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The Oviduct and Ovarian Cancer: Causality, Clinical Implications and “Targeted Prevention”

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Abstract

A novel origin for pelvic serous cancer (ovarian cancer) has been proposed in the distal oviduct. This has important implications, including both early detection in high-risk women and wisdom of relying on serological tests to detect a disease that begins so close to the peritoneal surfaces. With the recent discovery of -pre-malignant disturbances in gene function in the tubal mucosa the concept of targeted prevention is emerging whereby the interruption of a portion of the carcinogenic pathway will prevent cancer. This alternative to detecting early malignancy is a new paradigm in the quest to prevent this deadly disease.

Introduction

Epithelial ovarian cancer consists of a range of tumor types that can be distinguished by their molecular pathogenesis, likely site of origin and risk factors. (1–3). The fundamental parameter that pervades the management of these tumors is the extent of disease when diagnosed (4). Stage imposes an overwhelming impact on outcome, and traditionally, whether the tumor was classified as a serous, endometrioid or mucinous carcinoma, the outcome would depend on the extent and response to chemotherapy. Recently, there has been an expanding literature focusing on an origin in the oviduct, which has injected new life into what had been a stagnant discussion of the pathogenesis of particularly high-grade malignancies (5,6). The obvious questions that arise are 1) the impact of this new information on management and 2) its relevance to ongoing efforts to prevent this disease. This discussion will focus on three attributes of this concept. First it will address the evidence and caveats regarding origins of epithelial ovarian cancer; second it will outline the potential immediate benefits of this new information in terms of improving patient care; third it will address the concept of “targeted prevention”, in which new information on the site of origin influences future efforts to lower the incidence rate of this disease.

Causality

The BRCA+ model and serous tubal intraepithelial carcinoma (STIC)

Historically, primary fallopian tube malignancies have been viewed as uncommon relative to conventional ovarian carcinomas, and some estimates have placed the oviduct as nearly 50 times less common to be the initiating site [7,8]. Part of this disparity was attributed to the stringent criteria for the diagnosis of a primary tubal malignancy. Criteria include the presence of a dominant tumor mass in the fallopian tube plus a tubal intraepithelial carcinoma (TIC). Tumors fulfilling this requirement were uncommon, with an estimated incidence is 0.41 per 100,000 [8]. In retrospect, the reason for both the lack of frequency and this particular presentation was the need for both a tumor arising in the endosalpinx and fimbrial adhesions, which effectively barred the tumor from exiting the fallopian tube. This

guaranteed that the tumor would carry out the initial stages of its natural history within the tubal lumen.

In the population carrying BRCA1 or BRCA2 mutations (BRCA+), most symptomatic serous carcinomas are designated as ovarian in origin according to the traditional method of primary site assignment mentioned above. However, examination of prophylactically removed fallopian tubes and ovaries has made it possible to intercept these tumors early in their course. Thus pathology exams have shown that a large number of early serous carcinomas involve the fallopian tube, either as an invasive or intraepithelial carcinoma. Between 57 and 85% of these cases have exhibited involvement of the fimbriated end of the fallopian tube or its immediate vicinity (Table 1) [9–12]. These observations have increasingly focused attention to the distal fallopian tube as an initiating point for high grade serous malignancies.

In the fallopian tube model, serous tubal intraepithelial carcinoma (STIC) is the earliest morphologic manifestation of serous carcinoma. STICs are composed of “secretory cells”, the non-ciliated population of the endosalpinx. These cells, when neoplastic, exhibit three important features; 1) variable stratification, 2) increased nuclear cytoplasmic ratio and 3) loss of nuclear polarity, often with intraepithelial fractures or detached micro-clusters of cells in the tubal lumen. Most but not all STICs will show strong nuclear staining with antibodies to p53 as well as an increased proliferation index (MIB-1) compared to the background tubal epithelium [13].

Tubal intraepithelial carcinomas, ovarian and peritoneal serous cancer

The association of STIC with BRCA+ status support the concept that this entity is the more common early malignancy in women with this genetic risk factor. The obvious question of whether pelvic serous carcinomas without a documented history of a mutation in the BRCA genes initiate in the oviduct. Several studies, beginning with the report by Kindelberger et al, have confirmed this hypothesis.. Kindelberger et al. showed that 47% of tumors classified as serous ovarian carcinomas co-existed with aSTIC [14]. Carlson et al. similarly showed that complete examination of the fallopian tubes in women with primary peritoneal serous carcinomas disclosed a STIC in 47% [15]. In both studies, p53 mutation analysis in the STICs and remote tumors disclosed the same mutations, genetically linking the two. Moreover, a recent study from another group that examined paired STICs and remote tumors supported a genetic link between the two by examining anomalies in chromosomal number [16]. A fourth study by Roh et al. computed a slightly lower frequency of STIC in ovarian carcinomas (36%; Table 2) [17]. Two additional studies have computed frequencies of STIC between 33 and 64 per cent of pelvic serous cancers (18,19).

The possibility that STIC represents the earliest phase of all pelvic serous carcinoma must be viewed critically, given the lack of unanimity over the frequency of STIC in these tumors even in studies that systematically examine the fallopian tubes of women with pelvic serous cancer. Irrespective of how one views the pathogenetic significance of STIC, it is the earliest known malignant alteration in most BRCA+ women. The question is whether other mechanisms that have yet to be characterized fully are involved. STIC has also been shown to correlate inversely with another parameter used to estimate site of origin, which is the presence (or absence) of a dominant ovarian mass. A dominant mass is frequently found in endometrioid adenocarcinomas of the ovary, which are presumed to arise in endometriosis. As would be expected, endosalpingeal involvement by these tumors is uncommon and tubal intraepithelial carcinoma rare. A recent report showed a significant inverse relationship between a dominant ovarian mass, defined as a two-fold greater difference in the greatest dimension of the ovarian tumors, and both endosalpingeal involvement and STIC [17]. The issues of both dominant mass and STIC are entwined with site of origin and tumor type. It is

now accepted that the distinction of a high-grade serous and high-grade endometrioid carcinoma cannot be reliably made, both on histologic examination and immunohistochemistry; both are strongly associated with WT-1, p53, PAX2 and p16 immunostaining, markers of serous carcinomas (17, 20). A tumor mass that predominates in one ovary, particularly a serous carcinoma, does not guarantee origin in that organ (spread from contiguous disease in the tube or peritoneum cannot always be excluded), nor may a STIC guarantee a tubal primary in the setting of massive tubal and ovarian involvement. However, such associations do raise the possibility of both ovarian and tubal origins and caution against wholesale subscription to the tubal theory of serous carcinogenesis.

The p53 signature

The most compelling concept is therefore not whether all high-grade serous carcinomas come from the oviduct, but the existence of a carcinogenic sequence in the oviduct that can be quantified and studied. Following on early reports of foci of p53 immunostaining in the oviducts of women with BRCA1 or BRCA2 mutations, a series of studies have characterized an intramucosal abnormality that fulfills many of the criteria for a serous cancer precursor, termed the “p53 signature” (21,22). This, observation has underscored the significance of p53 mutations in the pathogenesis of pelvic serous carcinoma and the earliest malignant change, the STIC. The striking aspects of this phenomenon is its concentration in the oviduct rather than the ovary. Hutson et al. identified p53-immuno-positive ovarian cortical inclusion cysts in women with ovarian cancer and speculated that these were precursor lesions [23]. Barakat et al. performed a similar analysis of ovaries from women with BRCA mutations who were undergoing risk-reducing surgery, but found none [24]. Recently Folkins et al. confirmed the findings of Barakat et al, reporting only a single focus of p53 positive ovarian surface epithelium in 75 cases analyzed from this population[25]. Studies of the fallopian tubes have been more revealing.

Prior studies had shown that serous carcinomas were imbued with secretory cell characteristics and Piek et al. noted that the p53 positive cells that they observed were secretory in type [21]. Lee et al. confirmed this and noted further that the p53 signatures were most common in the fimbria, a site that Cass et al. and several others had confirmed to be the dominant site of origin for tubal carcinomas [22,26]. Moreover, Lee et al. linked p53 signatures to expression of γ -H2AX, which localizes to areas of DNA damage, and p53 mutations. In addition, they noted that the p53 signatures were equally common in women with and without known heritable BRCA1 or BRCA2 mutations, being present in approximately one third of each group. This finding strongly suggested that the initial events of serous carcinogenesis – DNA damage of secretory cells and p53 mutations – were influenced by factors not directly related to heritable BRCA mutations.

The possibility that a “generic” precursor to pelvic serouscarcinoma arose in the tube was strengthened further in a study by Saleemuddin et al. [27]. BRCA+ women were segregated into those with and without p53 signatures. The former group had a significantly older age of first birth and lower parity, reproductive factors associated with higher lifetime ovulation events that segregate with ovarian cancer risk. Two additional observations further strengthened the relationship between p53 signatures and pelvic serous carcinoma (Table 3). First, p53 signatures are sometimes seen in continuity with intraepithelial carcinomas and can share common p53 mutations [Lee, Carlson]. This is the most physically compelling evidence that the p53 signature precedes STIC. Second, intermediate lesions or – “tubal intraepithelial lesions in transition” (TILTs) – in which p53 positive epithelium displays a higher degree of proliferative activity but falls short of malignancy, have also been described [13]. Together this body of evidence indicates that an important precursor to pelvic serous carcinoma resides in the distal fallopian tube and that it is the earliest lesion in a continuum of the tubal serous carcinogenic sequence (Fig. 1). Studies have continued to

characterize this entity, using both cell culture and other models to establish a link between DNA damage, the tubal secretory cell and the p53 mutations that characterize early serous carcinogenesis and further refine the differences between precursors and early intraepithelial carcinomas (28).

Secretory cell outgrowths (SCOUTs) and the concept of a “precursor correlate”?

Recent studies have focused increasing attention to the precursor conditions that predate malignancies. Examples include micro-adenomas of the colon (colon cancer), pancreatic intraepithelial neoplasia (pancreatic carcinoma) and prostatic intraepithelial neoplasia (prostatic cancer)(29–31). Common features of these models include a relatively high frequency of the precursor in the general population, accumulation with age and a higher than expected prevalence in patients with malignancy. The p53 signature fulfills these criteria; however, it signifies a specific defining molecular event, the p53 mutation and the multi-gene theory of carcinogenesis requires additional events (Lee)(32,33). There is now evidence that a series of events, separated in both space and time, occur in the fallopian tube, and can be appreciated in discrete presumably clonal phenomena similar to p53 signatures. These entities are termed secretory cell outgrowths or SCOUTs (34–37). Like p53 signatures, SCOUTs harbor loss of PAX2, ALDH1 and other gene dysfunctions (Ning PC). Unlike p53 signatures, SCOUTs do not contain p53 mutations are distributed throughout the fallopian tube(35). This speaks to the notion of separation in space and time and designates the SCOUT as a “precursor correlate” that signals some of the alterations in gene function that, when combined with p53 mutations in the distal tube, characterize the direct precursor (p53 signature). As indirect precursors or precursor correlates, SCOUTs provide an important window into the plethora of molecular events that may precede malignancy. They will be discussed further in the last segment of this chapter.

Clinical Implications

This segment examines the practical issues faced by the caregiver who is caring for a woman at risk for or with a diagnosis of high-grade ovarian cancer. The first involves the processing and interpretation of fallopian tubes from risk reducing salpingo-oophorectomies (RRSOs). The second concerns classification of pelvic carcinomas.

The SEE-FIM protocol

Prophylactic salpingo-oophorectomies from women with mutations in BRCA or strong family histories of ovarian carcinoma should be submitted entirely and examined histologically. Most of the early cancers described in the preceding sections occur in grossly unremarkable specimen, so it is imperative that all the tissue be evaluated in order to confirm or exclude an early carcinoma and advise the patient as to their risks. The fallopian tubes and ovaries should be submitted entirely and be evaluated in serial sections by a pathologist with expertise in gynecologic malignancies. At Brigham and Women’s Hospital, the goal is to ensure sectioning and extensive examination of the fimbria (SEE-FIM protocol), because the majority of early serous tumors occur in this area, which is as follows:

- The entire tube is initially fixed for at least 4 hours to minimize loss of epithelium during manipulation.
- The distal 2 cm of the fimbriated end is transected.
- The fimbrial mucosa is sectioned longitudinally into as many sections as practical. The remainder of the tube is sectioned a 2 to 3 mm intervals.
- The tubal segments combined with the fully sectioned fimbriated end are submitted in toto.³⁸

Recent studies show increased rates of detection (from less than 2.5 to 17%) with more thorough sectioning.³⁹ Thus, protocols for examining the fallopian tubes in genetically susceptible patients will continue to evolve. If an area of concern is encountered, it can be evaluated by further serial sections.

Routine analysis of fallopian tubes in surgeries for benign diseases

The routine analysis of the distal fallopian tube in salpingectomies from benign disorders will occasionally uncover an early (intraepithelial) carcinoma in that site. The detection of these rare but early cancers will permit both a thorough workup of the patient for metastatic disease and in the right setting a rationale for genetic testing, which if positive could benefit others in the family.^{40,41} If the clinician wishes to pursue this policy, they should discuss with their pathologist the most reasonable way to submit and examine the distal one-third of the fallopian tube in routine hysterectomies.

Systematic analysis of fallopian tubes from women who are deemed at risk for ovarian cancer (i.e., those with known inherited mutations in the BRCA1 or BRCA2 genes).

Risk-reducing salpingo-oophorectomy (RRSO) should be reserved for women with known mutations in BRCA 1 or 2, or who have a family history consistent with one of the genetic syndromes associated with ovarian cancer and should include an evaluation by an genetic counselor. Bilateral salpingo-oophorectomy in women with BRCA mutations reduces the risk of an eventual pelvic cancer by greater than 90%.⁽⁴²⁾ Prophylactic surgery does not completely eliminate the risk of ovarian cancer in high-risk individuals, the risk being approximately 6%.⁽⁴³⁾ It is imperative that patients should be informed that prophylactic surgery does not protect them against the subsequent development of papillary serous carcinoma of the peritoneum. They should also be warned that about 7% of prophylactic operations detect occult ovarian or tubal carcinoma and that these lesions may not be appreciated until final pathology reports are available (Table 1). Pathologists should be instructed to submit the entire specimen for sectioning, so as to reduce the risk of missing a microscopic occult malignancy. Finally, the patient should be prepared for the consequences of surgical menopause.

In recent studies of women undergoing prophylactic salpingo-oophorectomy for BRCA1 or BRCA2 mutations (BRCA+), the risk of uncovering an early cancer has been estimated at from 4% to 17% averaging 8%, a figure that may vary both as a function of the age of the population and the thoroughness with which the specimen is examined.^(9–12, 44) From 57% to nearly 100% of these early cancers have been identified in the distal fallopian tube, the earliest malignancy being a tubal intraepithelial carcinoma (TIC) (Table 1) With this figure in mind the following points must be stressed:

1. Early malignancies can be both serous (STIC, 80%) and endometrioid (ETIC, 20%) (Callahan)
2. Twenty percent of these early serous cancers are not associated with an intraepithelial lesion in the fallopian tube; more extensive tubal sampling might uncover some, but most of the time it will not.(Rabban)
3. Advanced pelvic serous cancers in BRCA+ women are virtually identical in tumor distribution to the general population with this disease (i.e., less than half will have evidence of a tubal origin) (45). Although it may be tempting to attribute this to obliteration of the tubal mucosal origin by expanding tumor or some other sampling artifact, the reader is strongly cautioned that salpingectomy alone may not rid the patient of risk and leaving the ovary might even place them at a substantial risk of an eventual pelvic serous cancer (Table 2).

4. Prophylactic specimens from women with a family history of cancer but without a documented BRCA mutation are unlikely to contain an early malignancy (46). Virtually all of the genetically related pelvic serous cancer is linked to BRCA+.
5. TICS are rarely reported in fallopian tubes removed as part of surgery for nonmalignant and nonprophylactic reasons.

Pitfalls in histologic interpretation

As a consequence of the increasing surgical practice of prophylactic salpingo-oophorectomy for women with BRCA1 or BRCA2 mutations, more and more serous carcinomas are being discovered in the fallopian tube and at an early stage. In applying histologic criteria, the pathologist must be aware that the oviducts of these high-risk women may contain proliferations that are noticeable yet fall short of malignancy. Key to this approach is focusing on specific histologic parameters, such as both cellular atypia and loss of polarity, getting a second opinion if there is a question of the diagnosis, and using ancillary staining for p53 and MIB1 to support the diagnosis. The clinical management of patients with lesions of uncertain malignant potential should be the same as those with a non-invasive STIC. The patients should be advised that the risk of recurrence is low but not “baseline” i.e. the risk of 6% is approximately 4-fold higher than the general population (47).

High grade müllerian carcinomas

Excepting the RRSO, the pathologist will usually encounter serous cancer when it is advanced, in the symptomatic patient. In this setting the following issues are relevant.

- High grade endometrioid adenocarcinomas are synonymous with high-grade serous carcinomas:
- Some pathologic features are more common in high-grade carcinomas associated with BRCA1 or BRCA2 mutations (48):
- Occasional serous carcinomas in the endometrium may have a tubal origin:

Targeted Prevention

Targeted prevention can be defined in three contexts.

Intercepting early malignancy

The first pertains to intercepting a serous cancer precursor before it metastasizes to the peritoneal surfaces. In this model, a STIC will persist for a period of time prior to spreading, yet be detectable via exfoliative cytology or imaging. This is a concept that is being investigated but depends on the exploitation of nanotechnology and novel detection methods that are non-invasive. Unanswered question in this regard include the following:

- How long is the interval from STIC development to peritoneal spread? If STIC is a potential target for early detection, it must be present in a localized phase for a long enough period to permit early and maximize the efficacy of biomarker detection strategies. Although based on few cases, there is evidence that removal of these early cancers in BRCA+ women is effective (Carlson).
- Are early serous cancers more curable than advanced malignancies? Even if tubal intraepithelial carcinomas have spread to the peritoneum the earlier phases of spread may be associated with a tumor biology that is more treatable. This remains to be determined but is a logical argument and merits study.
- Could STICs be detected by imaging or biomarker surveillance? At this point, imaging methods are not sufficiently sensitive to detect a few cell layers of

proliferating cells in the distal fallopian tube, although these early tumors can be visualized (51). Nevertheless, there is interest in the concept of biomarker detection, even if oriented to proof of principal studies in which peritoneal washings or tubal lavage specimens are analyzed for biomarkers that reflect the presence of these small tumors. As Fig. 1 shows, the fallopian tube may harbor significant (detectable?) atypias for an interval of time before the development of metastatic disease.

Removing the fallopian tube in both high and low-risk women

The second context is one of removing the organ at risk. Currently there is a groundswell of interest in the routine removal of the oviducts from women who no longer intend to procreate. The established scenario is one in which a woman at genetic risk undergoes salpingo-oophorectomy after completing child-bearing, ideally by age 40. One variation on this theme is to retain the ovaries and remove only the fallopian tubes. This is considered risky by some, but may be pursued by individual women who are willing to take the risk. In another scenario, women who are not at increased risk would undergo salpingectomy at the time of routine hysterectomy (52). This will form a cohort of women who can be followed to determine if their risk of ovarian cancer is altered by this procedure and if so, how much. A corollary of this will be information from these cases to determine the precise frequency of early tubal cancer. If such cases are detected it will be possible to determine if the risk of a BRCA1 or BRCA2 mutation is higher and if so, if it will impact on management by other family members (53).

The ultimate question, and one that has yet to be fully answered, is the percentage of high-grade ovarian cancers that have their origins in the oviduct. As illustrated in Table 2, an appreciable percentage of pelvic serous cancers in all studies cannot be attributed to the fallopian tube based on histopathologic analysis alone. This has implications for the origin of these tumors, the direction of research and the expectations from prophylactic salpingectomy or fimbriectomy.

Identifying and interrupting vulnerable pathways to serous cancer

This question brings us back to the concept of SCOUTs, which are emblematic of early functional gene disturbances that presumably are a component of risk factor accumulation. At this point it is clear that the frequency of gene dysregulation rises as a function of age and increases further in women with malignancy, as seen in not only the oviduct but multiple organ systems. It is reasonable to assume that interruption or correction of one or more of these pathway disturbances will reduce the risk of ovarian cancer. Indeed, the success of tubal ligation, pregnancy and oral contraceptives in reducing the ovarian cancer risk could very well be a function of their impact on one of the components of the serous carcinogenic pathway (for example, oviducts from pregnant women are devoid of SCOUTs). Ultimately, it will be important to determine not only the events that transpire in the transition from a p53 signature to a tubal intraepithelial carcinoma, but the collection of functional gene alterations that precede this transition. Hidden within this series of seemingly random, age-related genetic or epigenetic disturbances could be critical events, the interruption of which could prevent ovarian cancer.

Bibliography

1. American Cancer Society. Cancer facts and figures 2007. www.cancer.org
2. Lancaster JM, Powell CB, Kauff ND, Cass I, Chen LM, Lu KH, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol.* 2007; 107:159–62. [PubMed: 17950381]

3. Shih I, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. *Am J Pathol.* 2004; 164:1511–8. [PubMed: 15111296]
4. Helm, CW.; Edwards, RP. Malignant lesions of the ovary. 2008 April. <http://www.emedicine.com/med/topic3306.htm>
5. Crum CP. Intercepting pelvic cancer in the distal fallopian tube: theories and realities. *Mol Oncol.* 2009 Apr; 3(2):165–70. Epub 2009 Feb 3. [PubMed: 19383378]
6. Gershenson DM, Tortolero-Luna G, Malpica A, Baker VV, Whittaker L, Johnson E, Follen Mitchell M. Ovarian intraepithelial neoplasia and ovarian cancer. *Obstet Gynecol Clin North Am.* 1996; 23:475–543. [PubMed: 8784888]
7. Rosenblatt KA, Weiss NS, Schwartz SM. Incidence of malignant fallopian tube tumors. *Gynecol Oncol.* 1989; 35:236–9. [PubMed: 2807017]
8. Stewart SL, Wike JM, Foster SL, Michaud F. The incidence of primary fallopian tube cancer in the United States. *Gynecol Oncol.* 2007; 107:392–7. [PubMed: 17961642]
9. Powell CB, Kenley E, Chen LM, Crawford B, McLennan J, Zaloudek C, et al. Risk reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. *J Clin Oncol.* 2005; 23:127–32. [PubMed: 15625367]
10. 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]
11. Callahan MJ, Crum CP, Medeiros F, Kindelberger DW, Elvin JA, Garber JE, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. *J Clin Oncol.* 2007; 25:3985–90. [PubMed: 17761984]
12. Leeper K, Garcia R, Swisher E, Goff B, Greer B, Paley P. Pathologic findings in prophylactic oophorectomy specimens in high-risk women. *Gynecol Oncol.* 2002; 87:52–6. [PubMed: 12468342]
13. Jarboe E, Folkins A, Nucci MR, Kindelberger D, Drapkin R, Miron A, et al. Serous carcinogenesis in the fallopian tube: a descriptive classification. *Int J Gynecol Pathol.* 2008; 27:1–9. [PubMed: 18156967]
14. Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. *Am J Surg Pathol.* 2007; 31:161–9. [PubMed: 17255760]
15. Carlson JW, Miron A, Jarboe EA, Parast MM, Hirsch MS, Lee Y, et al. Serous tubal intraepithelial carcinoma: its potential role in primary peritoneal serous carcinoma and serous cancer prevention. *J Clin Oncol.* 2008; 26:4160–5. [PubMed: 18757330]
16. Salvador S, Rempel A, Soslow RA, Gilks B, Huntsman D, Miller D. Chromosomal instability in fallopian tube precursor lesions of serous carcinoma and frequent monoclonality of synchronous ovarian and fallopian tube mucosal serous carcinoma. *Gynecol Oncol.* 2008; 110:408–17. [PubMed: 18597838]
17. Roh MH, Kindelberger D, Crum CP. Serous tubal intraepithelial carcinoma and the dominant ovarian mass: clues to serous tumor origin? *Am J Surg Pathol.* 2008 [Electronic publication ahead of print].
18. Przybycin CG, Kurman RJ, Ronnett BM, Shih IeM, Vang R. Are all pelvic (nonuterine) serous carcinomas of tubal origin? *Am J Surg Pathol.* 2010; 34:1407–16. [PubMed: 20861711]
19. Leonhardt K, Einenkel J, Sohr S, Engeland K, Horn LC. p53 signature and serous tubal in-situ carcinoma in cases of primary tubal and peritoneal carcinomas and serous borderline tumors of the ovary. *Int J Gynecol Pathol.* 2011; 30:417–24. [PubMed: 21804388]
20. Köbel M, Kalloger SE, Boyd N, McKinney S, Mehl E, Palmer C, Leung S, Bowen NJ, Ionescu DN, Rajput A, Prentice LM, Miller D, Santos J, Swenerton K, Gilks CB, Huntsman D. Ovarian carcinoma subtypes are different diseases: implications for biomarker studies. *PLoS Med.* 2008; 5:e232. [PubMed: 19053170]
21. Piek JM, van Diest PJ, Zweemer RP, Jansen JW, Poort-Keesom RJ, Menko FH, et al. Dysplastic changes in prophylactically removed fallopian tubes of women predisposed to developing ovarian cancer. *J Pathol.* 2001; 195:451–6. [PubMed: 11745677]

22. Lee Y, Miron A, Drapkin R, Nucci MR, Medeiros F, Saleemuddin A, et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. *J Pathol.* 2007; 211:26–35. [PubMed: 17117391]
23. Hutson R, Ramsdale J, Wells M. P53 protein expression in putative precursor lesions of epithelial ovarian cancer. *Histopathology.* 1995; 27:367–71. [PubMed: 8847068]
24. 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; 89:383–90. [PubMed: 10918170]
25. Folkins AK, Jarboe EA, Saleemuddin A, Lee Y, Callahan MJ, Drapkin R, et al. A candidate precursor to pelvic serous cancer (p53 signature) and its prevalence in ovaries and fallopian tubes from women with BRCA mutations. *Gynecol Oncol.* 2008; 109:168–73. [PubMed: 18342932]
26. 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; 106:1327–34. [PubMed: 16319259]
27. Saleemuddin A, Folkins AK, Garrett L, Garber J, Muto MG, Crum CP, et al. Risk factors for a serous cancer precursor (“p53 signature”) in women with inherited BRCA mutations. *Gynecol Oncol Gynecol Oncol.* 2008; 111:226–32.
28. Levanon K, Ng V, Piao HY, Zhang Y, Chang MC, Roh MH, Kindelberger DW, Hirsch MS, Crum CP, Marto JA, Drapkin R. Primary ex vivo cultures of human fallopian tube epithelium as a model for serous ovarian carcinogenesis. *Oncogene.* 2010; 29:1103–13. [PubMed: 19935705]
29. Zeki SS, Graham TA, Wright NA. Stem cells and their implications for colorectal cancer. *Nat Rev Gastroenterol Hepatol.* 2011 Feb; 8(2):90–100. Review. [PubMed: 21293509]
30. Ito R, Kondo F, Yamaguchi T, Kato K, Sakai Y, Saisho H, Yamazaki K. Pancreatic intraepithelial neoplasms in the normal appearing pancreas: on their precise relationship with age. *Hepatogastroenterology.* 2008 May–Jun; 55(84):1103–6. [PubMed: 18705338]
31. Epstein JI. Precursor lesions to prostatic adenocarcinoma. *Virchows Arch.* 2009; 454:1–16. [PubMed: 19048290]
32. Norquist BM, Garcia RL, Allison KH, Jokinen CH, Kernochan LE, Pizzi CC, Barrow BJ, Goff BA, Swisher EM. The molecular pathogenesis of hereditary ovarian carcinoma: alterations in the tubal epithelium of women with BRCA1 and BRCA2 mutations. *Cancer.* 2010; 116:5261–71. [PubMed: 20665887]
33. Shaw PA, Rouzbahman M, Pizer ES, Pintilie M, Begley H. Candidate serous cancer precursors in fallopian tube epithelium of BRCA1/2 mutation carriers. *Mod Pathol.* 2009; 22:1133–1138. [PubMed: 19543244]
34. Mehra K, Mehrad M, Ning G, Drapkin R, McKeon FD, Xian W, Crum CP. STICS, SCOUTs and p53 signatures; a new language for pelvic serous carcinogenesis. *Front Biosci (Elite Ed).* 2011 Jan 1; 13:625–34. [PubMed: 21196340]
35. Chen EY, Mehra K, Mehrad M, Ning G, Miron A, Mutter GL, Monte N, Quade BJ, McKeon FD, Yassin Y, Xian W, Crum CP. Secretory cell outgrowth, PAX2 and serous carcinogenesis in the Fallopian tube. *J Pathol.* 2010; 222:110–6. [PubMed: 20597068]
36. Laury AR, Ning G, Quick CM, Bijron J, Parast MM, Betensky RA, Vargas SO, McKeon FD, Xian W, Nucci MR, Crum CP. Fallopian tube correlates of ovarian serous borderline tumors. *Am J Surg Pathol.* 2011 Dec; 35(12):1759–65. [PubMed: 22089527]
37. Quick CM, Ning G, Bijron J, Laury A, Wei TS, Chen EY, Vargas SO, Betensky RA, McKeon FD, Xian W, Crum CP. PAX2-null secretory cell outgrowths in the oviduct and their relationship to pelvic serous cancer. *Mod Pathol.* 2011 Nov 11.
38. Medeiros F, Muto MG, Lee Y, Elvin JA, Callahan MJ, Feltmate C, Garber JE, Cramer DW, Crum CP. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol.* 2006; 30:230–6. [PubMed: 16434898]
39. Rabban JT, Krasik E, Chen LM, Powell CB, Crawford B, Zaloudek CJ. Multistep level sections to detect occult fallopian tube carcinoma in risk-reducing salpingo-oophorectomies from women with BRCA mutations: implications for defining an optimal specimen dissection protocol. *Am J Surg Pathol.* 2009; 33:1878–1885. [PubMed: 19898224]

40. Semmel DR, Folkins AK, Hirsch MS, Nucci MR, Crum CP. Intercepting early pelvic serous carcinoma by routine pathological examination of the fimbria. *Mod Pathol*. 2009; 22:985–988. [PubMed: 19407856]
41. Kwon JS, Daniels MS, Sun CC, Lu KH. Preventing Future Cancers by Testing Women With Ovarian Cancer for BRCA Mutations. *J Clin Oncol*. 2010; 28:675–82. [PubMed: 19841329]
42. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2002; 346:1609–1615. [PubMed: 12023992]
43. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med*. 2002; 346:1616–22. [PubMed: 12023993]
44. Colgan TJ, Murphy J, Cole DE, Narod S, Rosen B. Occult carcinoma in prophylactic oophorectomy specimens: prevalence and association with BRCA germline mutation status. *Am J Surg Pathol*. 2001; 25:1283–1289. [PubMed: 11688463]
45. Piek JM, Torrença B, Hermesen B, Verheijen RH, Zweemer RP, Gille JJ, et al. Histopathological characteristics of BRCA1- and BRCA2-associated intraperitoneal cancer: a clinic-based study. *Fam Cancer*. 2003; 2:73–8. [PubMed: 14574155]
46. Domchek SM, Gaudet MM, Stopfer JE, Fleischaut MH, Powers J, Kauff N, Offit K, Nathanson KL, Robson M. Breast cancer risks in individuals testing negative for a known family mutation in BRCA1 or BRCA2. *Breast Cancer Res Treat*. 2010; 119:409–14.
47. Mehrad M, Ning G, Chen EY, Mehra KK, Crum CP. A pathologist's road map to benign, precancerous, and malignant intraepithelial proliferations in the fallopian tube. *Adv Anat Pathol*. 2010 Sep; 17(5):293–302. Review. [PubMed: 20733351]
48. Soslow RA, Han G, Park KJ, Garg K, Olvera N, Spriggs DR, Kauff ND, Levine DA. Morphologic patterns associated with BRCA1 and BRCA2 genotype in ovarian carcinoma. *Mod Pathol*. (in press).
49. Jarboe EA, Miron A, Carlson JW, Hirsch MS, Kindelberger D, Mutter GL, Crum CP, Nucci MR. Coexisting intraepithelial serous carcinomas of the endometrium and fallopian tube: frequency and potential significance. *Int J Gynecol Pathol*. 2009; 28:308–15. [PubMed: 19483636]
50. Madore J, Ren F, Filali-Mouhim A, Sanchez L, Köbel M, Tonin PN, Huntsman D, Provencher DM, Mes-Masson AM. Characterization of the molecular differences between ovarian endometrioid carcinoma and ovarian serous carcinoma. *J Pathol*. 2010; 220:392–400. [PubMed: 19967725]
51. McAlpine JN, El Hallani S, Lam SF, Kalloger SE, Luk M, Huntsman DG, MacAulay C, Gilks CB, Miller DM, Lane PM. Autofluorescence imaging can identify preinvasive or clinically occult lesions in fallopian tube epithelium: a promising step towards screening and early detection. *Gynecol Oncol*. 2011; 120:385–92. [PubMed: 21237503]
52. Dietl J, Wischhusen J, Häusler SF. The post-reproductive Fallopian tube: better removed? *Hum Reprod*. 2011; 26:2918–24. [PubMed: 21849300]
53. <http://www.pointproject.org>
54. Vicus D, Shaw PA, Finch A, Rosen B, Murphy J, Armel S, Sun P, Narod SA. Risk factors for non-invasive lesions of the fallopian tube in BRCA mutation carriers. *Gynecol Oncol*. 2010; 118:295–8. [PubMed: 20722102]

Figure 1. Tubal intraepithelial carcinoma occurs predominately in the distal one-third of the fallopian tube (seen schematically) and consists of a non-invasive carcinoma with metastatic potential and p53 mutations (inset).

Figure 2.

Discrete events in the oviductal mucosa that precede serous cancer include secretory outgrowths (SCOUTs) that are widespread. More immediate precursors include p53 signatures and intraepithelial lesions in transition. Like precursors in other organs, these entities are relatively common and harbor p53 mutations. Occasionally, however, they may be seen in continuity with tubal intraepithelial carcinomas.

Figure 3.

A schematic of pathways and opportunities for serous cancer development and intervention. Gene dysregulations (step A) and mutations (step B) are age related, result in benign clonal expansions (step C) and may be vulnerable to targeted prevention. Once intraepithelial carcinoma develops (step D), the carcinogenic sequence is considered irreversible and will likely progress to exfoliation and implantation (step E).

Table 1

Frequency of tubal intraepithelial neoplasia (TIC) in risk reducing salpingo-oophorectomies of women with BRCA1 or BRCA2 mutations

Author	Number	Tumor(%)	Tubal involvement (%)
Colgan (2001)	39	5(13)	4(80)
Leeper (2002)	30	5(17)	3(60)
Powell (2005)	67	7(10)	4(57)
Carcangiu (2006)	50	6(12)	4(67)
Finch (2006)	159	7(4)	6(86)
Callahan (2007)	100	7(7)	7(100)*
Hirst (2009)	45	4(9)	4(100)
TOTAL	490	41(8)	32(78)

* Updated to 2010, 17/20 associated with TIC (85%)

Table 2

Frequency of STIC* in high grade serous carcinomas

Author	Diagnosis	No.	STIC(%)
Kindelberger (2007)	OVCA	44	20(45)
Carlson (2008)	PPCA	19	9(47)
Roh (2010)	OVCA	78	28 (36)
Przybycin (2010)	OVCA/PPCA	41	24(59)
Seidman (2011)	PPCA	51	28(56)
Leonhardt (2011)	PPCA	9	3(33)

*
serous tubal intraepithelial carcinoma

Table 3

Evidence supporting the tube as a source of pelvic serous carcinoma

1	Credible source (STIC in the distal tube) in 35–60%.
2	Occur in the setting of cellular DNA damage (γ -H2AX+).
3	Tumors have a secretory cell immunophenotype (HMFG2, PAX8(+).
4	Strong nuclear accumulation of p53 and PAX2 down-regulation in both tubal precursors (p53 signatures) and malignancies.
5	Sequence confirmed ovarian cancer-associated p53 mutations in p53 signatures and serous cancers.
6	Documented continuity between the p53 signature and intra-epithelial carcinoma with shared p53 mutations and loss of PAX2 expression.
7	Existence of lesions sharing features of both STIC and p53 signatures (tubal intraepithelial lesions in transition).
8	Widespread disturbances in gene expression in secretory cell outgrowths

(SCOUTs) in the fallopian tube shared with serous cancers.