The distal fallopian tube: a new model for pelvic serous carcinogenesis

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Purpose of review

Research over the past 50 years has yielded little concrete information on the source of pelvic serous cancer in women, creating a knowledge gap that has adversely influenced our ability to identify, remove or prevent the earliest stages of the most lethal form of ovarian cancer.

Recent findings

The distal fallopian tube is emerging as an established source of many early serous carcinomas in women with BRCA mutations (BRCA+). Protocols examining the fimbrial (SEE-FIM) end have revealed a noninvasive but potentially lethal form of tubal carcinoma, designated tubal intraepithelial carcinoma. Tubal intraepithelial carcinoma is present in many women with presumed ovarian or peritoneal serous cancer. A candidate precursor to tubal intraepithelial carcinoma, entitled the 'p53 signature', suggests that molecular events associated with serous cancer (p53 mutations) may be detected in benign mucosa.

Summary

A fully characterized precursor lesion is a first and necessary step to pelvic serous cancer prevention. The emerging data offer compelling evidence for a model of 'fimbrial-ovarian' serous neoplasia, and call attention to the distal fallopian tube as an important source for this disease, the study of which could clarify pathways to cancer in both organs and generate novel strategies for cancer prevention.

Keywords

BRCA, fallopian tube, fimbria, intraepithelial carcinoma, ovarian neoplasms, p53, primary peritoneal serous carcinoma, serous carcinoma

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Abbreviation

OSE ovarian surface epithelium

1040-872X

Introduction

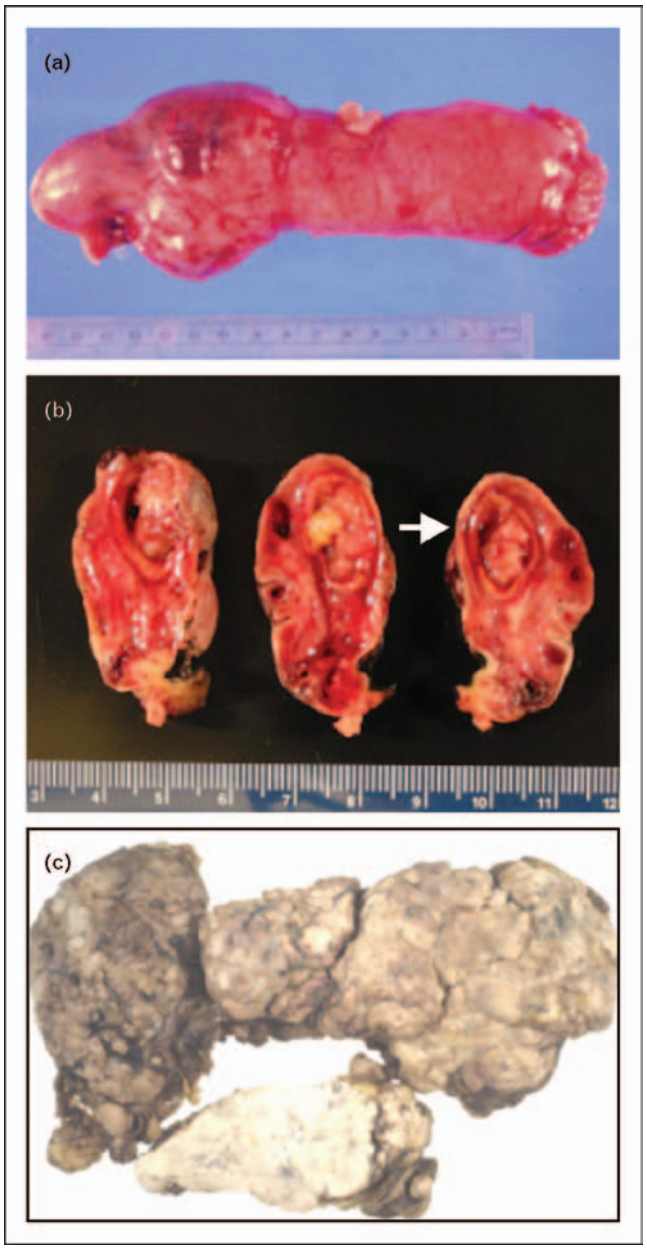
Epithelial ovarian cancer is diagnosed in over 22 000 women yearly in the United States, killing approximately 16 000 [1]. Worldwide, ovarian cancer accounts for approximately 114 000 deaths annually [2]. Efforts to prevent this disease have naturally focused on the mechanisms by which these tumors develop and have shown this disease to be heterogeneous. One group of tumors consists of endometrioid, mucinous and low-grade serous carcinomas, which are more likely to be discovered in the substance of the ovary, are often confined to one or more cysts and are more likely to proceed in a gradual or stepwise fashion from benign to malignant. The second group consists of serous carcinomas, a substantial proportion of which are discovered on the ovarian surface, often with involvement of the fallopian tubes, mesentery and omentum. Due to their propensity to spread early in their natural history, serous carcinomas of the ovary – specifically those involving the ovarian surface – are the most lethal form of epithelial ovarian cancer [3,4•].

The most enduring theory of ovarian carcinogenesis [5] holds that ovarian carcinomas arise from Mullerian metaplasia of the ovarian surface epithelium (OSE) or subcortical epithelial inclusions and develop as a function of genotoxic stimuli introduced to this epithelium during the reproductive years. While this model explains some forms of ovarian cancer, very few surface serous carcinomas have been encountered at a stage at which their ovarian origin could be pinpointed with confidence. Recent reports [6,7•–9•,10,11] have raised the intriguing prospect that the distal fallopian tube is a source for many pelvic serous carcinomas – a concept that, if proven, would dramatically alter the investigative and clinical response to this disease. The following is the evidence to support this concept and, with it, a proposed multidimensional model of pelvic serous carcinogenesis.

Assigning the primary site in pelvic serous carcinoma

Serous carcinoma is seen in three sites in the upper tract, including the fallopian tube, ovarian surface (or inclusions) and the peritoneal surfaces. Tumor origin is typically assigned to the organ presenting with the dominant tumor mass. The one exception is the peritoneum, which is classified as a primary site only if a candidate origin is not found in the endometrium, tube or ovary

Figure 1 Assignment of the primary site in pelvic serous tumors



Tubal carcinomas demonstrate mucosal involvement and the dominant mass is in the tube (a). A primary ovarian borderline serous tumor, seen as an intra-ovarian mass (b, arrows). If an omental or other pelvic mass is present and no other dominant mass is present, the tumor is often designated as a 'primary peritoneal' serous carcinoma (c) From Crum CP and Lee KR. Diagnostic Gynecologic and Obstetric Pathology, Elsevier Saunders 2006, with permission (originally Figure 21.35A).

(Fig. 1). Generally, pathologists and clinicians assign the primary site for serous carcinoma empirically, inasmuch as the origin cannot be pinpointed with precision [12]. The presence of an intraepithelial form of the carcinoma is used to verify the primary site for endometrial and tubal carcinomas. In contrast, intraepithelial carcinomas are not included as a requirement for tumors assigned to the ovary or peritoneum. *Thus, for the purposes of this review, the reader is reminded that the terms 'primary peritoneal serous carcinoma' and 'ovarian serous carcinoma' are used to describe dominant patterns of tumor growth and do not imply that the source of the tumor is known with absolute certainty. In this review, the term 'pelvic serous carcinoma', when used, encompasses all serous carcinomas of the upper genital tract.*

Tumor types and molecular pathways

Ovarian epithelial neoplasms can be divided into two groups. First, tumors of borderline malignancy, low-grade serous carcinomas, endometrioid and mucinous ovarian carcinomas predominate in the ovary, originate from intracortical Mullerian inclusion cysts or endometriosis and evolve gradually from benign to malignant. Molecular alterations include microsatellite instability and mutations in KRAS, BRAF, beta catenin and pTEN. Secondly, high-grade serous carcinomas may present as intraparenchymal tumors but most are discovered on the ovarian surface, often with involvement of the mesosalpinx, mesentery and omentum. The principal molecular alteration is a mutation in the p53 tumor suppressor gene. These tumors develop rapidly and are almost always discovered after peritoneal or serosal involvement has taken place [3,4•,13].

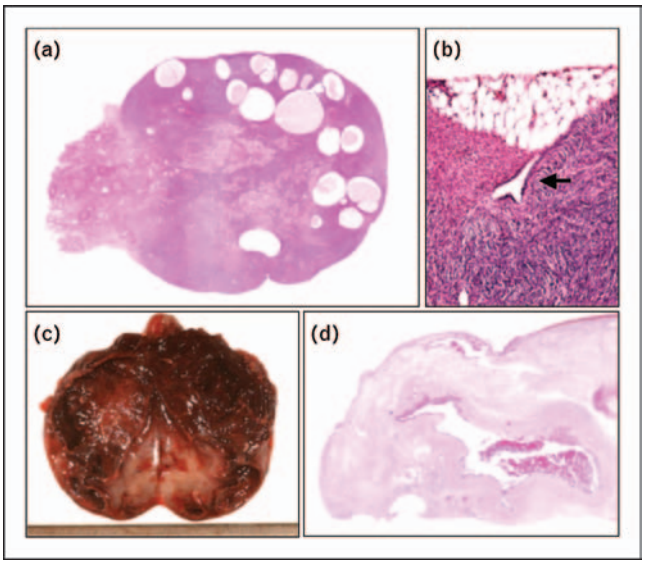
Although the above model resolves the varied histopathologic entities in the context of molecular pathogenesis, it has not shed light on the site of origin for surface serous carcinomas. The most enduring theory holds that these tumors arise from the OSE, developing *in situ* or within surface epithelial inclusions in the ovarian cortex (cortical inclusion cysts). What follows is the evidence supporting this pathway.

Evidence supporting the ovarian surface epithelium as a source of ovarian cancer

Epithelial ovarian cancers presumably derive from OSE or epithelial inclusions in the superficial cortex. This OSE recapitulates that which gives rise to the development of the fallopian tubes, uterus and endocervix during development and may be responsible for endometriosis in the ovary [14]. An alternate mechanism would deliver the Mullerian epithelium to the ovarian surface via transfer from another site, such as the endometrium or fallopian tube [15–17]. Support for both models exists [18–20].

Irrespective of the origins of the OSE and cortical inclusion cyst epithelium, the question that has been fundamental to research in ovarian carcinogenesis has been how this epithelium becomes malignant. Possible mechanisms include oxidative stress imposed by ovulation, altered biology following entrapment of the OSE in repaired ovulation sites, hormonal influences on both

Figure 2



Ovarian inclusion cysts (a and b) and endometriosis (c and d) are typically associated with mucinous, endometrioid and low-grade serous neoplasms. From Crum CP and Lee KR. Diagnostic Gynecologic and Obstetric Pathology, Elsevier Saunders 2006, with permission (originally Figures 22.7A and C, 22.36, 22.45).

epithelium and stroma, and carcinogens (such as talc) [21]. The ovulation model is supported by an inverse relationship between ovulation and ovarian malignancy, both in humans and in hens [22–24].

Tumors arising from inclusions presumably progress through a step-wise fashion to malignancy (Fig. 2). Serous carcinomas involving the ovarian surface are another matter, inasmuch as a defined multistep pathway has not been described. No consistent association between the OSE or the frequency of inclusions and ovarian cancer has emerged, despite rare reports [25–28] of 'ovarian carcinoma *in situ*' in BRCA+ women. Others [29,30] have noted subtle nuclear alterations in inclusion cysts and surface epithelium, some of which have been termed 'ovarian dysplasias'. Bell and Scully [31] examined 14 cases of early epithelial ovarian carcinoma; 'dysplastic' inclusions were identified in only three cases and most tumors were close to or on the ovarian surface and not associated with a definable precursor.

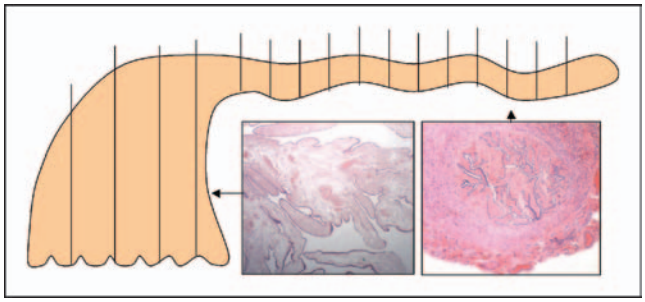
Barakat *et al.* [32] analyzed groups of high-risk women (BRCA1+) to test the hypothesis that this group would be enriched for premalignant histologic or genetic changes in the OSE. Like others, they noted some morphologic differences in inclusion cysts. There was no difference between the two groups based on biomarker expression, however, leaving the mechanism by which inclusion cysts progress to cancer unknown.

The fimbria as a source of pelvic serous carcinoma

Beginning with the first reports of early carcinoma in BRCA+ women in the late 1990s, the fallopian tube has progressively evolved as a candidate site for not only tubal but also pelvic serous carcinoma [33,34]. The conventional wisdom regarding ovarian carcinogenesis has been gradually revised by the increased use of prophylactic salpingo-oophorectomy to prevent serous carcinoma in women with heritable mutations in the *BRCA1* and *BRCA2* genes, which confer a respective lifetime risk of ovarian cancer of from 20 to 60% [35]. A series of studies [36] described tubal carcinoma as the only tumor in some prophylactic salpingo-oophorectomies, accompanied by the earliest manifestation of tubal cancer, entitled 'tubal intraepithelial carcinoma'. As larger series were described, increasing percentages were found to have tubal involvement [8•,37•].

The frequency of early tubal carcinomas in BRCA+ women has varied, depending on both the nature of the population and the extent to which the tubes were examined. Recent studies [8•,10,36,37•] have reported a tubal malignancy in 4–17% – a figure that will likely vary according to the age of the patients studied and the thoroughness with which the tubes and ovaries are examined. The proportion of cancers localized to the fallopian tube has steadily increased to as high as 100%, in part due to the use of protocols that maximize exposure of the mucosa [6,38]. Using a similar protocol (SEE-FIM, Fig. 3), Medeiros *et al.* [7•] documented a primary neoplasm in the distal fallopian tube of five of five BRCA+ cases with a malignancy. Finch *et al.* [8•] reported similar results. It should be emphasized that the most careful scrutiny will detect early tubal carcinoma in this population in a minority of patients (approximately 5%; Callahan M *et al.*, unpublished).

Figure 3 The SEE-FIM protocol for analysis of the fallopian tube in prophylactic salpingo-oophorectomies varies from the conventional approaches by longitudinal sectioning of the fimbria to maximize exposure of this epithelium (lower left) in addition to the proximal tube (lower right)



Is the tube preferentially involved in women who are BRCA+? Finch *et al.* [8•] cited three additional studies [39–41] that did not identify a difference in BRCA+ between women with tubal or ovarian cancer. Cass *et al.* [9•] reported that 43% of their tubal carcinomas were BRCA+; however, the distribution of the tubal tumor in both BRCA+ and negative women was identical, confined almost exclusively to the fimbria, suggesting that tubal carcinomas in BRCA+ and negative women arise in the same site.

A natural question prompted by the above is whether consecutive cases of ovarian or 'primary peritoneal' cancer co-exist with early tubal cancer and, if so, are the tumors in the tube and remote sites related? Kindelberger *et al.* [11] have recently surveyed a consecutive series of pelvic serous carcinomas in which the entire tubal epithelium was analyzed by the SEE-FIM protocol. They found that, after exclusion of primary fallopian tube carcinomas, approximately half of serous carcinomas co-existed with an intraepithelial carcinoma of the fimbria. They went on to demonstrate that in all cases, the early tubal cancer was genetically identical (based on p53 mutation status) to the ovarian or peritoneal tumor component – compelling evidence that the two are causally related. Currently, in our experience, careful examination of the fallopian tube from women with presumed primary peritoneal carcinoma will reveal an early cancer in the majority of cases (Carlson and Crum, unpublished) (Fig. 4).

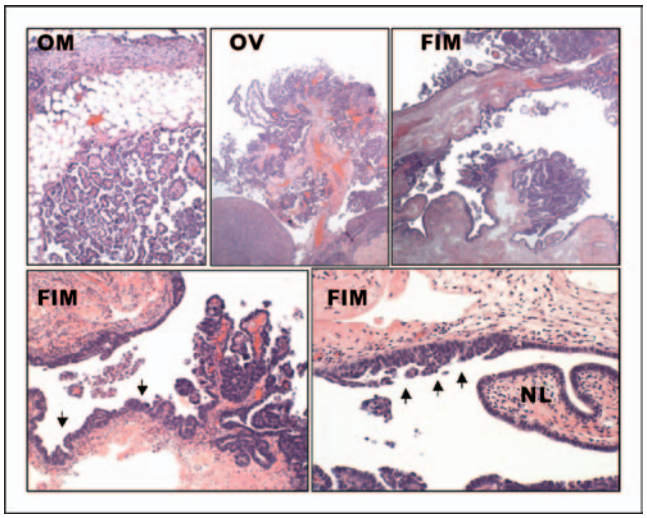
Kindelberger *et al.* [11] also described a smaller group of pelvic serous carcinomas that were more likely to be ovarian in origin. These tumors variously were associated with a dominant ovarian mass, or a candidate precursor lesion, such as endometriosis or a benign cystadenoma, fulfilling the criteria for emergence by a more traditional pathway (see below).

Early precursors to serous carcinoma in the tube (p53 signatures)

Precisely why the fimbria is a preferred location for early tubal carcinogenesis is unclear. The fimbria is exposed to the peritoneal cavity, is in close proximity to the ovarian surface and merges with the serosal mesothelium, forming a 'Mullerian–mesothelial' junction. This region also exhibits epithelial plasticity, often harboring reserve cells or nests of transitional metaplasia (Walthard cell rests). Benign tumors, including serous cystadenomas and cystadenofibromas, also reside in this site [42]. Moreover, the same factors implicated in ovarian carcinogenesis, such as ovulation, are in close proximity to the distal fallopian tube. Whether topography imposes a greater degree of biologic or 'genetic stress' on the fimbrial mucosa that comes into play in genetically susceptible individuals remains to be determined.

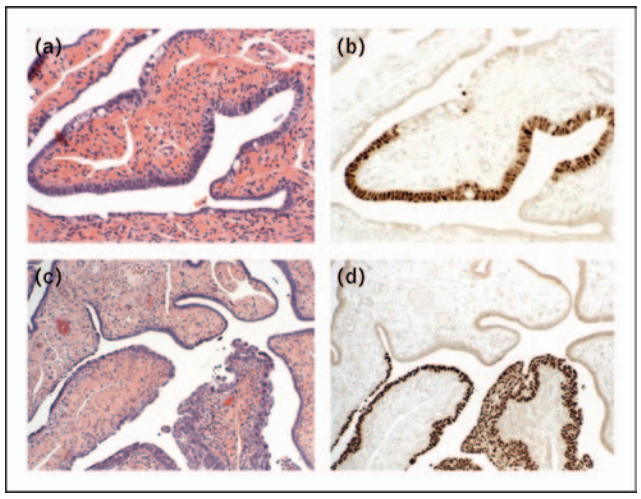
In a recent study [43], systematic p53 immunostaining of both BRCA+ and control fallopian tubes found that small linear p53 positive foci are relatively common in the fallopian tube and are not restricted to women with familial ovarian cancer. More importantly, these foci share many features with serous carcinomas in this site, including cell type involved (secretory), evidence of DNA damage and, in many cases, reproducible p53 mutations (Fig. 5). These foci, termed 'p53 signatures',

Figure 4



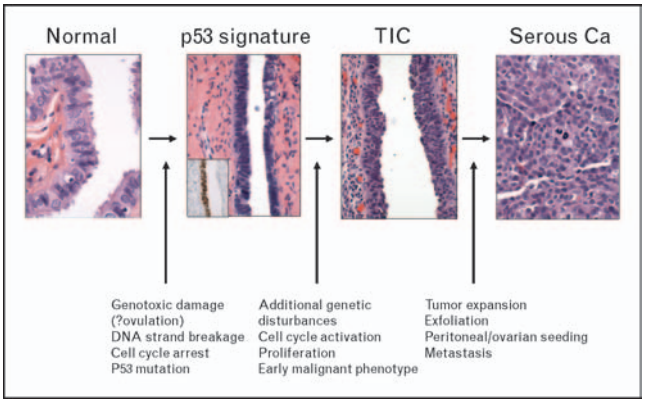
A typical 'primary peritoneal serous carcinoma' involving omentum (OM) and presenting with focal ovarian surface involvement (OV). Closer inspection of the fimbria (FIM, upper right) reveals a small exophytic carcinoma, associated with tubal intraepithelial carcinoma (FIM, lower left, arrows). Note the transition between normal (NL) and intraepithelial carcinoma (FIM, lower right, arrows).

Figure 5



The 'p53 signature' (a and b) is a nonneoplastic abnormality that commonly occurs in the fimbrial mucosa (a) and exhibits strong positivity for p53 (b). The p53 signature shares several features with tubal intraepithelial carcinoma (c), including p53 staining (d) and p53 mutations.

Figure 6 A model for serous carcinogenesis arising in the distal fallopian tube



Genotoxic injury (step 1) results in p53 mutation and the clonal expansion of a secretory-cell-specific population, designated the p53 signature. A subset of these p53 signatures undergoes cell proliferation (step 2), the risk of which may be increased by BRCA mutations and resulting in a fully developed tubal intraepithelial carcinoma (TIC). The latter has the capability of either expanding locally or metastasizing to the ovarian surface or peritoneum as a serous carcinoma (Serous Ca) (step 3). A similar scenario could take place in the ovary or peritoneum in preexisting endosalpingiosis or tubal adhesions.

localize to the same region of the tube (fimbria) as serous carcinomas are derived from. Like other precursor lesions in other systems, they are relatively common and do not invariably progress to malignancy.

A binary model for pelvic serous carcinogenesis

Based on recent studies, a provisional model for high-grade serous ovarian carcinoma can be developed that takes into account both a traditional ovarian origin and the more recently proposed tubal pathway, which is summarized in Fig. 6. The first step would entail oxidative stress to the secretory epithelial cells of the tube, leading to unrepaired DNA damage, cell cycle arrest and, in some, p53 mutations. The next major step would be re-initiation of cell growth by an unknown mechanism that overrides cell cycle arrest following DNA damage, leading to an intraepithelial carcinoma. The final step would entail either the escape of tumor cells via exfoliation, onto the pelvic or ovarian surfaces (and, in some cases, endometrium) or direct invasion of the fimbrial submucosa.

Five variables influencing serous tumor development and spread

Any model that addresses the pathogenesis of serous carcinoma must take into account at least five variables:

(1) *Location of susceptible epithelium.* Some ovaries have abundant inclusions, others endometriosis and others, still, exhibit minimal or no epithelial activity. As these are prerequisites for tumor development, the mechanism(s) by which they develop in these extra- ovarian sites is important [14].

(2) *Type of epithelium.* An increasing body of evidence indicates that target cell type has a major role in tumorigenesis. Moreover, the molecular events that impose a risk of cancer are also cell type-specific. The evolution of endometrioid, low-grade serous and mucinous tumors of the ovarian cortex involve a series of molecular events that are distinct from serous carcinoma. The differences in molecular pathway likely reflect the initial events and the responses of the cells to these events. For example, the tubal secretory cell presumably gives rise to tubal serous carcinomas. In contrast, cells within cortical inclusions and their derived low-grade serous tumors may arise from Mullerian metaplasia and may exhibit features intermediate between ciliated and secretory cells (Parast M, Drapkin R, Crum C, Hirsch MS, unpublished data).

(3) *Genotoxic injury.* The target epithelium, whether it is on the ovarian surface or the fimbrial mucosa, must be exposed to a genotoxic insult whether it is the result of ovulation, hormonal fluctuations or carcinogen exposure.

(4) *Risk factors for progression from precursor to early carcinoma.* The dominant known genetic risk factor for serous ovarian cancer is a BRCA mutation. No consistent evidence that the normal fallopian tubes or ovaries from BRCA+ women differ in their appearance from randomly selected women without a family history of ovarian cancer exists. Preliminary evidence also indicates that the prevalences of early or latent precursors (such as a p53 signature) are similar in both BRCA+ women and controls [43]. Thus, in this model, the BRCA mutation would increase the risk of transit from a precursor to cancer rather than the risk of precursor development.

(5) *Microenvironment supporting tumor growth and expansion.* Many large ovarian and peritoneal carcinomas are associated with a noninvasive or minimally invasive carcinoma of the distal fallopian tube. While it would seem counterintuitive to assign the primary site to the fimbria, this paradox can be explained by the host tissue microenvironment. As the tubal mucosa is resistant to implantation from endometrioid, mucinous and low-grade serous carcinomas, it is reasonable to assume that many intraepithelial carcinomas seen in the fimbria are primary lesions rather than implants. Secondly, both peritoneal and ovarian surfaces are well known targets for metastatic carcinoma. Taken together, these two variables *will favor growth of serous tumors in sites other than the distal fallopian tube, even those originating in the tube.*

Conclusions

A significant percentage of tumors currently classified as ovarian and primary peritoneal carcinoma are associated with, and genetically related to, an early serous carcinoma in the fallopian tube. For obvious reasons, serous carcinomas arising in the fimbria are suboptimal candidates for prevention by biomarker detection alone. It is critical to address two additional issues as soon as possible. The first is to determine the exact proportion of serous tumors in BRCA+ women that arise in the distal tube. The second is to determine the relationship between p53 signatures and pelvic serous cancer risk. In the short term this information could improve early detection and determine the most rational approach to prophylaxis in BRCA+ women. Ultimately, however, prevention is the more desirable objective and, as with other systems, will be optimized by targeting the most vulnerable step in pelvic serous carcinogenesis – the precursor lesion.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 82–83).

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