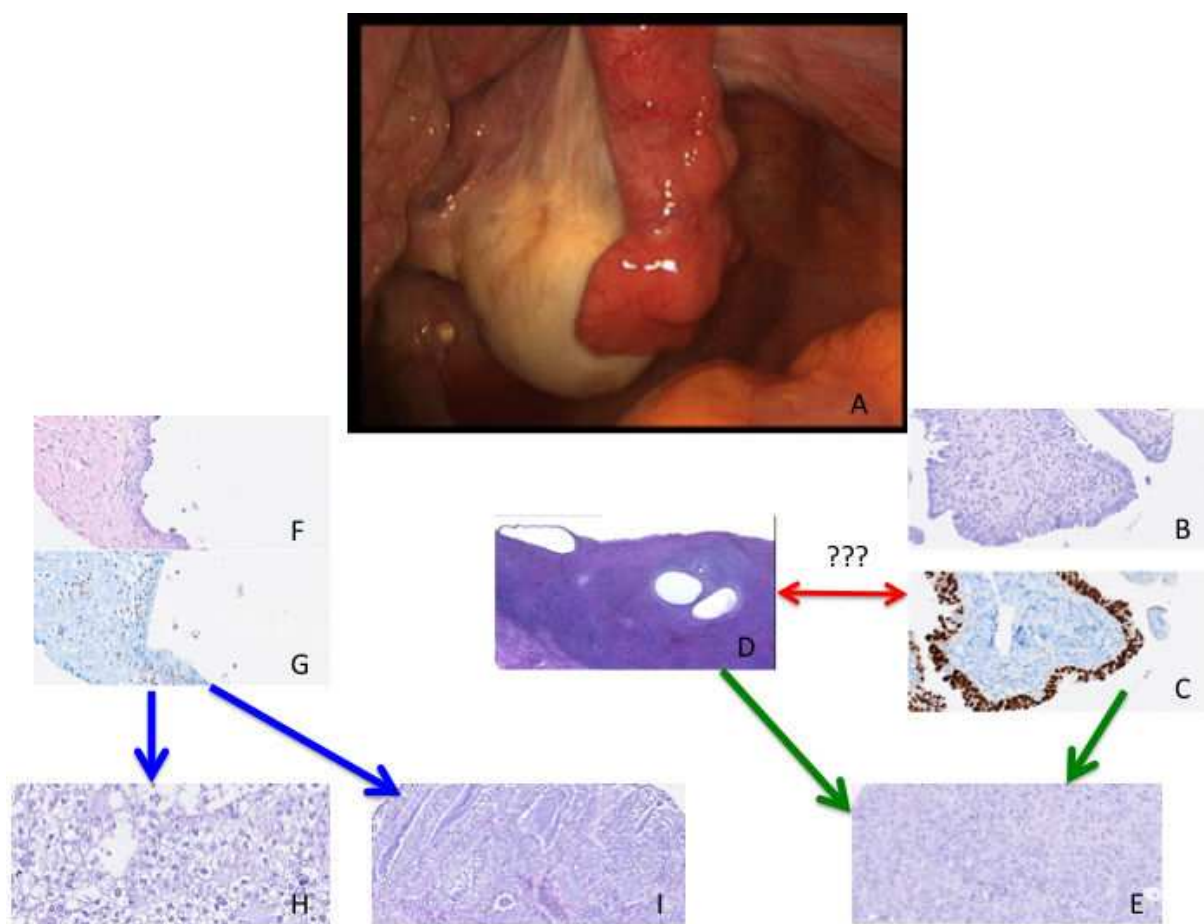


Figure 1. A-In this laparoscopic view, we can see the close anatomical interaction between the fallopian tube and the ovary; In the high-grade serous ovarian carcinogenesis, serous tubal intraepithelial carcinoma (STIC in photo B) may be the non-invasive precursor of high-grade ovarian cancer (E). STIC is characterized by a p53 immunohistochemical signature (C); On the other hand, ovarian epithelial dysplasia (see the inclusion cysts in D) may be also a preinvasive lesion in the high-grade serous ovarian carcinogenesis. This raises the question of the temporal relationships and chronology of events: what is the exact relationship between ovarian dysplasia and STIC ? In the clear cell (H) and endometrioid (I) ovarian carcinogenesis, endometriosis (F) may be a non-invasive precursor when there is loss of ARID1A expression (G). The fallopian tube may be considered as both as a source in the high-grade serous ovarian carcinogenesis and as a conduit for endometriosis in the clear cell and endometrioid ovarian carcinogenesis [60].

a. Once upon a time the ovarian hypothesis:

In 1971, Fathalla [7] developed the theory of incessant ovulation after noting the high frequency of ovarian cancer in nulliparous women and the high prevalence of peritoneal carcinosis of ovarian origin in battery hens (ovulation every 28 hours, rate of spontaneous ovarian cancer between 30 and 40% at 4 years of age). Inversely, the protective role of oral contraception, pregnancy and breastfeeding thanks to their inhibition of ovulation has been well-established [8-10]: repeated ovulations are pro-inflammatory events and could result in the formation of ovarian epithelium inclusion cysts in the OSE. These inclusion cysts, exposed as they are to cellular, paracrine and hormonal growth factors in the pro-inflammatory stromal microenvironment, could thus be the origin of a neoplastic process.

While 90% of cases of ovarian cancer are sporadic, 10% are hereditary in nature with a high proportion linked with BRCA mutations. There is a 35 to 60% cumulative risk at age 70 in case of BRCA 1 mutation. The risk is a little lower in case of BRCA2 mutations, lying between 10 and 27% [11]. These patients, their ovaries and tubes provide an excellent model for studies aiming at a better understanding of ovarian carcinogenesis. Due to the fact that bilateral adnexectomy is recommended in this group at risk, after the age of 35 and after completion of childbearing, these ovaries (and then the tubes, see below) have received particular attention in histopathological and molecular level studies. As a consequence histopathological anomalies called ovarian epithelial dysplasia (by analogy with other preinvasive lesions of the genital tract) were initially described in ovaries with a genetic risk (BRCA mutation) [12]. In view of the high risk of ovarian cancer in these patients if bilateral ovariectomy does not take place, these dysplastic lesions were therefore considered to be preinvasive with a potential towards cancer.

Similar dysplastic lesions were also revealed in areas adjacent to ovarian cancer, and also in the contralateral ovary in case of unilateral ovarian cancer without any genetic predisposition [13-18]. The molecular and histopathological similarities thus suggested that these dysplastic lesions were the initial phases of ovarian carcinogenesis.

More recently dysplastic anomalies were revealed in ovaries from patients who had undergone an ovulation stimulation process in a context of infertility [19, 20]. However since the histopathological, immunohistochemical and molecular characteristics differed from those of dysplastic lesions found in patients with a BRCA genetic mutation, it would appear that there may be several types of dysplasia that evolve differently (towards cancer in case of BRCA mutation, unlike the case after an *in vitro* fertilisation protocol) [21, 22].

b. ...and all of a sudden the tubal hypothesis:

In 2001, Piek *et al* [23] revealed for the first time 6 cases of tubal dysplasia including one case of severe dysplasia in a cohort of 12 patients with a genetic predisposition for ovarian cancer. Other studies have corroborated these results with nearly 10% Serous Tubal Intraepithelial Carcinoma (or STIC), 57% to 100% of which were located in the fimbriated end of the Fallopian tube [24-27]. These lesions consist of nonciliated cells exhibiting 3 or more of the following features: abnormal chromatin pattern, nuclear enlargement, marked nuclear pleomorphism, epithelial stratification and/or loss of polarity, and nuclear moulding. They are also characterised by high immunohistochemical expression of TP53 (expression level between 80% and 92%) and highly positive levels for proliferation marker Ki67 and DNA double-strand break marker γ -H2AX [24-27].

Other even earlier tubal lesions have also been described and it was possible to propose a serous carcinogenic sequence with a tubal origin: after a genotoxic stress and subsequent to various mutations (such as TP 53 mutation and BRCA mutation or epigenetic loss which play an important role in the maintenance of genomic integrity), very early histopathological anomalies of the tube would appear: these SCOUT lesions (Secretory Cell Outgrowths), characterised by a succession of at least 30 pseudostratified secretory epithelial cells with a low expression of PAX2, PTEN and Ki67, and no p53 mutation, would then evolve towards

p53 signatures [28, 29]. These p53 signatures, defined by a succession of at least 12 secretory cells with intense nuclear p53 staining and a low proliferative index, could evolve towards STIC (same TP53 molecular mutation suggesting a clonal relationship and a genetic identity). However, these p53 signatures are found in around 50% of normal control Fallopian tubes and it is not possible at the time of writing to tell which signature(s) might evolve towards STIC and which would not undergo this unfavourable evolution [30].

Finally, STIC lesions may metastasise in the ovary and adjacent peritoneum [31].

Several series of sporadic high-grade serous ovarian and serous peritoneal cancers (without BRCA mutation) were re-analysed and revealed the presence of the same serous carcinogenic sequence in almost 50% of cases [31].

c. Tubal or ovarian origin?

STIC lesions present preinvasive characteristics, as shown by the following elements:

- identical TP 53 mutations in STIC lesions and invasive cancer [32]
- up-regulation of other genes (RSF1, Cyclin E, p16, FAS, Stathmin 1, Lamnin 1) as it is the case in invasive ovarian cancer [33-35]
- genomic instability: telomeric shortening and chromosomic rearrangements [36-38]
- animal experiments: development of peritoneal carcinosis with a tubal origin

But, other arguments plead in favour of an ovarian origin. Notably, the fact that STIC lesions are not found in all genetic or sporadic series of ovarian cancer. If there are no STIC lesions or at the very least histological scarring due to STIC of the tube, what would the origin of the cancer be? So this raises the question of the temporal relationships and chronology of events: like for the chicken and the egg, do STIC lesions precede invasive cancer, or the contrary?

To conclude, although during the last century the postulate was raised that ovarian cancer originates in the ovary itself (which seemed logical and is the case for other organs), it would today appear that ovarian cancer has a dual origin, both tubal (predominating in case of genetic risk with BRCA mutation) and ovarian. It remains to be seen how and why one patient will have a cancer of tubal origin while another will have one of ovarian origin [31]. Furthermore, what triggers the transformation of normal secretory Fallopian tube epithelium into HGSC?

The solution is likely in the interaction between the tube and the ovary. Some authors have described the chronic inflammatory theory [39, 40]. They stated that there is less retrograde flow of inflammatory mediators from the genital tract and through the tube with tubal ligation, hysterectomy, oral contraception or pregnancy (closed cervix). For other authors, the release of inflammatory follicular fluid during ovulation may cause damage on the ovarian and fallopian tube epithelial cells [41, 42]. All these arguments point to the concept of tubo-ovarian cancer, i.e. a disease both in tube and ovary.

The potential clinical implications are discussed in the following paragraphs.

3. Endometrioid and clear cell cancers (see figure 1)

Women with CC and EC frequently present with endometriosis. In a review of 29 studies, Van Gorp *et al* [43] found a statistical association between endometriosis and endometriosis-associated ovarian cancers (EAOC): 36% of clear cell carcinoma were associated with endometriosis (11-70%), and 10% in case of endometrioid carcinoma (5-43%). A precursor lesion called atypical endometriosis was proposed. Atypical endometriosis (AE) is defined by the presence of hyperplasia or cytological atypia, increased nuclear/cytoplasmic ratio, mild hyperchromosomia, mild to moderate pleomorphism, crowded and occasionally stratified epithelial cells. AE has been identified adjacent to concomitant EAOC, with a demonstrated transition from benign endometriosis through AE to EAOC. At the molecular level, AE and EAOC share common molecular abnormalities such as PTEN and PIK3CA mutations, HNF 1b up-regulation, MET amplification and loss of ARID1A [44].

ARID1A (loss or mutation) and PIK3CA are early events and likely occur in precursor lesions as well as in EAOC: mutation of ARID1A gene (AT rich interactive domain 1A) was found in 41 to 57% of clear cell cancers and 30 to 48% of endometrioid cancers [31, 45-47]. ARID1A is a tumour suppressor gene and encodes BAF 250a protein that is involved in the multi-protein SWI/SNF chromatin-remodelling complex.

It has been well established that the SWI/SNF complex is involved in DNA repair through cell cycle arrest and apoptosis, cell survival after DNA damage (particularly by promoting γ H2AX induction) and genomic stability. ARID1A has recently been demonstrated to act as a negative regulator of the cell cycle through interaction with TP53 and its mutation may lead to cellular dysfunction as dysregulation of chromatin remodelling [48]. Moreover, loss of expression of this gene was recently found in benign endometriosis (20%) and AE (38.5%) adjacent to malignant lesions (57.7%), suggesting a chronological association from benign through atypical endometriosis to AEOC [44]. Samartzis *et al* [49] found also loss of ARID1A/BAF 250a expression in presumably benign ovarian endometriomas (n=3/20, 15%) particularly in the form of cell clusters that could suggest a clonal loss of BAF 250a and a risk of carcinogenic transformation [31].

Finally tubal ligation is protective against AEOC suggesting passage of endometriosis through the tube as a key oncogenic step with potential clinical implications (see below).

4. Clinical implications

The challenge is to detect a microscopic lesion during the occult period. We know also the preclinical natural history of HGSC which lasts on average 4 years as *in situ*, stage 1 and 2 cancers and approximately 1 year as stage 3 /4 cancers before they become clinically apparent [50].

To date, there is no screening test for ovarian cancer. ROCA screening (Risk of Ovarian Cancer) may be promising. It is based on a computerised Bayesian algorithm comparing each individual's CA125 profile to the pattern in ovarian cancer and healthy women. If the CA125 rate

is closer to known cases of ovarian cancer, the risk may be greater and a specific clinical assessment with ultrasonography is performed. UKCTOCS will report on the impact on mortality in January 2015 [51, 52].

In the other non invasive methods, evaluation of DNA obtained by Papanicolaou test to detect ovarian cancers is probably encouraging: 41% (9/22) of ovarian cancers were identified using a panel of mutated genes from liquid Papanicolaou smear specimens [53].

However, none of these methods can currently be considered as a safe alternative to risk-reducing surgery. It has been thoroughly demonstrated that carrying out preventive bilateral adnexectomy significantly reduces the risk of ovarian cancer (by over 98%) in at-risk groups (BRCA mutations, Lynch syndrome, family history of breast/ovarian cancer). Nevertheless, while operative morbidity can remain limited thanks to minimally invasive laparoscopic surgery, the complications of surgically induced menopause should not be minimised in women who are still young [54].

The new tubal theories in which the Fallopian tube is considered to be a conduit for EAOC (endometriosis as a precursor lesion) and as an origin for HGSC could result in a preference for exclusive bilateral salpingectomy instead of adnexectomy.

The current Canadian recommendations in British Columbia in gynaecological clinical and surgical practice are in line with this [55]:

- removal of Fallopian tube along with fimbriated end at the time of hysterectomy
- perform salpingectomy instead of tubal ligation
- genetic counseling and BRCA mutation screening in women at high genetic risk of HGSC, with risk-reducing surgery in patients with BRCA mutations

However, we believe a distinction should be drawn between HGSC and EAOC:

- in HGSC risk groups carrying out salpingectomy could be an attractive alternative in that it avoids inducing menopause [56], but this preventive attitude appears to be premature as yet since the origin of this cancer does not seem to be the tube in absolutely all cases, and also because the impact of salpingectomy on ovarian reserves is still the subject of debate. Kwon *et al* [58] have developed a simulation model comparing three strategies in the BRCA population: bilateral salpingo-oophorectomy, bilateral salpingectomy, bilateral salpingectomy with delayed oophorectomy. The authors conclude that prophylactic adnexectomy is best in terms of reducing the risk of ovarian and breast cancer. However, bilateral salpingectomy with delayed oophorectomy could be an interesting option in terms of cost-effective strategy and higher quality of life.
- in groups at risk of EAOC, the problem is not so much the Fallopian tube but rather that of endometriosis. Endometriosis very often develops early (sometimes during adolescence) and removal of the Fallopian tube could only be carried out far later and consequently would be of no interest. Only by drawing the distinction between (atypical) endometriosis with a risk of degeneration and benign endometriosis could efficient screening become possible. The use of specific markers such as ARID1A could be promising [54].

Finally, *ex vivo* optical imaging using reflectance and fluorescence may detect preinvasive lesions. McAlpine *et al* [58] were able to view STIC tubal lesions with 73% sensitivity, 83% specificity, 57% positive predictive value and 91% negative predictive value.

In the future, the development of real time *in vivo* high resolution imaging for STIC through fallopscopy (transcervical route) or salpingoscopy (confocal microlaparoscopy) could certainly be useful in patients with a genetic risk of ovarian cancer and who want to remain fertile, by allowing a precise histopathological diagnosis for the ovaries and tubes in real time and *in vivo* [59].

5. Conclusions

We have moved from one paradigm to another: instead of an exclusively ovarian origin, it appears that ovarian cancer may also have a tubal origin (probably in the majority of genetic risk cases) with the consequent questions concerning clinical implications and exclusively preventive salpingectomy.

We consider that more studies are still needed in order to validate these new concepts. It is clear now that, just as for breast cancer, ovarian cancer is a heterogeneous disease involving specific molecular signatures. Molecular characteristics may likely define personalized treatment specific to subtypes as is the case in breast cancer [31].

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