Published in final edited form as:

Diagn Histopathol (Oxf). 2008 August ; 14(8): 352–365. doi:10.1016/j.mpdhp.2008.06.009.

Recent advances in the understanding of the pathogenesis of serous carcinoma: the concept of low- and high-grade disease and the role of the fallopian tube

Joseph Carlson, Michael H. Roh, Martin C. Chang, and Christopher P. Crum

Division of Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Summary

In the past 50 years, the concept of serous ovarian cancer has been progressively refined, with the distinction of the borderline serous tumour, identification of a smaller subset of well-differentiated serous malignancies and, recently, closer attention to the pathogenesis of high-grade serous malignancies. High-grade serous carcinoma, traditionally presumed to arise within Müllerian inclusion cysts of the ovarian surface, cortex and peritoneum, has recently been linked to the distal fallopian tube. This review addresses the disparate forms of serous neoplasia, which reflect both different genetic abnormalities and stages of differentiation of Müllerian epithelium. The significance of these different origins is addressed in the context of ovarian cancer prevention.

Keywords

fallopian tube; BRCA; serous carcinoma; ovarian neoplasms; primary peritoneal carcinoma; p53

Introduction

Epithelial carcinoma of the ovary is a common malignancy in women and, after lung, breast, colorectal and pancreatic carcinomas, is the fifth most frequent cause of cancer in women.¹ Approximately 15% of epithelial ovarian tumours are borderline tumours (low malignant potential). The malignant group consists of a diverse histological profile, including tumours resembling endocervix or gastrointestinal mucosa (mucinous), endometrium (endometrioid), fallopian tube (serous) and unspecified glycogenated epithelium (clear cell tumours). The proposed origin for all of these tumours is Müllerian epithelium that has found its way into the ovarian cortex. The most common explanations for serous/tubal differentiation include ovarian surface epithelium that has undergone Müllerian metaplasia, endometrial tissue (endometriosis) derived from such metaplastic foci or transported directly from the endometrial cavity to the ovary, and fallopian tube epithelial cells that have implanted on the ovarian surface or become adhered to the ovary and incorporated into the parenchyma (endosalpingiosis).^{3,4} Repeated ovulation presumably assisting this process by producing defects in the ovarian surface and encouraging the incorporation of such epithelium.⁵

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Endometrioid tumours have traditionally been linked to ovarian endometriosis, which can be demonstrated in approximately 50% of cases. Mucinous tumours theoretically arise from either endometriosis (Müllerian mucinous) or Müllerian inclusions (intestinal mucinous). Low-grade serous tumours presumably arise from Müllerian inclusions, commonly found in the ovarian cortex and mesothelial surfaces.⁶ The origin of high-grade serous carcinomas, however, remains controversial. This controversy has been based primarily on the lack of concrete morphological data linking these tumours to cortical inclusions or the ovarian surface epithelium. Superimposed on this conundrum is the fact that not all ovarian carcinomas are readily classified into one of these types. In particular, the distinction between high-grade endometrioid and serous carcinomas in the female genital tract is not always clear-cut.⁷

This review will address recent advances in the histopathological and molecular classification of pelvic serous neoplasia, from the perspective of both biological behaviour and cell of origin. The discussion will address low- and high-grade serous malignancies.

Low-grade serous neoplasms

Low-grade serous tumours are composed of cells that closely mimic the fallopian tube, including the presence of both ciliated and secretory differentiation. They are the most common epithelial tumours of the ovary, accounting for about 30% of ovarian neoplasms. They are less frequently reported in Asia. Overall, approximately 70% are benign or borderline when detected. Although most women with serous malignancies are in their sixth or seventh decades when diagnosed, the borderline tumours present at an average age of 45 years and can be encountered in the second and third decades. Seventy per cent are confined to one or both ovaries when diagnosed and disease-free survival is > 98%. Only 15–30% of higher stage borderline tumours recur, signifying that pelvic spread is generally not an adverse prognostic indicator. The most common and most benign form of spread is the non-invasive implant. Other features of borderline tumours that have been increasingly scrutinized are micropapillary epithelial growth pattern, microinvasion in the stroma, lymph node spread and invasive implants.

By the 1990s the ‘invasive’ peritoneal implant emerged as an important prognostic indicator, distinguishing borderline tumours with a good versus poor outcome. The 7-year disease-free survival in patients with non-invasive implants is 95.3%; with invasive implants it is 66%.^{8–10}

In addition to the category of implant, two other indices that conceivably would impact on prognosis – the presence of microinvasion in the supporting stroma and lymph node spread, have been described.^{11,12} Taken together, these features have resulted in a progressive refinement in the classification of low-grade serous tumours to include conventional borderline tumours (also termed proliferative serous cystadenomas) and those with complex microarchitecture, variously termed borderline serous tumours with micropapillary features and low-grade micropapillary serous carcinomas. Reasons for the disagreements in terminology are legion, but in practice stem from the fact that irrespective of the term used to classify the primary tumour, the presence or absence of invasive implants is the paramount question, determining the likelihood of extra-ovarian tumour growth, recurrence and death.^{8–10}

The origin of the majority of low-grade serous tumours is presumed to be ectopic Müllerian epithelium. This epithelium exhibits the same immunophenotype as epithelium derived from the salpinx, although its origin is disputed. The most easily understood is the transfer of salpingeal epithelium from the tube to the ovarian surface or sites of ovulation, leading to cortical inclusion cysts (CICs) or endosalpingiosis.¹³ Alternatively, retrograde regurgitation of endometrial epithelium (and stroma) could produce the same result, giving rise to similar

inclusions, including endometriosis. A third mechanism would be through the presence of a specialized ovarian surface epithelium (OSE) that is capable of Müllerian metaplasia.¹⁴ Irrespective of the mechanism by which this epithelium becomes entrapped within the ovarian cortex, the fundamental requirement for most (but not all) low-grade serous tumours appears to be *ovarian stroma* and a resulting ovarian stromal–epithelial relationship that plays some role in neoplastic transformation.

The mechanisms by which neoplastic transformation occurs in Müllerian inclusions are not well understood. A common but not universal component of this process is a mutation in K-Ras.¹⁵ More obvious, if equally mysterious from a mechanistic standpoint, is the shift in differentiation that takes place in the target Müllerian epithelium. Studies have implicated homeobox regulatory (HOX) genes in this process, suggesting that the expression of HOX 11 mediates the salpingeal phenotype. In this model, other cell-type-specific transitions from CIC to neoplasia are regulated by the respective HOX gene, with mucinous tumours expressing HOX 9 and endometrioid tumours expressing HOX 10. In the former, a more rapid transition likely takes place from CIC to an intestinal ovarian mucinous tumour, given the relative lack of benign-appearing CICs with an intestinal mucinous phenotype. In this model, the activation of HOX 9 would occur concurrently with neoplastic transformation. Endometrioid (and derived Müllerian mucinous tumours) would be predated by a stable endometrioid (HOX 10) phenotype on which subsequent events would be superimposed to develop their respective neoplasms.¹⁶ⁱ

Central to the low-grade serous neoplasm – and all serous tumours – is the target epithelium and its differentiation programme. Salpingeal epithelium has two predominant cell types, secretory and ciliated cells. A third cell type, and one which is most conspicuous in the region of the fimbria, is a sub-columnar reserve cell similar to what has been described in the cervix and endometrium. These reserve cells appear to arise from the epithelium near the distal portion of the tube and probably gives rise to some of the metaplastic epithelia (Walthard cell rests) that are often seen there. The ciliated and secretory cells are largely independent, both immunohistochemically and functionally, the latter verified by cell culture studies.¹⁷ However, there is circumstantial evidence that the two may be related to a common progenitor cell. Low-grade serous neoplasms, which are presumed to be clonal in origin, typically exhibit both ciliated and secretory differentiation, the former evidenced by staining for LHS28 and p73, and the latter by localization of bcl-2, HMFG2 and PAX-8 (Parast M, Crum C, Hirsch M, unpublished observation). Thus, a fundamental characteristic of low-grade serous tumours, including those classified as borderline and low-grade serous carcinoma, is a molecular pathway that permits expansion of a tumour cell population with the ability to execute the transition to both ciliated and secretory cells (Figs 1 and 2).

Cell cycle proteins are identified almost exclusively in the non-ciliated cell population, suggesting on the surface that ciliated cells emerge from a less differentiated precursor pool.¹⁸ While this may be true, it would be premature to declare the ciliated population terminally differentiated. Cell culture studies of bovine oviduct have shown that ciliated cells can be plated, at which time they lose their cilia and begin to grow. This suggests that ciliated cells possess considerable independence and are capable of reentering the proliferative compartment, at least in vitro.¹⁹ⁱⁱ Whether this proliferative compartment is secretory *per se* is unclear.

Figures 2–4 illustrate three scenarios that might be encountered in low-grade serous tumours. The first is a typical borderline tumour with some epithelial complexity, illustrating the different cell types involved (Fig. 2). The second is a biphasic borderline serous tumour, undergoing increasing complexity with stromal invasion. The latter is mirrored on the surface of the tumour and in the peritoneum, where the disease is sufficiently extensive to be classified

as a low-grade serous carcinoma (Fig. 3). The ‘morphological gap’ between the polar ends of this tumour is clear, indicating that at least two events, initiation and progression, took place. In the third, a low-grade serous tumour with florid micropapillary architecture is associated with non-invasive and invasive peritoneal implants, the latter features presumably reflecting the higher risk of adverse outcome expected from such tumours (Fig. 4).²⁰

High-grade serous neoplasms

Serous carcinomas account for up to 60% of all epithelial carcinomas and are the most lethal.²¹ Over 80% are stage III or greater when diagnosed and this group carries a 5-year survival of 20–30%. In contrast, endometrioid and mucinous carcinomas carry a 60–80% 5-year survival due to their much higher likelihood of being discovered when at least apparently confined to one or both ovaries. These unfortunate statistics for serous carcinomas apply principally to the high-grade category, which are by far the most common and make up a significant proportion of the 12 000–15 000 women who die of ovarian carcinomas each year. Serous carcinomas are particularly common in women with a heritable heterozygous mutation in BRCA1 or BRCA2, who may also rarely develop endometrioid tumours.^{22,23}

The gross presentation of pelvic serous malignancies varies widely, but the rarest is the unilateral (stage I) tumour confined within a cyst. The more common presentations include either bilateral ovarian involvement with surface nodules or tumours that predominate in the omentum with relative sparing of the ovaries, except for surface implants. Rarely, serous carcinomas present as a dominant mass in the fallopian tube, typically with fimbrial adhesions that seal the tumour within the endosalpinx, resulting in a sausage-like tumour mass replacing the entire tube. Assigning the primary site of origin is typically difficult, in as much as the entire tube and ovary can be obliterated. Although this review will use the generic term ‘pelvic serous carcinoma’, thus avoiding any commitment (and controversy) in the general sense, standards have been proposed for assigning site of origin. They are as follows:

1. Primary ovarian carcinomas have the bulk of the tumour in the ovarian parenchyma with no other obvious source.
2. Primary tubal carcinomas must have a large tumour mass in the salpinx with evidence of origin from the endosalpinx, including a tubal intraepithelial carcinoma (TIC). Ovarian involvement must be minimal and confined to the surface.
3. Primary peritoneal carcinoma must have dominant intraperitoneal tumour mass with minimal ovarian surface involvement and *no other plausible source*.²⁴

Despite the fact that pathologists have relied on the above algorithm or a similar approach to assign primary site, several observations have prompted investigators to revisit the concept of tumour origin in serous tumours. The most obvious is that approximately one-half of ovarian carcinomas are not associated with an obvious pre-existing conditions in the ovarian parenchyma.²⁵ This has supported the theory of a more rapid evolution for many serous malignancies. Three sources in the microenvironment are as follows:

1. *Müllerian cortical inclusion cysts (MICs)*. Several studies have previously scrutinized MICs in an attempt to identify early neoplasia. Deligdisch et al proposed that MICs underwent epithelial dysplasia.²⁶ One strategy has been to immunostain MICs for evidence of accumulation of p53 protein, which commonly occurs in serous carcinomas. Wells identified p53-positive inclusions in women with serous carcinoma and suggested that such lesions were precursors.²⁷ Boyd performed similar studies and identified mutations in p53 in inclusions adjacent to serous carcinomas (Boyd J, unpublished observations). However, the frequency of this event relative to the frequency of serous carcinomas was not clear. Bell and Scully reviewed a large consultation practice and were able to identify only 13 cases of early serous carcinoma

that were sufficiently small to ascertain their origin. All had minimal tumour in the ovarian cortex but just three had evidence of a transition from a precursor lesion.²⁸ Barakat et al examined ovaries from BRCA+ women and were not able to identify early 'pre-neoplastic' abnormalities in the ovarian cortex.²⁹ Thus, while MICs remained the principal suspect in serous carcinogenesis, investigators were limited in their ability to establish a consistent relationship between the two. This is in contrast to endometrioid and mucinous tumours, where the ovarian cortex is the presumed source in most cases because of the presence of endometriosis or the absence of an extra-ovarian source. Figure 5 illustrates a serous carcinoma arising in an MIC in a woman with a BRCA mutation.

2. *Endometriosis.* Up to 15% of ovarian malignancies are associated with concurrent ovarian endometriosis or an endometriotic cyst.³⁰ The strongest association is between endometriosis and endometrioid and serous carcinomas, and serous carcinomas are much less likely to be associated with endometriotic cysts. Nevertheless, recent reports have identified serous malignancies in some endometriotic cysts and increased p53 accumulation in these neoplasms.^{31,32} This is not unexpected in view of the fact that serous carcinomas can arise in the endometrium. However, it suggests that the endometrioid precursor epithelium is less susceptible to this pathway. An example of such a case is depicted in Figure 6.
3. *The fallopian tube.* Beginning in the late 1990s, the fallopian tube began to emerge as an important, if not, exclusive source for pelvic serous carcinoma.³³ The emergence of this organ as an important participant was delayed for the simple reason that very few serous carcinomas were assigned to this site. In fact, tubal carcinoma was estimated to be nearly one-fiftieth as common as its ovarian counterpart. Nevertheless, the notion that MICs spontaneously arose from the ovarian surface was challenged by those who proposed a route that did not require spontaneous transformation of the pelvic mesothelium, i.e. the migration of salpingeal epithelium from the distal tube to the ovarian cortex. This scenario assigned the ultimate source to the tube and was supported by the ovarian cancer model seen in hens, where tubal primaries were well established.^{34,35} Concurrent with this concept was a change in the perception of early serous carcinoma in BRCA+ women. As recently as 2003, Piek et al noted that in *symptomatic* BRCA+ women, > 90% of the tumours were classified as ovarian in origin.³⁶ However, as sporadic reports of early tubal carcinomas began to emerge, investigators recommended complete examination of both tubes and ovaries in women undergoing risk-reducing salpingo-oophorectomy. As these cases began to accumulate, the number of tubal primaries increased.^{37–42} Women with BRCA1 and BRCA2 mutations carry a significant risk of pelvic serous carcinoma that reaches as high as 60% (BRCA1) if followed indefinitely. The risk is highest for women over the age of 40 and currently, many of these women undergo risk-reducing surgery when they approach this age. The tubes and ovaries are typically sectioned in toto at 2-mm intervals and scrutinized by the pathologists, who must exclude both invasive carcinoma and its non-invasive counterpart, tubal intraepithelial carcinoma (TIC). Similar to its counterpart in the endometrium, serous endometrial epithelial carcinoma (serous EIC), TIC carries a risk of spread to adjacent pelvic surfaces. The proportion of healthy women whose tubes or ovaries disclose a malignancy varies, but in most studies is < 10%. Recent studies by Finch et al and Callahan et al placed the percentage at 6–7%. Based on these studies and one by Cass et al, the origin of these early carcinomas is almost exclusively the *distal* fallopian tube (fimbria).⁴³ At Brigham and Women's Hospital, a modified protocol (SEE-FIM) has been instituted that amputates and sections the fimbria at 2-mm intervals in a longitudinal fashion. The degree to which this strategy increases detection of early carcinoma is unclear, but it is used empirically to maximize exposure of the fimbrial mucosa.

Recent studies have shown that a high percentage of early carcinomas in BRCA+ women can be traced to the distal fallopian tube rather than the ovary and in many the only manifestation is an early carcinoma (TIC, Fig. 7). In the study by Finch et al, six of seven carcinomas involved the distal tube.⁴² Callahan et al presented data supporting an origin in the distal tube in all of their seven cases. Since that study an additional three cases have been diagnosed at Brigham and Women's Hospital. In all, only 1 of 10 appeared to arise within the ovary, within a large MIC (Fig. 5). These studies imply that a very high percentage of carcinomas arising in BRCA + women occur in the distal tube. Based on the literature, the great majority are serous in type. However, it is important to emphasize that two of the cases we have seen were distinctly endometrioid in appearance and were p53 immunonegative, suggesting that the BRCA mutation places these women at risk for both types.

Although the majority of pelvic serous carcinomas in BRCA+ women appear to arise in the distal fallopian tube, the origin(s) of serous carcinomas in women without a documented BRCA mutation – 85% of all serous carcinomas – has not been scrutinized in detail. In prior reports, tubal involvement has been estimated to occur in < 20% and intraepithelial carcinomas (TIC) have been the subject of case reports, presumably signifying a field effect rather than a causal event. In a recent study, we surveyed a consecutive series of pelvic serous carcinomas and examined the fallopian tubes in detail using the SEE-FIM protocol to determine the frequency of TIC. In all, approximately three of four cases exhibited endosalpingeal involvement. When cases fulfilling the criteria for peritoneal or tubal primary neoplasms were excluded, one-half of the remaining cases contained evidence of TIC in the fimbria (Fig. 8). One-quarter contained endosalpingeal involvement without documented TIC and another quarter contained circumstantial evidence (cystadenoma, dominant ovarian mass, endometriosis) of an ovarian origin.⁴⁴ In five cases with both TIC and ovarian carcinoma, a discrete p53 mutation was shared by both tumours (Fig. 8). Although this finding does not confirm that the TICs were the initial event in tumourigenesis, they are identical in appearance to their counterparts in BRCA+ women and are logical candidates for an early phase in serous carcinogenesis.

In a follow-up study, we examined a series of women with tumours classified as primary peritoneal in origin. This group of neoplasms traditionally has been presumed to arise from the peritoneal surface, within MICs or endometriosis. Consecutive cases were selected which met the 2001 WHO criteria for primary peritoneal serous carcinoma (PPSC) and fallopian tube involvement was assessed in eight consecutive, prospectively accrued samples with complete tubal exam, using the SEE-FIM protocol. Five of the eight (63%) cases with both tubes available for analysis contained endosalpingeal involvement and four (50%) had TIC (Fig. 9). Based on this, we concluded that TIC is frequently present in PPSC and that the fimbria is a candidate site of origin for many of these tumours.⁴⁵ What is evident in both studies, however, is that not all primary peritoneal serous carcinomas can be attributed to the distal fallopian tube.

We recently looked for potential differences between tumours that appear to arise from the ovary – by virtue of a dominant ovarian mass – and those that are characterized by a similar distribution of tumour in both. A significantly higher percentage of the latter were associated with involvement of the endosalpinx, suggesting that a higher percentage of such tumours could have originated from the distal fallopian tube.⁴⁶ However, differences in expression of tubal secretory cell markers (PAX8) and p53 were virtually identical, implying that both cell type and mechanism of tumour development will not distinguish the two origins. This is indirect evidence that a common cell of origin is responsible for all serous carcinomas, and supports prior assertions that the tube (or its equivalent) is responsible for all high-grade pelvic serous carcinomas.

A serous carcinogenic sequence and its precursor

Three components of serous cancer, TIC, invasive and metastatic serous carcinoma, are well enough defined to construct a model of progression that includes non-invasive neoplasms. However, a non-malignant precursor to this process has not been defined. Wells and colleagues described p53-positive MICs in the ovarian cortices of women with serous cancer. Boyd, in unpublished reports, described similar changes, and confirmed the presence of p53 mutations. In the fallopian tube, Piek et al described tubal ‘dysplasias’, defined as non-cancerous but probably precancerous. Recently, in our efforts to detect early serous carcinomas in BRCA+ women, we immunostained selected cases for the tumour suppressor protein p53. p53 Protein is over-accumulated in serous carcinomas and can be appreciated as a strongly positive intranuclear signal in approximately 85% of cases. We found that during our review of these cases, normal-appearing, non-dysplastic mucosa occasionally exhibited strong nuclear staining. These foci, which we term ‘p53 signatures’, shared several features in common with early fallopian tube carcinomas detected in BRCA+ women (Fig. 10).⁴⁷ These are summarized as follows:

1. Strong accumulation of p53, similar to serous carcinoma.
2. Discrete location, usually involving part of or an entire plica.
3. Predominating in the distal fallopian tube with 70–85% involving the fimbriae.⁴⁸
4. A specific cell phenotype – the secretory cell – that has been proposed as the origin for fallopian tube carcinoma (Fig. 6). This epithelial phenotype is distinct from that seen in borderline and well-differentiated serous carcinomas of presumed ovarian origin. The benign serous tumours exhibit a mixed cell population (ciliated and secretory) similar to cortical Müllerian inclusions. Similarly, well-differentiated serous carcinomas retain one of the biomarkers that characterize ciliated epithelium (p73).⁴⁹
5. Immunohistochemical evidence of DNA damage, in the form of co-localized γ -H2AX immunostaining, indicative of double-stranded DNA breakage (Fig. 5).⁵⁰
6. Frequent detection of p53 mutations identical to those isolated from ovarian cancer.
7. A high frequency in fallopian tubes containing TIC.
8. The occasional demonstration of continuity between p53 signatures, TIC and lesions with proliferative activity intermediate between the former two.

The p53 signatures are distinct from intraepithelial carcinoma in two respects. First, they demonstrate minimal proliferative activity and second, minimal or no nuclear atypia. However, in cases of tubal carcinoma, we have occasionally identified a second form of signature that exhibits increased proliferative activity, is discontinuous to the carcinoma and does not fulfil all morphological criteria for intraepithelial carcinoma. These non-proliferative and proliferative p53 signatures suggest that the transition from a non-proliferative p53 signature to intraepithelial carcinoma is not always abrupt.⁵¹

Evidence for transition from p53 signature to tubal intraepithelial carcinoma

We have made two morphological observations suggesting that p53 signatures are capable of transition to TIC. One was a case in which a non-proliferative p53 signature was in direct continuity with a TIC; the transition was marked by a conspicuous increase in proliferative (MiB1) activity cyclin E staining. The second was spatially separate lesions that were intermediate between p53 signatures and TICs, containing increased nuclear stratification, intermediate levels of MiB1 and cyclin E activity and, often, p53 mutations. The latter entity suggests a more gradual transition from p53 signature to TIC.

Parallels can be made between the fimbrial model and traditional models of ovarian carcinogenesis: because the fimbriated end of the fallopian tube is in immediate proximity to the ovarian surface, mechanisms proposed for carcinogenesis of the ovarian surface epithelium (OSE) could be applied to the fimbrial mucosa. One of the more intriguing proposes a scenario in which ovulation leads to the release of oxidants, which in turn cause DNA damage to adjacent epithelial cells. The risk of damage diminishes geometrically as a function of increasing distance from the point of follicle rupture. This mechanism would explain the high frequency of p53 signatures in the fimbriae, diminishing rapidly in prevalence in the more proximal tube. DNA damage can result from, or be encouraged by, a wide range of factors, including DNA proliferation, hormonal stimuli and defects in both BRCA and p53 function. Nevertheless, given the relationship between oxidative injury and DNA damage, p53 stabilization and the role of p53 as both a component of the DNA damage response and as an intracellular antioxidant, the p53 signature emerges as an attractive early marker of serous carcinoma risk.

Taken together, the above observations suggest that several variables influence the actual or perceived origin of pelvic serous carcinoma:

1. *Location of the target epithelium.* Müllerian inclusions accumulate with age and are implicated in the pathogenesis of both benign and malignant epithelial neoplasms, yet only a subset of women have these inclusions. Theoretically, ovaries that do not harbour inclusions are less likely to develop epithelial ovarian tumours. In a given individual (such as a young BRCA+ woman who does not have ovarian inclusions), ovarian carcinoma would be predicted to be less common than tubal carcinoma (which is the case).
2. *Initiating event.* Oxidative stress, possibly from ovulation, would influence the development of p53 signatures. Like most precursor lesions, these would be considerably more common than invasive carcinoma and could occur in both tube and ovary.
3. *Genetic risk factor,* such as BRCA+, increases the risk and reduces the average age of tumour development. Apparently the presence of a BRCA mutation increases the risk of both endometrioid and serous malignancies in the tube.
4. *Permissibility of the microenvironment for tumour growth.* Large bulky tumours replacing the endosalpinx are much less common than TICs or smaller invasive tumours. In contrast, the mesothelial surfaces, including ovarian cortex, permit the formation of massive tumours. These facts suggest that intraepithelial carcinomas of the tube are more likely to grow in adjacent or remote sites, such as the ovarian cortex and peritoneum, as suggested by the study of Kindelberger et al.⁴⁴ Because tumours in the latter locations may be larger, they are often (perhaps mistakenly) designated as primaries in these sites. While this misclassification does not alter management, it profoundly influences the perception of tumour origin that is critical to early prevention.

Summary

Both low- and high-grade pelvic serous carcinomas appear to arise from Müllerian epithelium, and the target epithelium is similar, irrespective of location, be it tube, ovary or peritoneum. However, the presence of ovarian stroma appears particularly important to the lower grade serous tumours, suggesting that epithelial–stromal interactions influence the early events leading to tumour development. Central to this process is the frequent preservation of both a secretory and ciliated cell phenotype. Higher grade tumours, most of which exhibit p53 mutations, are strongly associated with not only the ovary but the distal fallopian tube, and early on (p53 signatures and TICs) appear to arise from cells of secretory differentiation.

Although these tumours may express antigens associated with ciliated cells (such as p73), they are best viewed as either more poorly differentiated or following a pathway of differentiation more typical of the secretory cell. The choice depends in part on whether the secretory cell is viewed as a direct precursor to the ciliated cell or whether the two diverge from a common progenitor. A more complete understanding of these differentiation pathways, their site specificity and their vulnerability to early genotoxic events will be vital to understanding the pathogenesis of pelvic epithelial cancer and proposing approaches to cancer prevention.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66. [PubMed: 17237035]
2. Kosary, CL. Cancer of the Ovary; SEER Survival Monograph; National Cancer Institute; 2008.
3. Scully RE, Young RH, Clement PB. Tumors of the ovary, maldeveloped gonads, fallopian tube and broad ligament. *American Registry of Pathology, AFIP* 1998:51–79.
4. Auersperg N, Wong AST, Kyung-Chul C, Kang KS, Leung PCK. Ovarian surface epithelium: biology, endocrinology, and pathology. *Endo Rev* 2001;22:255–288.
5. Brewer MA, Johnson K, Follen M, Gershenson D, Bast R Jr. Prevention of ovarian cancer: intraepithelial neoplasia. *Clin Cancer Res* 2003;9:20–30. [PubMed: 12538447]
6. Lee, KR. Surface epithelial stromal tumors of the ovary. In: Crum, CP.; Lee, KR., editors. *Diagnostic Obstetric and Gynecologic Pathology*. Philadelphia: Elsevier; 2006.
7. Alektiar KM, McKee A, Lin O, et al. Is there a difference in outcome between stage I–II endometrial cancer of papillary serous/clear cell and endometrioid FIGO Grade 3 cancer? *Int J Radiat Oncol Biol Phys* 2002;54:79–85. [PubMed: 12182977]
8. Bell DA, Weinstock MA, Scully RE. Peritoneal implants of ovarian serous borderline tumors: histologic features and prognosis. *Cancer* 1998;62:2212–2222. [PubMed: 3179935]
9. Gershenson DM, Silva EG. Serous ovarian tumors of low malignant potential with peritoneal implants. *Cancer* 1990;65:578–585. [PubMed: 2297647]
10. Bell KA, Smith Sehdev AE, Kurman RJ. Refined diagnostic criteria for implants associated with ovarian atypical proliferative serous tumors (borderline) and micropapillary serous carcinomas. *Am J Surg Pathol* 2001;25:419–432. [PubMed: 11257616]
11. Camatte S, Morice P, Atallah D, et al. Lymph node disorders and prognostic value of nodal involvement in patients treated for a borderline ovarian tumor: an analysis of a series of 42 lymphadenectomies. *J Am Coll Surg* 2002;198:332–338. [PubMed: 12229940]
12. Prat J, de Nictolis M. Serous borderline tumors of the ovary. A long-term follow-up study of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion. *Am J Surg Pathol* 2002;26:1111–1128. [PubMed: 12218568]
13. Piek JM, Kenemans P, Verheijen RH. Intraperitoneal serous adenocarcinoma: a critical appraisal of three hypotheses on its cause. *Am J Obstet Gynecol* 2004;191:718–732. [PubMed: 15467531]
14. Drapkin, Hecht
15. Singer G, Stohr R, Cope L, et al. Patterns of p53 mutations separate ovarian serous borderline tumors and low- and high-grade carcinomas and provide support for a new model of ovarian carcinogenesis: a mutational analysis with immunohistochemical correlation. *Am J Surg Pathol* 2005;29:218–224. [PubMed: 15644779]
16. Naora H. The heterogeneity of epithelial ovarian cancers: reconciling old and new paradigms. *Expert Rev Mol Med* 2007;9:1–12. [PubMed: 17477890]
17. Umezū T, Hanazono M, Aizawa S, Tomooka Y. Characterization of newly established clonal oviductal cell lines and differential hormonal regulation of gene expression. *In Vitro Cell Dev Biol Anim* 2003;39:146–156. [PubMed: 14505432]
18. Piek JM, van Diest PJ, Zweemer RP, et al. Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer. *J Pathol* 2001;195:451–456. [PubMed: 11745677]

19. Joshi MS. Isolation, cell culture and immunocytochemical characterization of oviduct epithelial cells of the cow. *J Reprod Fertil* 1988;83:249–261. [PubMed: 3294395]
20. Smith Sehdev AE, Sehdev PS, Kurman RJ. Noninvasive and invasive micropapillary (low-grade) serous carcinoma of the ovary: a clinicopathologic analysis of 135 cases. *Am J Surg Pathol* 2003;27:725–736. [PubMed: 12766576]
21. Seidman JD, Horkayne-Szakaly I, Haiba M, et al. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. *Int J Gynecol Pathol* 2003;23:41–44. [PubMed: 14668549]
22. BRCA ref to serous ca
23. Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. *J Clin Oncol* 2007;25:3985–3990. [PubMed: 17761984]
24. Lee, KR.; Russell, P.; Tavassoli, FA., et al. Surface epithelial-stromal tumors. In: Tavassoli, FA.; Devilee, P., editors. *Tumors of the Breast and Female Genital Organs*. Lyon: WHO, IARC Press; 2003. p. 117-145.
25. Horiuchi A, Itoh K, Shimizu M, Nakai I, et al. Toward understanding the natural history of ovarian carcinoma development: a clinicopathological approach. *Gynecol Oncol* 2003;88:309–317. [PubMed: 12648580]
26. Deligdisch L, Gil J, Kerner H, Wu HS, Beck D, Gershoni-Baruch R. Ovarian dysplasia in prophylactic oophorectomy specimens: cytogenetic and morphometric correlations. *Cancer* 1999;86:1544–1550. [PubMed: 10526284]
27. Hutson R, Ramsdale J, Wells M. p53 protein expression in putative precursor lesions of epithelial ovarian cancer. *Histopathology* 1995;27:367–371. [PubMed: 8847068]
28. Bell DA, Scully RE. Early de novo ovarian carcinoma. A study of fourteen cases. *Cancer* 1994;73:1859–1864. [PubMed: 8137211]
29. Barakat RR, Federici MG, Saigo PE, Robson ME, Offit K, Boyd J. Absence of premalignant histologic, molecular, or cell biologic alterations in prophylactic oophorectomy specimens from BRCA1 heterozygotes. *Cancer* 2000;89:383–390. [PubMed: 10918170]
30. Nezhat F, Cohen C, Rahaman J, Gretz H, Cole P, Kalir T. Comparative immunohistochemical studies of bcl-2 and p53 proteins in benign and malignant ovarian endometriotic cysts. *Cancer* 2002;94:2935–2940. [PubMed: 12115382]
31. Oral E, Ilvan S, Tustas E, et al. Prevalence of endometriosis in malignant epithelial ovary tumours. *Eur J Obstet Gynecol Reprod Biol* 2003;109:97–101. [PubMed: 12818453]
32. Mhawech P, Kinkel K, Vlastos G, Pelte MF. Ovarian carcinomas in endometriosis: an immunohistochemical and comparative genomic hybridization study. *Int J Gynecol Pathol* 2002;21:401–406. [PubMed: 12352189]
33. Schubert EL, Lee MK, Mefford HC, et al. BRCA2 in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to BRCA1 or BRCA2. *Am J Hum Genet* 1997;60:1031–1040. [PubMed: 9150150]
34. Fredrickson TN. Ovarian tumors of the hen. *Environ Health Perspect* 1987;73:35–51. [PubMed: 3665870]
35. Giles JR, Shivaprasad HL, Johnson PA. Ovarian tumor expression of an oviductal protein in the hen: a model for human serous ovarian adenocarcinoma. *Gynecol Oncol* 2004;95:530–533. [PubMed: 15581958]
36. Piek JM, Torrens B, Hermesen B, et al. Histopathological characteristics of BRCA1- and BRCA2-associated intraperitoneal cancer: a clinic-based study. *Fam Cancer* 2003;2:73–78. [PubMed: 14574155]
37. Rose PG, Shrigley R, Wiesner GL. Germline BRCA2 mutation in a patient with fallopian tube carcinoma: a case report. *Gynecol Oncol* 2000;77:319–320. [PubMed: 10785486]
38. Paley PJ, Swisher EM, Garcia RL, et al. Occult cancer of the fallopian tube in BRCA-1 germline mutation carriers at prophylactic oophorectomy: a case for recommending hysterectomy at surgical prophylaxis. *Gynecol Oncol* 2001;80:176–180. [PubMed: 11161856]
39. Levine DA, Argenta PA, Yee CJ, et al. Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. *J Clin Oncol* 2003;21:4222–4227. [PubMed: 14615451]

40. Powell CB, Kenley E, Chen LM, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. *J Clin Oncol* 2005;23:127–132. [PubMed: 15625367]
41. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol* 2006;30:230–236. [PubMed: 16434898]
42. Finch A, Shaw P, Rosen B, Murphy J, Narod SA, Colgan TJ. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. *Gynecol Oncol* 2006;100:58–64. [PubMed: 16137750]
43. Cass I, Holschneider C, Datta N, Barbuto D, Walts AE, Karlan BY. BRCA-mutation-associated fallopian tube carcinoma: a distinct clinical phenotype? *Obstet Gynecol* 2005;106:1327–1334. [PubMed: 16319259]
44. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. *Am J Surg Pathol* 2007;31:161–169. [PubMed: 17255760]
45. Carlson JW, Kindelberger D, Parast M, Hirsch MA, Miron A, Lee Y, Crum CP. Evidence that many primary peritoneal serous carcinomas (PPSC) originate in the distal fallopian tube.
46. Roh M, Kindelberger D, Crum CP. Tumor presentation in pelvic serous cancer: A clue to pathogenesis? *Mod Pathol* 2008;21:221A.
47. Lee Y, Miron A, Drapkin R, et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. *J Pathol* 2007;211:26–35. [PubMed: 17117391]
48. Folkins AK, Jarboe EA, Lee Y, Ince TA, Drapkin R, Crum CP. A candidate precursor to pelvic serous cancer (p53 Signature) and its prevalence in prophylactically removed ovaries and tubes from BRCA + women.
49. Parast MM, Drapkin R, McKeon F, et al. Evidence that high and low grade ovarian serous tumors reflect different cells of origin.
50. Motoyama N, Naka K. DNA damage tumor suppressor genes and genomic instability. *Curr Opin Genet Dev* 2004;14:11–16. [PubMed: 15108799]
51. Jarboe E, Folkins A, Nucci MR, et al. Serous carcinogenesis in the fallopian tube: a descriptive classification. *Int J Gynecol Pathol* 2008;27:1–9. [PubMed: 18156967]

Figure 1. Immunophenotype of Müllerian inclusion cysts (a). Bcl-2 highlights secretory cells; two ciliated cells do not stain (b). Ciliated cell markers include p73 (c) and LHS28 (d), the latter staining the ciliary bodies.

Figure 2. A borderline serous cystadenoma with a mixed epithelial type illustrates some gland complexity (a). Ciliated cells are highlighted by LHS28 (b) and p73 (c). Bcl-2 marks a more basally located population of secretory-type cells (d).

Figure 3.

Mixed borderline and invasive serous tumour. The cyst cavity contains a raised, irregular tumour (a). At low power both the interior (I) and serosa (S) contain tumour (b). The interior of the cyst contains both conventional appearing borderline morphology (c) and an invasive component (d), which is present on the serosa (e) and omentum (f), emblematic of a well-differentiated serous carcinoma.

Figure 4.
A borderline tumour with micropapillary architecture (micropapillary carcinoma) (a) with
invasive implants on the peritoneum (b).

Figure 5. Serous carcinoma arising in association with an Müllerian inclusion cyst (MIC) in a BRCA+ woman who underwent a prophylactic salpingo-oophorectomy. A gross photograph depicts an irregular cyst wall (a). The tumour is closely associated with a large MIC (b,c). There is focal involvement of the surface of the contra-lateral ovary (d).

Figure 6.

Serous carcinoma arising in an endometriotic cyst. A low-power image shows the cyst; tumour is present on the surface (arrows) (a). The cyst lining contains endometrial tissue (arrow) with a focus of tumour (T) (b,c). Metastatic carcinoma is present in the tubal serosa (d).

Figure 7. Serous carcinoma in a BRCA+ woman often presents as tubal intraepithelial carcinoma (a), most of which are strongly p53 positive (b).

Figure 8. Tubal intraepithelial carcinoma associated with an ovarian serous carcinoma (a,c), both of which are strongly p53 positive (b, d) and share an identical p53 mutation.

Figure 9.

A large omental mass (upper panel). The serious carcinoma in the omentum (Om) coexisted with fimbrial carcinoma (Fim) and tubal intraepithelial carcinoma.

Figure 10.

A candidate precursor to pelvic serous carcinoma (p53 signature) is illustrated in the left panel and contrasted with tubal intraepithelial carcinoma on the right. Both entities share several features (see text) but are distinguished by a low proliferative (MiB1) index and minimal atypia in the p53 signature. From Lee et al,⁴⁷ with permission.