

The origin of ovarian cancers - hypotheses and controversies

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1. ABSTRACT

Ovarian cancer is the prime cause of death from gynecological malignancies in the Western world. In spite of its importance, it is poorly understood and its prognosis remains poor. The most common and lethal of all ovarian cancer subtypes are the high grade serous ovarian carcinomas (HGSOCs). A major problem in their clinical management is the current uncertainty about their cell type of origin, which limits means of early detection and prevention. It has not been resolved whether all HGSOCs originate in oviductal fimbriae or in ovarian surface epithelium (OSE). This review summarises evidence for these two hypotheses and considers the alternative possibility that HGSOCs may arise at both sites. This concept is based on the common embryonic origin of OSE and fimbriae in the coelomic epithelium and evidence of overlapping differentiation between these epithelia in the adult, which suggests incomplete commitment and pluripotentiality. This hypothesis would account for OSE and fimbriae giving rise to identical carcinomas, and for their susceptibility to neoplastic transformation that is absent in the adjacent extraovarian serosa and oviductal ampulla.

2. INTRODUCTION

Cancers of the ovary are the 5th leading cause of cancer-related deaths and the prime cause of deaths from gynecological malignancies among women in the Western world. In spite of their importance, the causes and natural history of these cancers are among the least understood among major human malignancies. Furthermore, in spite of intensive research, the 5-year survival from ovarian cancers has remained at only about 40% for the last 50 years (Table 1). One of the main obstacles to improved outcomes is the lack of adequate means to detect the tumors early, when they are still curable (Figure 1). This problem is confounded by the variability among ovarian cancer subtypes (Figure 2) (1), and is directly related to the fact that it is still uncertain where, histologically, the majority of ovarian cancers arise. Over 85% of ovarian malignancies are categorized as epithelial ovarian cancers, and among these, the most common and most lethal are the high grade serous ovarian carcinomas (HGSOCs). The present review deals specifically with HGSOCs and, in particular, with two current conflicting hypotheses regarding their site of origin.

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Table 1. Ovarian cancer incidence and death count in the United States

Year	Incidence	Death count
2009	21500	14600
2005	19842	14787
2004	20069	14716
2003	20445	14657
2002	20792	14682
2001	19710	14414
2000	19672	14060
1999	19676	13627

There has been no improvement in the survival rate among women with ovarian cancer within the time period shown. Data are from the Ovarian Cancer National Alliance (USA) (<http://www.ovariancancer.org/>), based on the SEER Program report of January 1, 2008, with the projection to 2009.

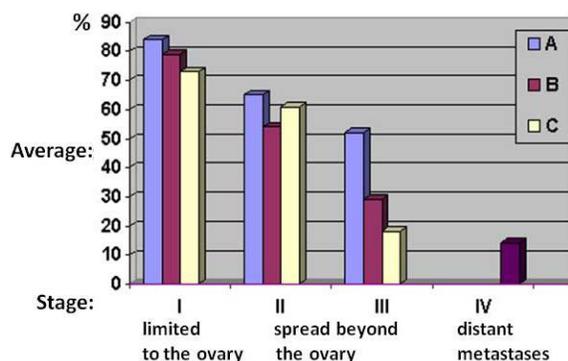


Figure 1. Expected 5-year survival rate for each stage of ovarian cancer. The percentage of survivors is divided by stage subtype (A, B, or C), except for stage IV, which is not divided. Within each stage, group A are the least advanced, and group C are the most advanced tumors, B being intermediate. The data are from the International Federation for Gynecology and Obstetrics (FIGO) (<http://www.igo.org/>), 2010.

3. HETEROGENEITY OF OVARIAN CANCERS

3.1. Morphologic subtypes

Serous ovarian carcinomas, by definition, exhibit serous, i.e. oviductal differentiation, in contrast to other epithelial ovarian carcinomas which undergo endometrioid, mucinous or clear-cell differentiation. Thus, epithelial ovarian cancers mimic the derivatives of the Mullerian ducts, i.e. the epithelia of the oviduct, uterus and cervical canal. Clear cell carcinomas are an exception since they resemble renal clear cell carcinomas. In recent years, evidence has accumulated indicating that endometrioid and clear cell carcinomas may arise in sites of endometriosis and the composition of mucins in ovarian mucinous carcinomas resembles mucins of the G.I. tract, suggesting that some of these neoplasms may be derived from extraovarian sources. Forms of ovarian cancer other than epithelial are sex cord-stromal tumors which include granulosa cell tumors, and rare types such as germ cell tumors (Figure 2) (1).

3.2. Molecular profiles

As indicated above, the epithelial ovarian cancers comprise a variety of subtypes, defined by their morphology and differentiation. They are also

characterized clinically by different progression, responses to therapy and prognosis. The histologic subtypes of epithelial ovarian cancers can further be classified on the basis of molecular profiles. Two groups have been defined on the basis of specific combinations of mutations and gene inactivation (2): Type I tumors include low-grade serous, low-grade endometrioid, clear cell and mucinous carcinomas. These tumors are slow growing, frequently discovered at low stages, and share lineages with preinvasive and benign precursors. Type II tumors include the high-grade serous, high-grade endometrioid, and undifferentiated carcinomas, with the great majority being classified as serous. These carcinomas are usually detected late, don't have well defined precursors and account for most deaths due to ovarian cancer. As a group, type I tumors are genetically more stable than type II tumors and display specific mutations in the different histologic cell types. KRAS, BRAF, and ERBB2 mutations occur in most low-grade serous carcinomas, whereas TP53 mutations are rare in these tumors. Low-grade endometrioid carcinomas have mutations of CTNNB1, PTEN and PIK3CA, while most mucinous carcinomas have KRAS mutations and clear cell carcinomas exhibit PIK3CA activating mutations. In contrast, the high-grade serous carcinomas, the predominant type II tumors, are highly unstable genetically, are characterized by p53 mutations in over 90% of cases, but rarely contain the mutations found in type I tumors (reviewed in 3).

3.3. Scope of the review

There now is evidence that endometrioid and clear cell ovarian carcinomas may in fact originate in endometriosis, and that at least some mucinous ovarian carcinomas are metastases from cancers of the GI tract (reviewed in 3). These findings will not be discussed further in this review, which deals primarily with the origin of the high grade serous ovarian carcinomas (HGSOCS), the most common and most lethal of all ovarian neoplasms.

4. ORIGIN OF HIGH GRADE SEROUS OVARIAN CARCINOMAS (HGSOCS)

4.1. The putative precursors of HGSOCS

4.1.1. Ovarian surface epithelium, OSE

Anatomically, OSE is the part of the pelvic peritoneum which overlies the ovary (Figure 3). It is thus a mesodermally derived mesothelium. In terms of physiologic functions, little is known beyond the fact that OSE seems to contribute to follicular rupture at ovulation by secreting proteases (4) and subsequently proliferates to heal the ovulatory defect. However, it is important to note that OSE differs in multiple ways from extraovarian peritoneum, both structurally and functionally (5). For example, while OSE has estrogen and progesterone receptors as well as Met receptors for hepatocyte growth factor and lacks Ca125, extraovarian peritoneum is Ca125 positive but lacks ovarian steroid- and Met receptors. Most importantly for the purposes of this review, OSE is separated from the underlying stroma by a thick collagenous layer, the tunica albuginea (Figure 3), and is very loosely attached to underlying tissues. In contrast, the extraovarian peritoneum is in close contact with the stroma and is firmly attached to it. As a result, in contrast to the extraovarian peritoneum, OSE has unusually limited access

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<u>Categories</u>	<u>% of all ovarian cancers</u>	<u>Epithelial Subtypes</u>	<u>%</u>	<u>Differentiation</u>
Epithelial	85-95	Serous high grade	65	Fallopian tube
Sex cord-stromal	5- 8	Serous low grade	3	Fallopian tube
Germ cell	3-5	Endometrioid	10	Endometrium
Metastatic	4-6	Clear Cell	10	Renal CC carcinoma*
Other	1	Mucinous	3	Endocervix, G.I. tract

*CC, clear cell

Figure 2. The subtypes of ovarian malignant tumors and their relative frequencies.

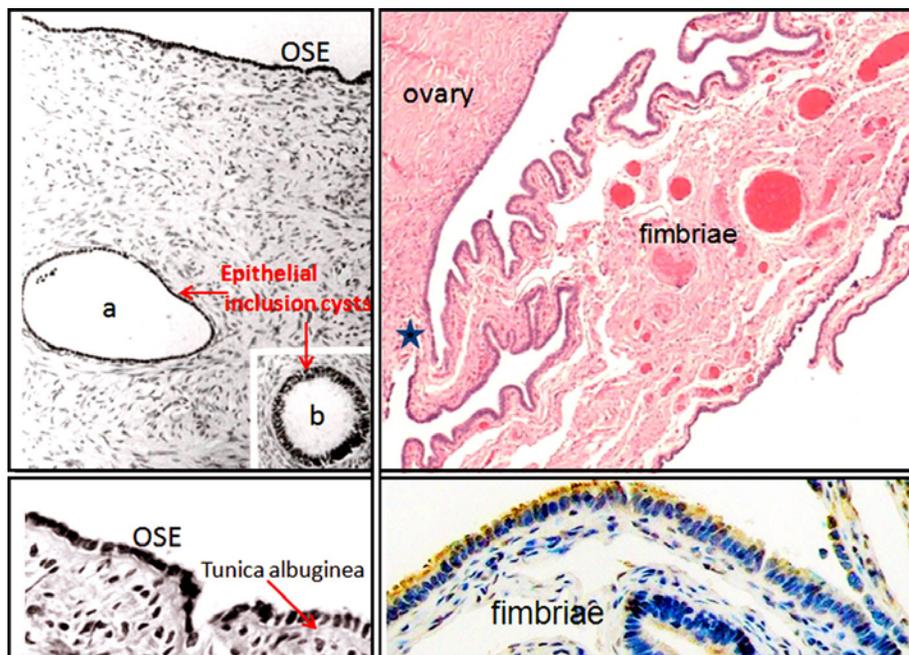


Figure 3. The two proposed sources of the HGSOCS: On the left, the ovarian surface epithelium (OSE) which is the part of the pelvic peritoneum that overlies the ovary. Two epithelial inclusion cysts are pictured in the figure: ‘a’ is lined with OSE, ‘b’ is lined with columnar epithelium that can be interpreted as either metaplastic OSE or fimbrial epithelium that has been displaced into the ovarian stroma. On the right, oviductal fimbriae. The star at the junction of the ovary and the fimbriae is the site of the attachment of an ovarian fimbria. It may be mistaken for an adhesion, but this is unlikely in view of the absence of other nearby indications of adhesions. Hematoxylin/eosin, except for the lower, high power view of the fimbriae which has been stained for cilia with antibody LhS28 (Abcam).

to metabolic exchanges with the stroma and circulation, as well as to growth factors and hormones; thus, it resides in a niche that keeps it in an isolated, quiescent state, which is ideal for a population of stem cells. In support of this concept, it was recently reported that OSE expresses several classical stem cell markers (6). The concept of OSE as pleuripotential stem cells is also in keeping with other stem cell-like characteristics that have been described (7), and with the ability of OSE to differentiate to a fibroblastic or an epithelial phenotype, depending on microenvironmental conditions (5, 8). It is further worth mentioning that malignant tumors arising in extraovarian

peritoneum are mesotheliomas, which differ profoundly in structure, function and clinical characteristics from OSE-derived ovarian carcinomas, indicating that they originate in fundamentally different progenitor cells.

4.1.2. Fimbrial epithelium

The fimbriae comprise the most distal part of the oviduct (Figure 3). They sweep the ovarian surface at ovulation, capture ovulated oocytes, and transport them towards the oviductal ampulla through ciliary motion and peristalsis. In contrast to OSE, fimbrial epithelium is a columnar, highly differentiated secretory ciliated

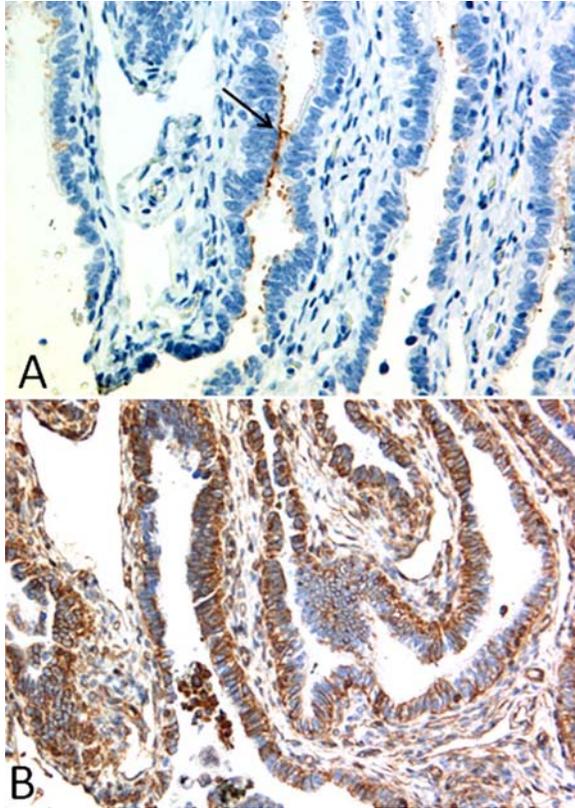


Figure 4. Evidence for the mesothelial origin of the oviductal fimbriae: expression of the mesothelial markers (A) mesothelin (arrow) and (B) vimentin.

epithelium, which undergoes well-defined changes in response to the hormonal changes during the menstrual cycle. It is composed of two cell types, i.e. secretory and ciliated cells. The secretory cells are thought to be the progenitor cells which repopulate the epithelium during cell turnover, while the ciliated cells appear to be terminally differentiated (9). There is currently no information regarding stem cells in fimbrial epithelium. Embryologically, the fimbrial epithelium is derived from the Mullerian ducts which, in turn, originate in the coelomic epithelium (embryonic mesothelium) close to the part of the coelomic epithelium which will differentiate into OSE (5,10). Though epithelial morphologically, the Mullerian ducts are sometimes referred to as a mesoepithelium because they have retained mesothelial features, such as vimentin expression (11). They differentiate into the oviducts, endometrium, and cervical epithelium. Mature fimbrial epithelium is thus a mesodermally derived epithelium which exhibits typical epithelial features, such as cilia and E-cadherin, but its mesothelial origin is also reflected by its expression of mesothelin and vimentin (Figure 4).

4.2. The controversy: whence HGSOCS?

Before discussing the pros and cons of the OSE vs. fimbrial origin hypotheses, it should be pointed out that there seems to be general agreement that the majority of

early stage HGSOCS appear in epithelial inclusion cysts rather than on the ovarian surface. This raises the question how the precursors of the cysts reach the stromal location. Morphologically, the epithelial lining of the inclusion cysts is of two types: flat to cuboidal, resembling OSE, and columnar ciliated, resembling fimbrial epithelium (Figure 3). OSE-lined cysts tend to be in the majority and are generally larger (8). The means by which either the OSE-derived or the fimbria-derived precursors reach the stromal location is still not defined and requires further investigation. It has been proposed that OSE cells are trapped within ovulatory defects at the time of ovulation and subsequently form cysts. However, this is unlikely, since women who had undergone many pregnancies i.e. had had fewer ovulations, have more, rather than fewer inclusion cysts (12, 13). This conclusion is supported by immunohistochemical evidence that OSE cells, trapped in ovulatory defects, dissociate and undergo epithelio-mesenchymal transition rather than forming cysts (5). The more convincing proposal for OSE-derived inclusion cyst formation is that, as first proposed by Scully (12) OSE-lined cysts are formed through interepithelial adhesions which occlude invaginations of the ovarian surface (5, 12, 13) (Figure 5). It has been suggested that fimbrial epithelium (benign or STIC-derived) sheds from the fimbriae and attaches to the ovarian surface or that it attaches to the ovarian surface as part of adhesions. The fimbrial epithelial fragments are then thought to enter the ovarian stroma at the time of ovulation through the ovulatory defect in the OSE. Difficulties with this hypothesis are 1) that the ovulatory defect is hardly wider than the oocyte, and collapses immediately after ovulation which would make it difficult to allow passage of an epithelial fragment before the defect is repaired; 2) the tissue underlying the ovulatory defect is not stroma but a blood clot, which is shortly followed by the formation of the corpus luteum. To date, there is no evidence that normal or neoplastic fimbrial epithelium, or for that matter any epithelial inclusion cysts, have been observed in these regions. It seems more likely that fimbrial epithelium may attach to the ovarian surface with adhesion formation, and subsequently be incorporated into newly formed ovarian surface invaginations that proceed to form inclusion cysts.

4.2.1. The contenders: OSE vs. oviductal fimbriae

4.2.1.1. Evidence for the origin in the OSE

For many years it was accepted that most, if not all, subtypes of ovarian epithelial cancers arise in the ovarian surface epithelium (OSE), i.e. the pelvic mesothelium which overlies the ovary and lines epithelial inclusion cysts within the ovarian stroma. (Fig.3). This assumption implied that adult OSE is composed of pleuripotential uncommitted cells capable of differentiating along the different pathways of the Mullerian duct derivatives (4, 14, 15). Early lesions within epithelial inclusion cysts were described initially by Scully (12, 13) and supported by others (14, 15, 16) who observed dysplastic lesions and early stage ovarian cancers contiguous with normal OSE within OSE-lined epithelial inclusion cysts. Evidence has also been presented of preneoplastic changes at the molecular level (16, 17,18). Furthermore, the capacity of

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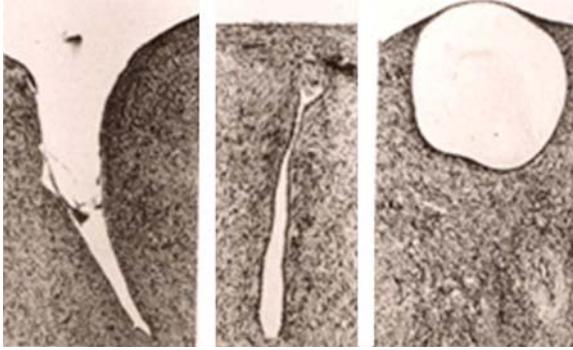


Figure 5. Evidence for the possible origin of OSE-lined epithelial inclusion cysts through fusion of adjacent OSE lined invaginations.

OSE to undergo metaplasia was demonstrated by changes from flat to columnar cell shapes in association with the immunohistochemical demonstration of the tubal differentiation markers E-cadherin, Epcam, cilia, and oviduct-specific glycoprotein OVGP1 (oviductal glycoprotein) in the columnar cells within the same inclusion cysts (16,19, 20). The idea that OSE is a source of HGSOCS is supported in that mesothelin, which is a differentiation marker highly specific for mesothelium among normal tissues, is one of the most prominent markers of HGSOCS (1), and that vimentin, the characteristic intermediate filament of normal mesodermal tissues, is abundant in HGSOCS.

OSE loses mesenchymal characteristics such as calretinin (19) and acquires epithelial features such as HBME-1, EMA, TAG-72, PAX8, and E-cadherin as its location changes from the ovarian surface to invaginations to epithelial inclusion cysts (8, 19). Whether this change in differentiation is an early step towards transformation to carcinomas rather than mesotheliomas is unknown; but it indicates that OSE cells, once within the stroma, undergo fundamental changes that reflect their pluripotentiality and are presumably initiated by the microenvironment. The stroma contains multiple local and circulation-derived factors that may modify differentiation as well as play a role in transformation. Another source of bioactive agents is the content of the inclusion cysts: OSE secretes many active agents including cytokines (IL-1, IL6, M-, G-, and GM-CSF), growth factors (TGFbeta, TNFalpha) and hormones (GnRH, inhibin) (5). These agents diffuse into the pelvic cavity if secreted by OSE on the ovarian surface, but within cysts they can reach high concentrations that have major effects.

Further support for the hypothesis that HGSOCS originate in the OSE came from several studies where OSE was transformed to malignant tumors that resemble high and low grade serous ovarian carcinomas, both in animal models (21 - 23) and in cultured human OSE (24 - 27).

A major defect in the hypothesis that OSE is the source of HGSOCS has been the lack of early stage cancers and precursor lesions, both of which have been observed only rarely. Interestingly, the advent of the fimbrial

hypothesis may have provided a solution to this problem: Almost invariably, when HGSOCS are found at surgery, they are very large, while coexisting serous tubal intraepithelial carcinomas (STICs) within the fimbrial epithelium are microscopic. Since according to the fimbrial hypothesis the STICs are the source of the cancers in the ovary, it follows that the malignant cells grow very much faster in the ovarian, than in the tubal environment, presumably through powerful growth-promoting ovarian stromal factors. If neoplastic transformation took place within an OSE-lined inclusion cyst, exposure to these factors would be immediate, resulting in rapid growth and, subsequently, a very brief time-window in which the growing cancer could be detected in its early stages.

4.2.1.2. Evidence for the origin in oviductal fimbriae

The origin of the HGSOCS in OSE became seriously questioned as a result of evidence that they may arise in the the Fallopian tube fimbriae and only secondarily be deposited on the ovarian surface. This idea was first proposed in 2001 by Piek *et al.* (28) who reported the presence of dysplastic and hyperplastic lesions on fimbriae of 11 of 12 prophylactic salpingo-oophorectomy specimens removed from BRCA mutations carriers, while none were found in the control specimens. Histologically, the fimbrial lesions closely resembled HGSOCS and showed increased proliferation and over-expression of p53, as well as reduced p21 and p27. The authors subsequently proposed that oviductal fimbriae might be an extraovarian source of HGSOCS (29), implying that the tumor cells would be deposited on the ovarian surface either by retrograde flow or when fimbriae sweep the ovary at ovulation in the process of collecting the ovulated oocyte and transporting it to the oviductal ampulla by ciliary movement (Figure 3). This hypothesis has since received much supportive evidence (reviewed in 3, 9, 30, 31).

It has been shown that about 70% of women with ovarian or peritoneal serous carcinomas, irrespective of family history, also harbour STICs (32). Occasionally, STICs are contiguous with co-existing HGSOCS (33). STICs characteristically appear in fimbriae of the distal fallopian tube and appear to originate in the secretory cells within the fimbrial epithelium. They exhibit strong immunohistochemical p53 staining indicative of p53 inactivation/mutation in over 90% of cases, which is also characteristic for ovarian HGSOCS, as well as evidence of DNA damage in the form of γ -H2AX immunostaining (31, 34). P53 staining was also detected in areas of overtly benign fimbrial epithelium. These regions, named “P53 signatures” were proposed to be early indicators of a predisposition to STIC formation; at present, their significance is questionable since they have now been detected in approximately 50% of normal tubal epithelia (35). Arguments for the origin of HGSOCS in STICs are most strongly supported by the presence of cases where identical p53 mutations were found in the STICs and in coexisting HGSOCS (32, 36).

Several culture models of human fimbrial epithelial cells have recently been established (37) and transformed to lines resembling HGSOCS (38), which will contribute to our understanding of fallopian tube epithelial physiology and pathology including its role in ‘ovarian’ tumorigenesis.

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Table 2. Evidence indicating that the origin of HGSOCS is in the oviductal fimbriae, or in the ovarian surface epithelium (OSE), or applies, with modifications, to both fimbriae and OSE

Evidence for the origin of SHGOCS in oviductal fimbriae	Evidence for the origin of SHGOCS in OSE	Comments
Large number of STICs in BRCA mutation carriers		
Increased number of STICs in women with HGSOCS		Not all HGSOCS coexist with STICs
Close histologic resemblance of STICs to HGSOCS		
Monoclonal origin: Identical p53 mutations in coexisting STICs and HGSOCS in a significant number of cases (32)		Not all cases have identical p53 mutations in STICs and concurrent HGSOCS
	OSE expresses multiple stem cell markers (6)	Stem cell marker profile of fimbriae is not yet defined
	OSE-lined inclusion cysts undergo morphologic and functional tubal metaplasia (16, 19).	Such metaplasia may be an early preneoplastic step
	Pleuripotentiality: tubal and mucinous metaplasia, epithelio-mesenchymal transition, endometrioid characteristics under experimental conditions (5, 15, 19, 41, 42)	
p53 signatures, indicating inactivation or mutations occur in secretory cells of normal fimbriae as well as in STICs and HGSOCS (34)	P53 signatures occur in OSE (6, 17)	The frequency of p53 signatures in normal oviducts is approx. 50% (35)
STICs likely represent an early precursor of HGSOCS	Early stage HGSOCS in OSE-lined cysts have been found, though rarely (13, 15, 16)	The rare finding of early stage HGSOCS within the ovary may be the result of their rapid growth in the ovarian environment
STICs are sometimes contiguous with HGSOCS (33), suggesting that cancer cells arising in the STICs were deposited on the ovarian surface.	Transition from tubal metaplasia to carcinoma occurs in OSE-lined inclusion cysts (16)	Fimbriae sweeping the ovarian surface at ovulation may either deposit or pick up neoplastic cells.
Tubal secretory cells have been transformed to HGSOCS in culture. (37, 38).	OSE cells have been transformed to HGSOCS in cultures of human OSE (24-27). and in animal models (21-23)	
Ovarian cancers in hens originate in the oviduct	Ovarian cancers in hens originate in the OSE	Ovarian and tubal carcinomas in the hen, differ at the molecular level. (43), suggesting separate origins
PAX8 is a marker for tubal epithelium, and HGSOCS, but is absent in OSE.	PAX8 is absent in OSE on the ovarian surface, but is present in OSE lining epithelial inclusion cysts (19, 44).	
Small amounts of mesothelin are secreted by fimbrial epithelium (19)	Mesothelin is a specific differentiation marker for mesothelia, and a major marker in HGSOCS (1)	Mesothelin in fimbriae (19) reflects the mesothelial origin of the Mullerian ducts and thus of the oviductal epithelium
Oral contraception is associated with fewer STICs (45).	Incidence of HGSOCS is proportional to the No. of ovulations, which cause OSE rupture and exposure to oncogenic agents (41).	
HGSOCS gene expression profile resembles fimbrial epithelium, differs from OSE	HGSOCS gene expression profile resembles OSE once OSE has undergone tubal metaplasia	

5. AMBIGUITIES AND AN ALTERNATIVE HYPOTHESIS

The controversy whether the HGSOCS arise in the oviductal fimbriae or in the OSE is still ongoing, though, as shown above, convincing evidence for either position has been presented. The reasons for this impasse are several: first, many of the arguments used for either side apply to both hypotheses (Table 2); second, proposed mechanisms, sometimes accepted as fact, still require experimental proof; thirdly, there is not a single piece of evidence that is positive in 100% of cases in favor of either the fimbrial or the OSE hypothesis and would definitively exclude one or the other of the two potential sources of HGSOCS. Together, this scenario suggests strongly that HGSOCS arise in both the OSE and fimbrial epithelium. But such a concept raises an important question: How could two epithelia that differ profoundly structurally and functionally, and are located on different organs, give rise to identical carcinomas?

A possible answer to this question lies in the developmental history of OSE, the oviduct and extraovarian peritoneum. All of these structures originate in the mesodermally derived embryonic coelomic epithelium, i.e. the embryonic mesothelium, which lines the primitive peritoneal and pelvic cavities even before the ovary develops within the gonadal ridge (Figure 6). Initially, the coelomic epithelium is highly pleuripotential, being capable of developing into multiple structures. As development proceeds, much of the pleuripotential coelomic epithelium becomes subdivided into embryonic fields (Figure 7) which initially overlap but become increasingly restricted in size and competence. While OSE retains a degree of pleuripotency, other parts of the coelomic epithelium become committed to form discrete, specialized regions capable of differentiating along only one differentiation pathway. Among these pathways, various parts of the coelomic epithelium form all the peritoneal linings (mesothelia), the OSE, the Mullerian ducts and their derivatives, the mesonephros and the follicular cells of the primordial ovarian follicles. Importantly, the Mullerian ducts form as invaginations of the same coelomic epithelium in regions adjacent to the future OSE (Figure 6). Therefore, it is likely that the primordia

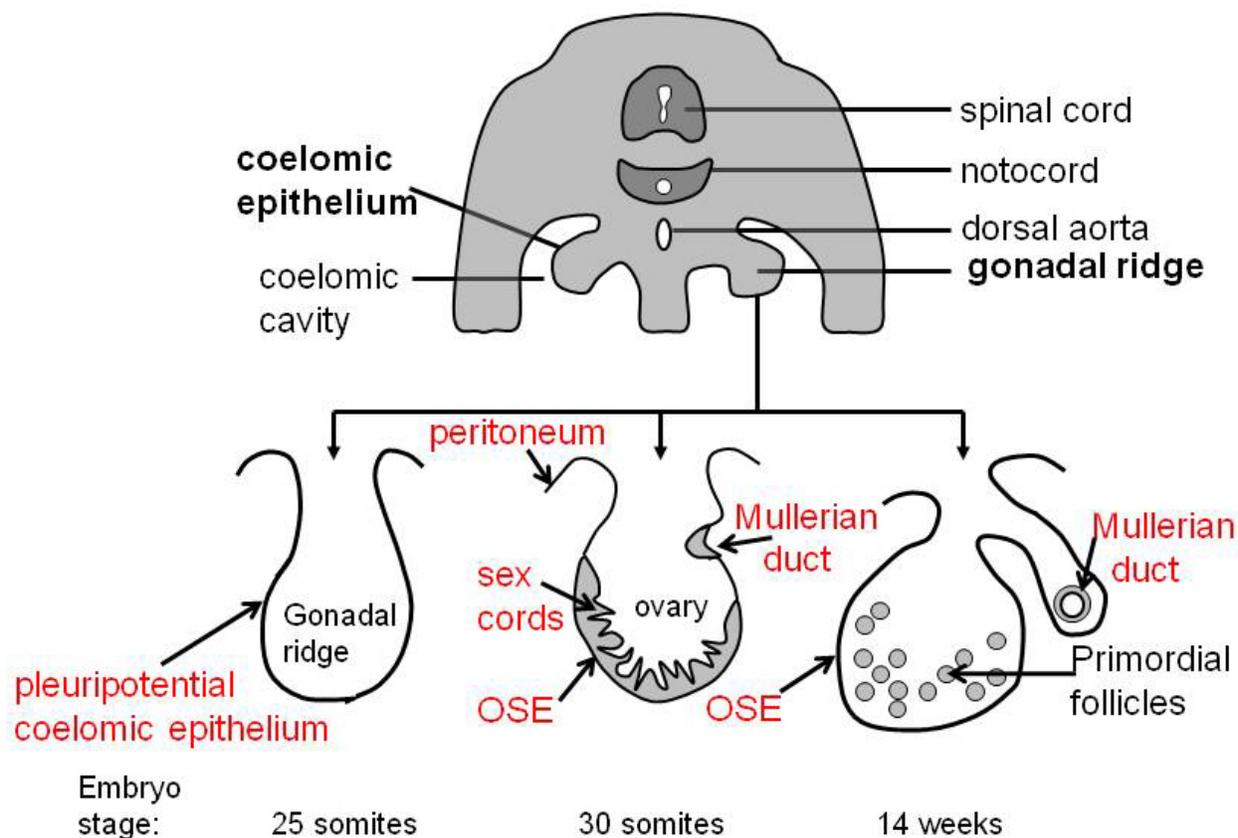


Figure 6. Diagram representing stages in the embryonic development of the ovary and Mullerian duct. The gonadal ridge will differentiate into the stromal component of the ovary, and the part of the coelomic epithelium overlying the gonadal ridge will form the OSE. The Mullerian ducts will form through invagination of the coelomic epithelium close the OSE.

of the OSE and the Mullerian ducts were originally parts of a common multipotential embryonic field, but whereas the Mullerian derivatives become firmly determined as tubal, endometrial and cervical epithelia as the Mullerian ducts invaginate and encounter specific inductive signals, the OSE retains a more primitive, pleuripotential state, presumably as a result of a lack of appropriate inductive influences at crucial stages of embryonic development. The presence of stem cell markers in the OSE (6) supports this idea. The hypothesis that OSE and fimbriae once shared an embryonic field was tested by an immunohistochemical comparison of the distribution of differentiation markers in OSE, fimbriae and the tubal ampulla (10, 19). The results showed that the differentiation markers of adult OSE and fimbriae overlap (Figure 8) which is strong evidence that they are derived from a common embryonic field. These results suggest that, while the extraovarian peritoneum and the oviductal ampulla may be terminally differentiated, the intervening OSE and the distal fimbriae represent less firmly committed, plastic transitional epithelial regions with shared phenotypic characteristics.

Many coelomic epithelium-derived epithelia remain anatomically contiguous in the adult, in spite of their widely differing structures and functions which define them as parts of separate organs. Though not obvious, this

continuity includes the OSE and the Fallopian tube, which frequently remain connected by a narrow epithelial isthmus extending onto the ovary from the fimbriae – the “ovarian fimbriae” (Figure 3) (19, 39).

Sites of epithelial transition from one form of differentiation to another in other parts of the body are known to be prone to neoplastic progression. Examples of this phenomenon are the squamo-columnar junction of the uterine cervix and the esophageal-gastric junction. The susceptibility of transitional epithelia to neoplastic progression is most likely linked to their plasticity and an incomplete commitment to a differentiated state. The only physical contact between fimbriae and OSE that is maintained in the adult are the tenuous ovarian fimbriae, in contrast to the above examples. But even if physical contact in the adult was lacking, incomplete commitment can be maintained. The presence of stem cell markers (6) and of overlapping differentiation markers (10, 19) (Figure 8) suggests that OSE and distal fimbrial epithelium, which formed an epithelial transition during development, have remained incompletely committed and differentiated, which may account for their susceptibility to transformation. The extraovarian peritoneum, OSE and tubal epithelium, which are all derived from coelomic epithelium, can be considered as a continuum with an area of increased

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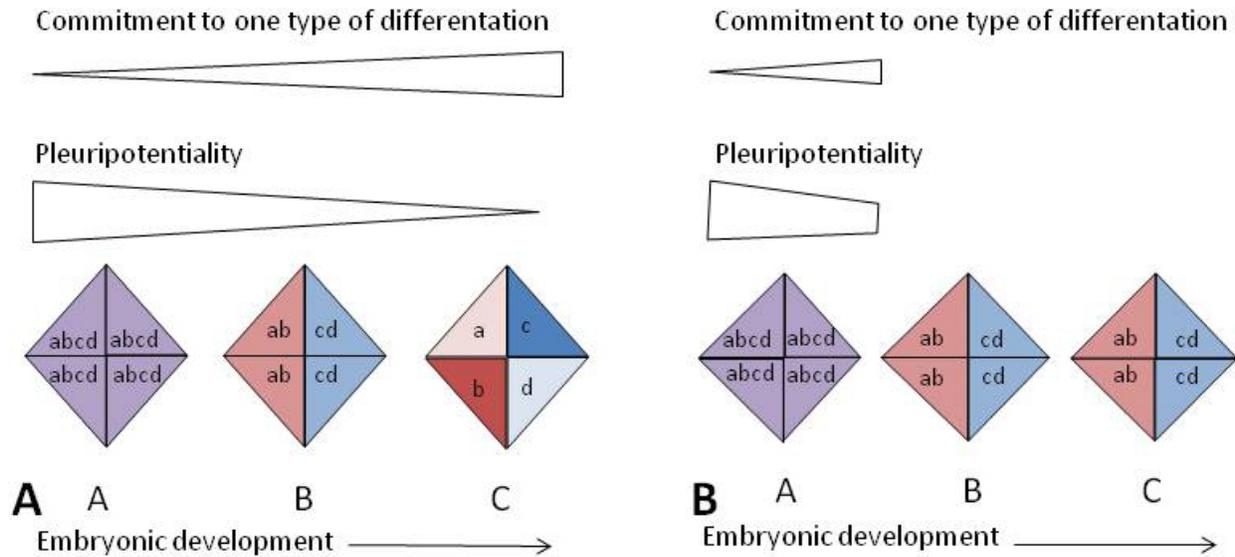


Figure 7. Embryonic fields demarcate regions within the embryo that are initially pleuripotential and competent to differentiate along several pathways. As development progresses, the embryonic fields become subdivided into smaller sections, and in each, pleuripotentiality is gradually reduced while commitment to a specific fate progressively increases, until, in many cell types, it becomes restricted to one form of differentiation (Figure 7A). a, b, c, d represent 4 differentiation pathways leading to 4 distinct cell types. In Figure 7A, all 4 quadrants in the diamond A, are competent to develop into any one of the 4 cell types. In diamond B, 2 quadrants are committed to cell types a and b only and have lost the capacity to differentiate into c or d, while the other two quadrants can develop into cell types c or d only. In C, the cells are fully committed as each quadrant can differentiate into only one of the 4 cell types. In Figure 7B, the sequence in diamonds A and B resembles Figure 7A. However, further development does not lead to further commitment, and the cells remain pleuripotential, i.e. competent to differentiate along more than one pathway. In general, the resemblance between adult tissues tends to be proportional to their proximity within embryonic fields during development. As many differentiation inducers act via gradients, there can be overlap in differentiation between adjacent fields, which can carry over into adulthood as shown in Figure 8.

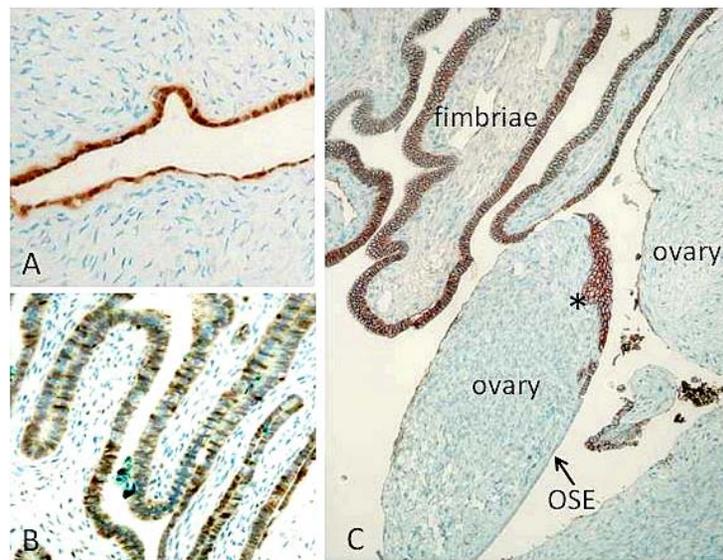


Figure 8. Overlap of differentiation between OSE and fimbriae. A. Calretinin is a known marker for mesothelia, including OSE, while fimbriae are generally negative. But occasionally (B), fimbriae show a mixture of calretinin-positive and calretinin-negative epithelial cells. C. E-cadherin is abundant in fimbriae, while OSE is generally E-cadherin negative (arrow). But occasionally, regions of OSE are positive for E-cadherin (asterisk).

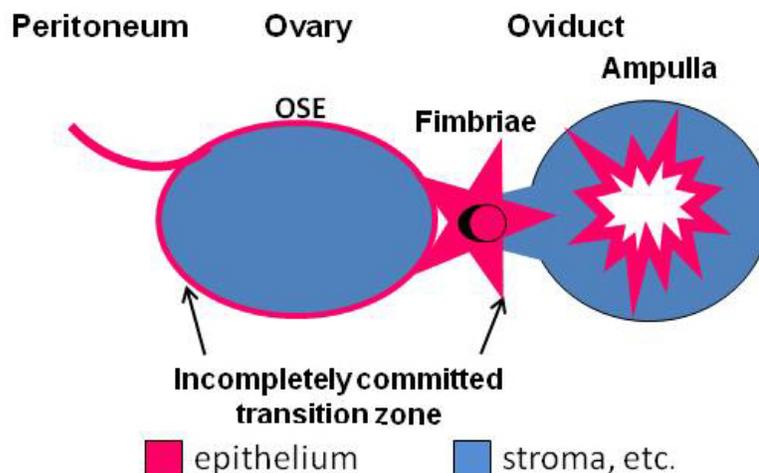


Figure 9. Diagrammatic representation of the continuity between the extraovarian pelvic peritoneum, OSE and tubal epithelia, based on their common origin.

susceptibility to neoplastic progression encompassing the OSE and the distal fimbriae (Figure 9). This approach provides possible answers to several currently unanswered questions, including the following:

Why would fimbriae and OSE give rise to identical carcinomas (HGSOCS) when they are parts of different organs and have very different phenotypes? Because they are derived from the same embryonic field within a common precursor, the coelomic epithelium (embryonic mesothelium) and have retained the potential to exhibit similar features.

Why do tumors arise in distal fimbriae and OSE but not in the remaining oviduct and the extraovarian peritoneum? Because only OSE and the distal fimbriae are derived from the zone of transition between these two epithelia and remained incompletely committed.

If tubal secretory cells are the source of SHGOCs, why are there no tumors in the ampulla, which has the most secretory cells? Because the ampulla is terminally differentiated and beyond the zone of transition.

6. CONCLUSIONS

It is striking that, in spite of a tremendous research effort in recent years, the question of the origin of HGSOCS has not been conclusively resolved. This is due to a considerable degree to the facts that many aspects of the current hypotheses are difficult to prove experimentally, and that many of the arguments used for either side apply to both hypotheses (Table 2). Furthermore, there is not a single piece of evidence that is positive in 100% of cases in favor of either the fimbrial or the OSE hypothesis and would definitively exclude one or the other of the two potential sources of

HGSOCS. In view of the close developmental relationship between the oviductal fimbriae and OSE, and overlap in their differentiation in the adult, it seems reasonable to accept the possibility that HGSOCS arise in both OSE and fimbriae. This solution would account for the resemblance between the carcinomas arising in the OSE and fimbriae, would provide guidelines for further steps in clinical management, and would hopefully lead to improvements in the outcomes of these deadly disease. (3, 9, 45).

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