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Original Article

Serous Carcinogenesis in the Fallopian Tube: A Descriptive Classification

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Summary: The fimbria is the most common site of early serous cancer (tubal intraepithelial carcinoma or STIC) in women with BRCA mutations (BRCA+). A candidate serous cancer precursor—the p53 signature—has been found in nonneoplastic secretory cells of the fimbria, suggesting serous carcinogenesis in the tube (SCAT). This study surveyed fallopian tubes from 3 populations to characterize the morphological and immunohistochemical correlates of SCAT. The SCAT sequence was defined by strong nuclear p53 staining and DNA damage (γ-H2AX+) in secretory cells and subdivided morphologically by (1) degree of nuclear stratification, (2) proliferative index, and (3) degree of disorganized growth. Fallopian tubes from women without a current ovarian cancer, women with BRCA mutations, and women with a coexisting pelvic serous cancer were completely examined. p53 signatures exhibited cuboidal to pseudostratified, polarized p53+ epithelial segments with variable nuclear enlargement and a MiB1 index of 0% to 30%. Tubal intraepithelial carcinomas contained from single (uncommon) to multilayered, poorly polarized, uninterrupted neoplastic cell populations that completely displaced the normal mucosa; MiB1 index exceeded 45% and was usually more than 70%. An uncommon third category, p53-positive foci with features intermediate between p53 signatures and STICs, exhibited preserved epithelial polarity, pseudostratification, incomplete replacement of the adjacent normal ciliated cells, and a MiB1 index between 40% and 75%. Transitions from 1 category to another were documented. Combined with recent reports associating STICs with pelvic serous cancer, this continuum of epithelial change validates the SCAT sequence and the fimbrial secretory cell as the site of origin for many serous carcinomas. **Key Words:** Serous carcinogenesis—Intraepithelial carcinoma—Fallopian tube neoplasms—BRCA—p53—Fimbria.

Approximately 25,000 women in the United States develop ovarian cancer each year, and more than one half die of their disease (1). The most lethal of these tumors is serous carcinoma largely because it is invariably discovered after having spread to the adjacent peritoneal surfaces (2). Because of this mode of spread, serous tumors have traditionally been assumed to arise from the ovarian surface epithelium (OSE). However, although the OSE or an equivalent extraovarian source (such as fallopian tube) has been considered integral to the development of many ovarian epithelial malignancies, the precise percentage of serous carcinomas arising in this pathway has not been ascertained (3–5).

Beginning in the late 1990s, the following evidences have accumulated to support an alternate origin other than OSE for serous carcinoma, specifically the distal fallopian

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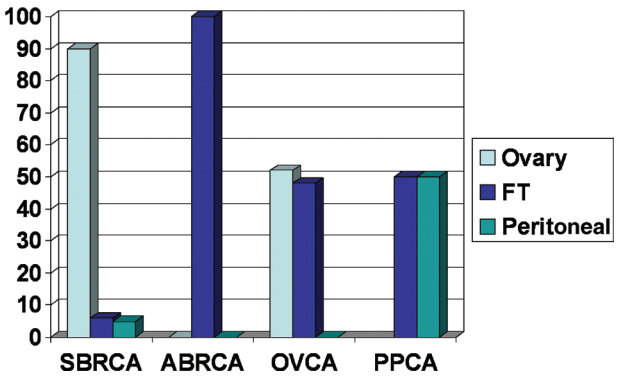

FIG. 1. Relative frequencies of pelvic serous carcinomas classified as ovarian, tubal, and peritoneal in SBRCA women, ABRCA women, and consecutively accessioned cases of presumed OVCA and PPCA. Cases were classified as tubal in origin if tubal intraepithelial carcinoma was detected on complete examination of the distal fallopian tube. ABRCA indicates asymptomatic BRCA; OVCA, ovarian serous carcinoma; PPCA, peritoneal serous carcinoma; SBRCA, symptomatic BRCA (8, 11, 13).

tube (fimbria) (6–11): (1) After early reports of sporadic cases of fallopian tube cancers in BRCA+ women, recent studies have established that most asymptomatic early carcinomas in prophylactic adnexectomy specimens occur in the fimbria (8,9). This is in marked contrast to previous reports of symptomatic BRCA+ women with serous cancer, most of which were classified as ovarian in origin, as depicted in Figure 1 (12,13). (2) Tubal carcinomas in BRCA(+) and BRCA(−) women have a similar topographic (fimbrial) distribution (7). (3) Nearly half of consecutive series of ovarian and peritoneal serous cancers coexist with a plausible tubal primary in the form of an early (intraepithelial) tubal carcinoma (11). (4) A candidate "latent" precursor lesion to pelvic serous carcinoma has been described recently in the distal fallopian tube (14). This precursor, termed the "p53 signature," shares many attributes with serous carcinomas, including location (fimbria), cell of origin (secretory cell), DNA damage (γ-H2AX localization), and p53 mutations (Table 1) (14). Taken in the context of the frequent coexistence of both p53 signatures and early tubal cancers in the same patient, these findings provide compelling evidence for a serous carcinogenic sequence (serous carcinogenesis in the tube [SCAT]) in the distal fallopian tube that precedes not only tubal but also extratubal (ovarian and peritoneal) serous malignancies.

The purpose of this report is to review our experience with the range of epithelial alterations associated with strong p53 accumulation in the distal fallopian tube of women with and without BRCA mutations. The goal was to develop a provisional descriptive classification encompassing this range of visible alterations for the SCAT sequence. The methods used and the outcome of this study are detailed below.

MATERIALS AND METHODS

Case Review

This study was approved by the institutional review board at Brigham and Women's Hospital and included a study of fallopian tubes that had been submitted in their entirety for pathological examination by the protocol sectioning and extensively examining the fimbria between January 1, 2005 and March 15, 2007 (Fig. 2). This protocol entails amputation of the fimbrial segment and sagittal sectioning of this segment to increase the amount of surface areas available for review. This protocol, and some of the cases described in this review, have been described previously (8).

CASES STUDIED

Cases for review were culled from the following sources: (1) Thirty-three cases of consecutively analyzed fallopian tubes from women without pelvic serous carcinoma (14). (2) Seventy-five cases of consecutively analyzed fallopian tubes from women undergoing risk-reduction salpingo-oophorectomy for BRCA mutations, including 5 women with early tubal carcinoma (Folkins, Jarboe, and Crum, unpublished data) (14). (3) Twenty cases of consecutively analyzed fallopian tubes from women with pelvic serous carcinomas, in which tubal intraepithelial carcinoma was identified (11).

In all cases, bilateral fallopian tubes were entirely removed and submitted for histological analysis.

Parameters Defining the SCAT Sequence

Prior studies have established a strong relationship between p53 mutations and early serous carcinoma in the

TABLE 1. *Data supporting the distal fallopian tube as a source of serous carcinogenesis*

1. Similarity in expression profile between ovarian serous carcinomas and fallopian tube epithelium.
2. Existence of tubal carcinomas in animal models (hens) at high risk for ovarian cancer.
3. Detection of early tubal carcinoma in over 70% of malignancies detected in BRCA+ women after risk-reducing salpingo-oophorectomy.
4. Detection of early tubal carcinoma in one half of ovarian and primary peritoneal serous carcinomas, irrespective of family history.
5. Confirmed metastatic potential of noninvasive carcinomas of the distal fallopian tube.
6. Identical p53 mutations in tumors of the distal tube and remote ovarian and peritoneal serous carcinomas.
7. Presence of a putative precursor (p53 signature) in the distal tube that shares characteristics with tubal carcinomas, including evidence of DNA damage, p53 mutations, secretory cell specificity, and fimbrial location.
8. Rarity of p53 signatures in the normal ovarian cortex from BRCA+ women.
9. Continuity between p53 signatures and early tubal carcinomas, supporting a transition from one to the other.

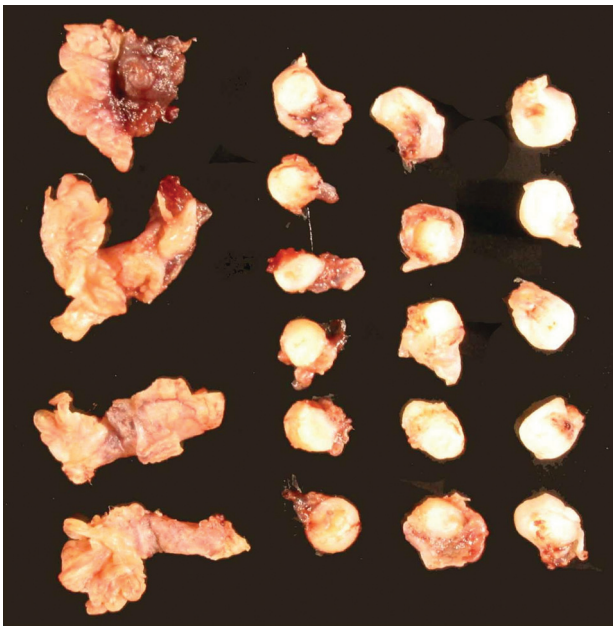

FIG. 2. The SEE-FIM protocol. In this protocol, the distal tube is sectioned longitudinally to increase exposure of the fimbrial mucosa (8).

distal fallopian tube (11,14). p53 nuclear accumulation and p53 mutations have been described in nonneoplastic tubal secretory epithelium and colocalized with evidence of DNA damage (γ-H2AX localization) (14–16). Because these features are shared with early serous carcinomas, we defined discrete and strong p53 nuclear immunostaining in at least 12 consecutive secretory cells as a requisite for inclusion into the SCAT sequence. This number was chosen to limit inclusion of only unique, nonrandom-appearing p53 staining patterns. This was in contrast to the more random-appearing, scattered nuclear staining that does not involve more than 2 to 3 consecutive nuclei and is commonly seen in the fallopian tubes.

Parameters Subdividing Intraepithelial Lesions Within the SCAT Sequence

Parameters used included (1) length or number of cells in the p53-positive epithelium; (2) number of cell layers; (3) stratified versus pseudostratified arrangements of the cells; (4) degree of morphologic homogeneity (as in a single population of secretory versus secretory and ciliated cells intermixed); (5) nuclear atypia, manifesting primarily as enlarged nuclei with prominent nucleoli; (6) polarity; and (7) MiB1 index. Attention was paid to 3 possible categories of lesions, including benign-appearing p53-positive epithelium, obvious tubal intraepithelial carcinomas, and lesions that fell between these 2 end points. The following definitions were applied in classifying p53-positive foci according to these 3 categories.

p53 Signatures

This lesion was defined as a linear stretch of at least 12 consecutive, morphologically benign, p53-positive secretory cells with a low proliferative index. The cells in this lesion can be seen as either uninterrupted sequences or interrupted by intervening ciliated cells that were p53 negative.

Serous Tubal Intraepithelial Carcinomas

Serous tubal intraepithelial carcinomas (STICs) are classified in the literature by the presence of malignant cells replacing the tubal epithelium, with a high N/C ratio, nuclear pleomorphism, high mitotic index, and disorganized growth (17,18). The criteria used in this article are similar, but due to the variability in presentation, are organized into 2 groups. Invariably, tubal intraepithelial carcinomas exhibited the following: (1) a discretely different population of epithelial cells that replaced the normal mucosa and was characterized by (2) an elevated N/C ratio with more rounded nuclei, (3) loss of cell polarity, (4) prominent nucleoli, and (5) absence of ciliated cells. Additional features that were commonly but not invariably present included (6) epithelial stratification, (7) small fracture lines in the epithelium, and (8) exfoliation of small epithelial cell clusters from the surface with or without degenerative changes. In the context of the above, variations in nuclear morphology (pleomorphism) were also common and helpful. However, because heterogeneity in nuclear morphology is also common in normal tubal mucosa, this was not one of the principal criteria for a diagnosis of STIC.

p53-Positive Foci With Features Intermediate Between p53 Signatures and STICs

Lesions in this category exhibited some features of STIC, including nuclear enlargement and prominent nucleoli, but maintained cell polarity and preservation of pseudostratification. MiB1 index was increased but often less than that seen in the STICs.

Immunohistochemistry

All fallopian tube cases were stained for p53. A positive score required strong nuclear staining that obscured nuclear

TABLE 2. *Summary of components of the serous carcinogenesis sequence*

Component	n	Mean MiB1 Index (Range)	γ-H2AX+ (%)
p53 signature	113	3% (0–30)	55/61 (90%)
Intermediate p53-positive focus	4	51% (40–75)	4/4 (100%)
STIC	34	72% (40–95)	7/7 (100%)

STIC indicates serous tubal intraepithelial carcinoma.

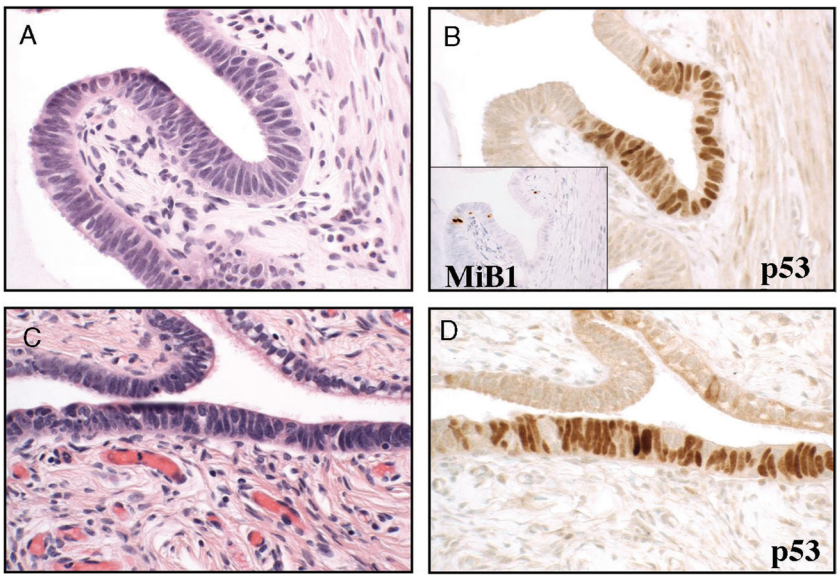

FIG. 3. Morphologically inconspicuous p53 signatures. An uninterrupted sequence of unremarkable-appearing secretory cells (A) shows strong nuclear positivity for p53 (B) and minimal proliferative activity (C; inset). Ciliated cells are interspersed among a sequence of p53-positive secretory cells (D).

detail. Staining for MiB1 was performed on 48 cases. In each case, a MiB1 index, reflecting percentage of cells with intense nuclear staining, was reported. Forty-nine cases were stained for γ-H2AX, the phosphorylated form of the core histone H2AX that is a recognized marker for, and localizes to the vicinity of, double-stranded DNA breakage. Punctate intranuclear staining was required to be scored as positive.

Antigen retrieval was performed on 5-μm tissue sections in citrate buffer (20 mM, pH 6.0) at 120°C for 30 seconds. Sections were incubated with antibodies directed against p53 (DO-1; Immunotech, Westbrook, ME) at a 1:1200 dilution, MIB-1 (corresponding to Ki-67; M7240, DAKO, Carpinteria, CA) at a 1:200 dilution, or γ-H2AX (JBW301, Upstate Cell Signaling Solution, Charlottesville, VA) at a 1:300 dilution, at room temperature for 40 minutes. Antigen-antibody complexes were localized using the EnVision system using horseradish peroxidase and 3,3′-diaminobenzidine (DAKO).

RESULTS

One hundred fifty-eight p53-positive foci were identified in 256 fallopian tubes. None were excluded from this study. These foci were categorized as follows:

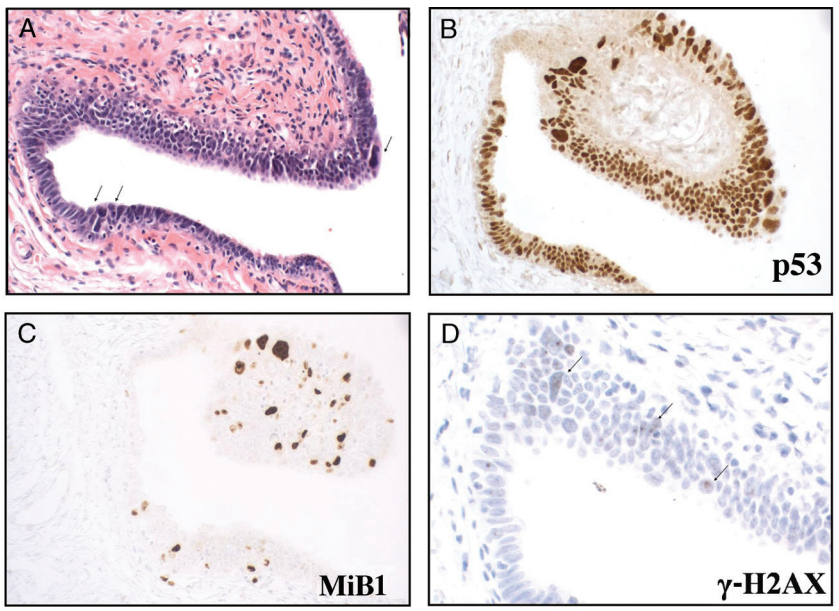

FIG. 4. p53 signature showing nuclear enlargement. Scattered enlarged nuclei (arrows) are recognizable on an hematoxylin-eosin–stained section (A) that also exhibit strong p53 immunopositivity (B). MiB1 index (C) is mildly increased in this signature. Dot-like nuclear staining for γ-H2AX is also present in the secretory cells (D; arrows).

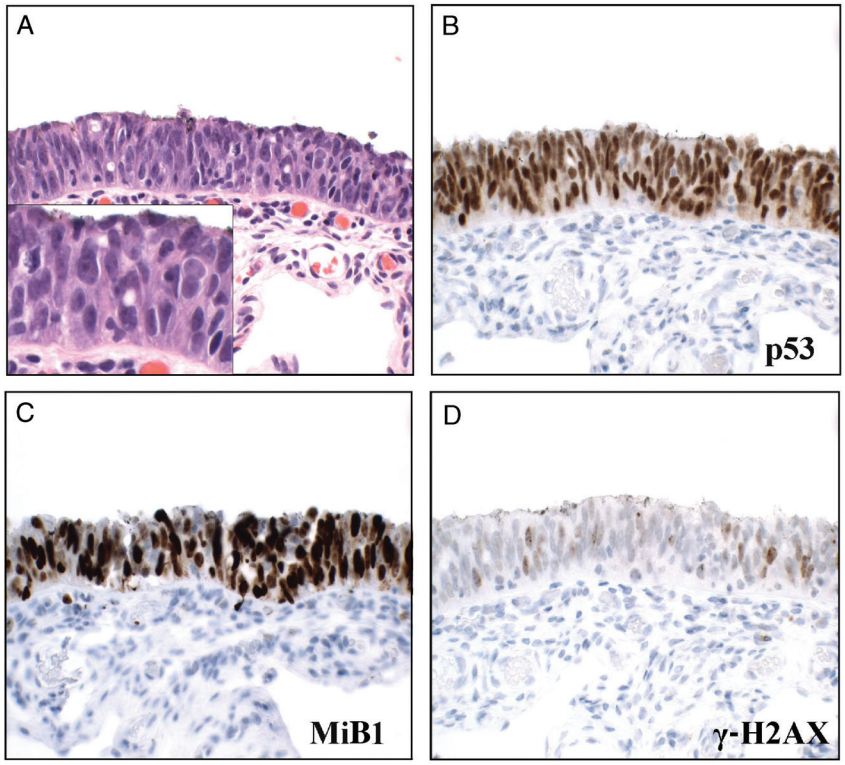

FIG. 5. Serous tubal intraepithelial carcinoma (STIC). In this classic example of a fairly cohesive STIC malignant cells exhibit stratification, round to elongated nuclei, and prominent nucleoli (A and inset). The cells exhibit uniformly strong nuclear staining for p53 (B) and a high MiB1 index (C). Dot-like nuclear staining for γ-H2AX is seen in many cells (D; arrows).

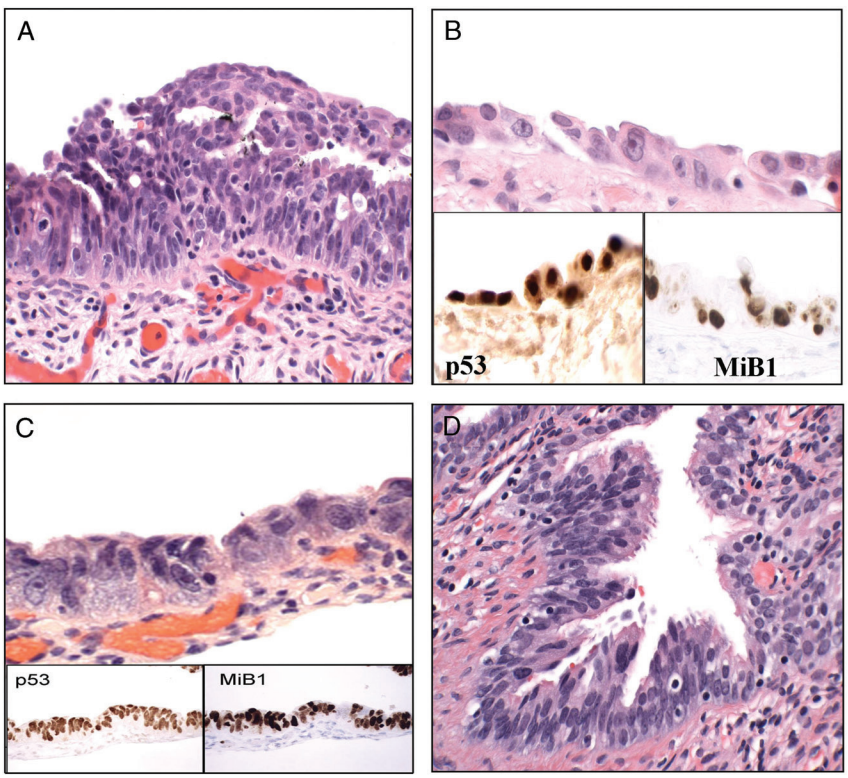

FIG. 6. Serous tubal intraepithelial carcinomas. A, Marked stratification, irregular lines of separation (fracture), and exfoliation characterize this serous tubal intraepithelial carcinoma (STIC). B, Minimal stratification is seen in this "thin" STIC with loss of polarity and markedly atypical nuclei. C, This STIC in a patient who previously received chemotherapy for breast cancer exhibits degenerative changes. D, Benign tubal epithelium exhibiting architectural complexity with pseudostratification and scattered atypical-appearing nuclei can be mistaken for neoplasia; note, however, the diffuse presence of cilia.

Categories

Benign-Appearing p53-Positive Epithelium (p53 Signatures)

One hundred thirteen p53 signatures were identified (Table 2 and Figs. 3 and 4). Cases in this category were characterized by linear arrangements of at least 12 consecutive p53-positive nonciliated cells. Excluded were random-appearing p53 staining and occasional small discrete foci of p53 positivity involving less than 12 consecutive secretory cells. Two groups of p53 signatures were identified. The first group consisted of linear arrays of p53-positive cells that were morphologically indistinguishable from the surrounding epithelium. These were observed in both uninterrupted stretches of secretory cells (Fig. 3A, B) and secretory cells interrupted by intervening (in a 2-dimensional plane) ciliated cells (Fig. 3C, D). The second group consisted of p53 signatures with mild nuclear enlargement, conveying a subtle but discernible contrast with the adjacent normal mucosa (Fig. 4). The 2 patterns of p53 signatures suggested a gradient of increasingly autonomous growth relative to the adjacent epithelium.

MiB1 immunostaining was performed on 69 signatures and revealed a proliferative index that was typically less than 10% with few exceptions (Fig. 3B inset, Fig. 4C). In some instances, the index was less than in adjacent cells, and in others, slightly increased relative to adjacent mucosa, albeit equivalent to other areas of normal epithelium in the sample. The intensity of p53 positivity varied, with some foci containing moderate and others intense nuclear staining. Both patterns were associated with γ-H2AX dot-like immunostaining indicative of DNA damage (Fig. 4D); γ-H2AX positivity was seen in 90% (55/61) of signatures stained.

Serous Tubal Intraepithelial Carcinomas

Thirty-four tubal intraepithelial carcinomas were identified (Table 2 and Figs. 5 and 6). MiB1 index (performed on 22 STICs) ranged from 40% to nearly 100%. In 86% of STICs, the index focally exceeded 70%. However, in some instances, the index did not exceed 50%. One hundred percent (7/7) STICs stained for γ-H2AX were positive.

p53-Positive Foci With Features Intermediate Between p53 Signatures and STICs

This category was uncommon and consisted of 4 foci from 2 cases. These foci demonstrated (1) preservation of pseudostratification and epithelial polarity and often (2) interdigitated with normal-appearing ciliated epithelial cells. However, these areas were characterized by (3) an increased range of proliferative activity that was usually

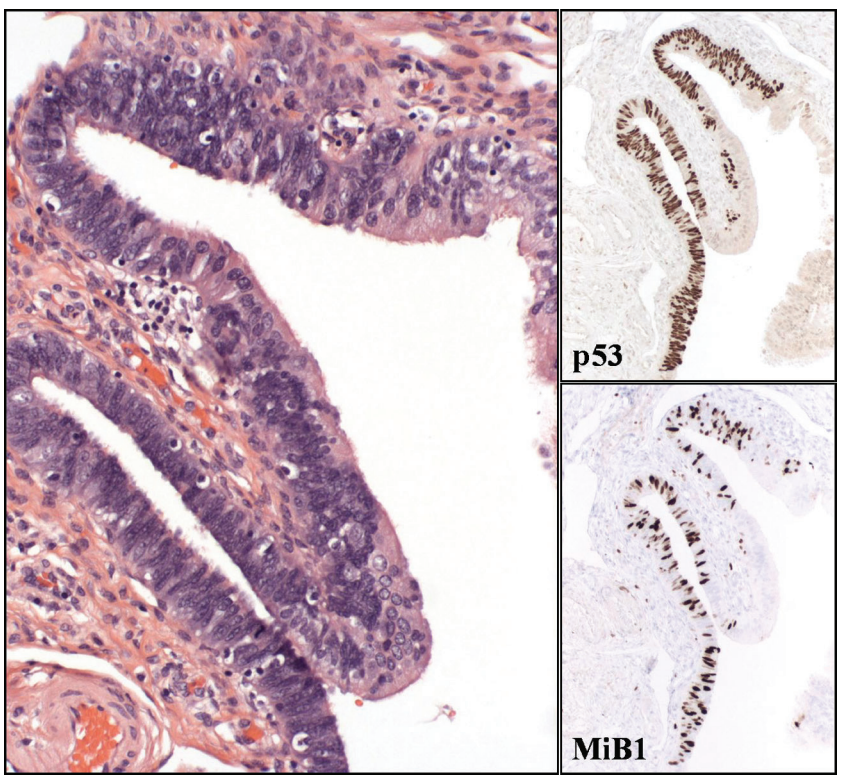

FIG. 7. p53-positive epithelium intermediate between p53 signature and serous tubal intraepithelial carcinoma. This uncommon entity exhibits strong p53 immunostaining and increased proliferative activity, but polarity is preserved, and the p53-positive cells are admixed with normal-appearing ciliated cells.

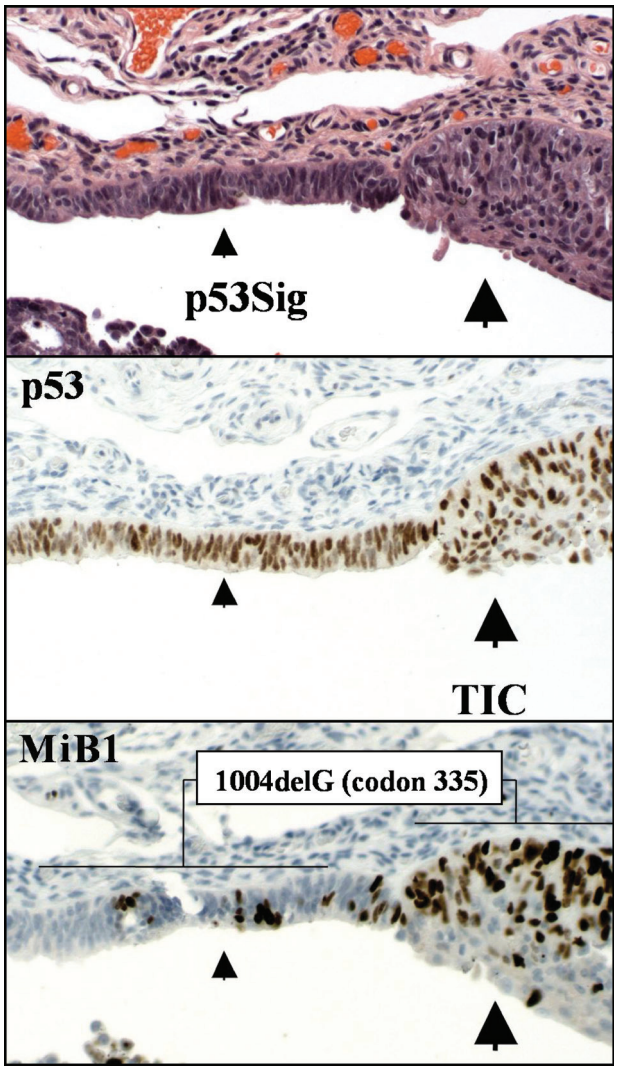

FIG. 8. Continuity between a p53 signature and an serous tubal intraepithelial carcinoma. Both segments were positive for the same p53 mutation.

less than, but overlapped with, STICs. γ-H2AX positivity was present in all 4 foci (Table 2 and Fig. 7).

Continuity Between p53 Signatures and STICs

Direct continuity between p53 signatures and STICs was observed in 2 cases. In some, the transition from p53 signature to STIC was abrupt. In others, the transition was more gradual, including the presence of a lesion with features intermediate between p53 signature and STIC (Fig. 8).

DISCUSSION

There is now evidence that a serous carcinogenic pathway exists in the distal fallopian tube. First, serous carcinoma can be primary in the fallopian tube, and when it does occur, it typically is located in the fimbria. Evidence for this includes the report by Cass et al. (7) that showed that all primary tubal cancers were detected in the fimbrial region, irrespective of BRCA status. In addition, Medeiros et al. (8), Finch et al. (9), and Leeper et al. (10) also documented most early cancers in BRCA+ women in the distal tube. Second, a putative precursor to pelvic serous carcinomas has been identified in the same location (fimbria) where serous carcinomas arise. Earlier reports mentioned p53 staining in the ovaries and fallopian tubes of BRCA+ women or women with ovarian cancer. A spectrum of precursor lesions had not been previously described in detail (19,20). Recently, the "p53 signature"—as described by Lee et al. (14)—has been shown to have several attributes that overlapped with tubal serous carcinomas (Table 1). Based on evidence from studies of both BRCA+ women and consecutive cases of pelvic serous carcinoma, tubal serous carcinomas may predate a significant percentage of pelvic serous carcinomas, including tumors classified as peritoneal or ovarian. Moreover, because the p53 signature shares several features with early tubal cancer, it is reasonable to assume that a serous carcinogenesis sequence (SCAT) can be defined histopathologically by molecular, morphological, and immunohistochemical parameters. This is supported by a third observation, that p53 signatures may be seen in continuity with tubal intraepithelial carcinomas, which in turn typically share the same p53 mutation with coexisting tumors on the surface of the ovaries or peritoneum (14).

The descriptive information gathered to this point from study of the distal tube has revealed a continuum of p53-positive epithelial changes that fulfill the requirements for SCAT. As summarized in Figure 9, this sequence would initiate with a series of events after unrepaired DNA damage and p53 mutations. Based on the appearance of some p53-positive epithelia manifested by either small numbers of involved cells or evidence of cell degeneration, not all foci of strong p53 immunostaining are capable of expanding. Most p53 signatures exhibit evidence of clonal expansion with a low proliferative activity. Some are morphologically inconspicuous, particularly p53 signatures in which the p53-positive secretory cells interdigitate with ciliated cells. Others consist of homogeneous linear arrangements of secretory cells that exhibit mild nuclear enlargement on hematoxylin-eosin staining. This constellation of findings is consistent with other paradigms of clonal p53 mutations, including so-called p53 patches in sun-exposed cutaneous epithelium. This series of epithelial changes is equally common in both BRCA+ women and women without serous carcinoma, consistent with an event that occurs relatively

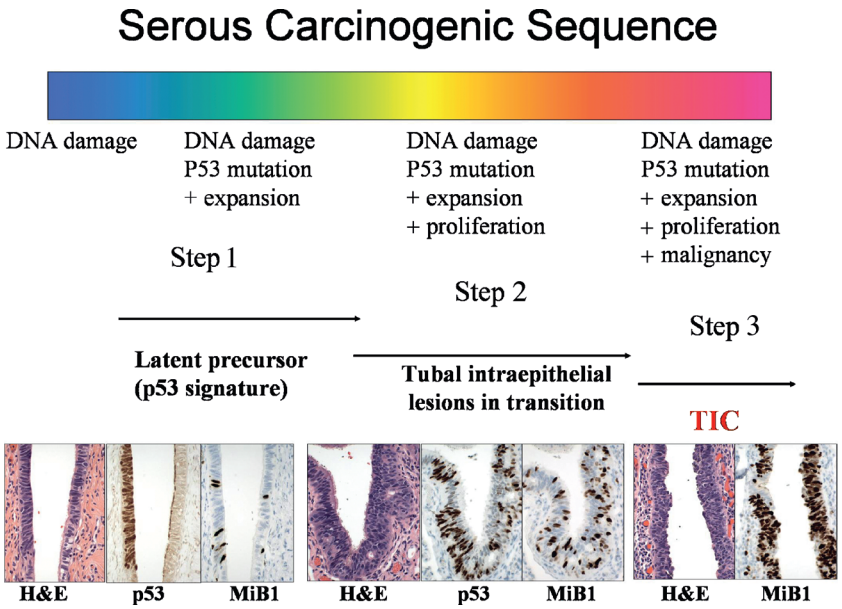

FIG. 9. Model of the sequential carcinogenesis sequence in the fimbria. The fundamental characteristics shared by all steps in the process are p53 accumulation and evidence of DNA damage (γ-H2AX). H&E indicates hematoxylin and eosin.

commonly in approximately one third of the population, irrespective of family history.

The link between p53 signatures and STIC is supported by 2 observations. The first is the direct continuity between the two, a connection that is not commonly seen but well documented in some (14). Whether STICs are invariably preceded by p53 signatures is unknown and would require extensive serial sectioning to resolve given the relatively small size of p53 signatures relative to STICs. However, the second observation is that of a possible intermediate lesion bridging the 2 extremes. This lesion was observed in 2 cases, one with a documented BRCA mutation. We propose a provisional designation of "Tubal Intraepithelial Lesion in Transition" for these p53-positive epithelia that exhibit features intermediate between p53 signatures and STICs. This is not recommended as a diagnostic term in as much as the reproducibility of this entity between pathologists, and its clinical significance, are unknown. Rather, we introduce this term to call attention to the existence of diagnostically problematic entities in the SCAT sequence.

The existing data indicate that most serous tubal carcinomas arise in the fimbria. Tubal carcinomas that diffusely expand the organ are less common, some of which are associated with hydrosalpinx. For those involving the fimbria, there is circumstantial evidence that these neoplasms can spread to pelvic surfaces and produce tumors that are indistinguishable from primary peritoneal and ovarian serous carcinomas (11). Assuming this, the question that remains unanswered is whether women with BRCA mutations are more vulnerable to primary fimbrial carcinomas than women without a known family history. The answer to this question may lie in a better understanding of the factors influencing risk of primary serous carcinomas of the ovary, many of which may be difficult to distinguish from endometrioid adenocarcinomas and may arise by a number of mechanisms, including in the OSE or inclusions, endometriotic cysts, and in association with lower-grade cystadenomas or adenofibromas. If these pathways were less common in BRCA+ women, or developed over a time frame that excluded many of the women presenting for prophylactic surgery, it might explain the apparently more impressive association between the distal tube and early serous malignancies in the BRCA+ population. The initial reports of coexisting STIC and ovarian or peritoneal serous cancers in women who are not selected for BRCA status suggest that approximately 50% can originate from the distal tube, a figure that is less than that observed in the studies of asymptomatic BRCA+ women (Fig. 1).

At present, the most pressing issue for pathologists will be identifying those proliferations in the tubes of BRCA+ women that merit chemotherapy, which is a function of both sensitivity and specificity. Of 4 TICs (3 serous, 1 endometrioid) identified in BRCA+ women in our practice in the past 2 years, 2 were detected only after additional levels in the tissue block, prompted by 1 case each of positive peritoneal cytology and a microscopic ovarian surface implant. This suggests that routine sectioning of the fimbria, even with protocol designed to maximize

exposure of the mucosa, might miss small lesions. Because of this, a policy of obtaining multiple sections through the fimbrial block in prophylactic salpingo-oophorectomies from BRCA+ women should be considered. A second and as yet poorly documented finding in BRCA+ women is occasional endometrioid malignancies in the distal tube, including intraepithelial carcinomas. Resolving the pathogenesis and pathological features of this subset of neoplasms, irrespective of genetic risk factors, is another unresolved challenge.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66.
2. Scully RE, Young RH, Clement PB. Tumors of the ovary, maldeveloped gonads, fallopian tube and broad ligament. In: *AFIP Atlas of Tumor Pathology, Series III*. Washington, DC: AFIP; 1998: 51–79.
3. Deligdisch L, Gil J, Kerner H, et al. Ovarian dysplasia in prophylactic oophorectomy specimens: cytogenetic and morphometric correlations. *Cancer* 1999;86:1544–50.
4. Barakat RR, Federici MG, Saigo PE, et al. Absence of premalignant histologic, molecular, or cell biologic alterations in prophylactic oophorectomy specimens from BRCA1 heterozygotes. *Cancer* 2000;89:383–90.
5. Bell DA, Scully RE. Early de novo ovarian carcinoma. A study of fourteen cases. *Cancer* 1994;73:1859–64.
6. Piek JM, Kenemans P, Verheijen RH. Intraperitoneal serous adenocarcinoma: a critical appraisal of three hypotheses on its cause. *Am J Obstet Gynecol* 2004;191:718–32.
7. Cass I, Holschneider C, Datta N, et al. BRCA-mutation-associated fallopian tube carcinoma: a distinct clinical phenotype? *Obstet Gynecol* 2005;106:1327–34.
8. 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;30:230–6.
9. Finch A, Shaw P, Rosen B, et al. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. *Gynecol Oncol* 2006;100:58–64.
10. Leeper K, Garcia R, Swisher E, et al. Pathologic findings in prophylactic oophorectomy specimens in high-risk women. *Gynecol Oncol* 2002;87:52–56.
11. Kindelberger D, 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;31:161–9.
12. Jarboe EA, Folkins A, Callahan MJ, et al. Pathology of BRCA-associated ovarian cancers, including occult cancers. In: Lu KH, ed. *Hereditary Gynecologic Cancer: Risk, Prevention, and Management*. London: Taylor & Francis; In press.
13. Piek JM, Torrenga B, Hermsen B, et al. Histopathological characteristics of BRCA1- and BRCA2-associated intraperitoneal cancer: a clinic-based study. *Fam Cancer* 2003;2:73–8.
14. 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.
15. Rios-Doria J, Fay A, Velkova A, et al. DNA damage response: determining the fate of phosphorylated histone H2AX. *Cancer Biol Ther* 2006;5:142–4.
16. Thiriet C, Hayes JJ. Chromatin in need of a fix: phosphorylation of H2AX connects chromatin to DNA repair. *Mol Cell* 2005;18: 617–22.
17. Alvarado-Cabrero I, Cheung A, Caduff R. Tumours of the fallopian tube. In: Tavassoli FA, Devilee P, eds. *Tumors of the Breast and Female Genital Organs. World Health Organization Classification of Tumours*. Lyon: IARC Press; 2003:209.
18. Anderson MC, Robboy SJ, Russell P. The fallopian tube. In: Robboy SJ, Anderson MC, Russell P, eds. *Pathology of the Female Reproductive Tract*. London: Churchill Livingston; 2002:436.
19. Hutson R, Ramsdale J, Wells M. p53 protein expression in putative precursor lesions of epithelial ovarian cancer. *Histopathology* 1995; 27:367–71.
20. 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;195:451–6.