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The association of serous tubal intraepithelial carcinoma with gynecologic pathologies and its role in pelvic serous cancer

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HIGHLIGHTS

- We investigated the possible shared primary sites of pelvic serous carcinomas (PSC).
- STIC was mostly located at the fimbria, contacting the peritoneal cavity and ovaries.
- Findings suggested fallopian tubes as the primary sites, but further studies are needed to investigate the accurate carcinogenesis.

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ABSTRACT

Objectives. Possible primary sites of pelvic serous cancers are, fallopian tubes, ovaries or peritoneum. Recent studies have revealed that a portion of these tumors originates from serous tubal intraepithelial carcinoma (STIC) at the distal end of fallopian tubes. In this study, the association of STIC with pelvic serous carcinomas and the pathologic parameters that indicate the tubes as the primary site were assessed.

Methods. In total, 495 pairs of fallopian tubes obtained via total abdominal hysterectomy and bilateral salpingo-oophorectomy between 2011 and 2013 were examined according to SEE-FIM protocol. Hematoxylin and eosin-stained slides were examined by pathologists. Suspicious areas were immunostained with p53 and Ki-67 to diagnose STIC precisely.

Results. Of the 495 cases, 110 cases were malignant. Among 34 cases of non-uterine serous carcinomas, 13 were diagnosed with STIC. STIC was located at the fimbrial end of the fallopian tubes in 12 cases. No STIC was identified in the gynecologic malignancies other than non-uterine serous pelvic carcinomas and benign gynecologic pathologies. Comparison of the ovarian and tubal cancer cases with and without STIC did not reveal a factor that helps to define the primary site. STIC was an important factor associated in a higher portion of the cases with bilateral ovarian cancer.

Conclusion. The role of STIC in carcinogenesis continues to be discussed as it is unknown whether STIC is the precursor lesion or just associates with the malignancies. Discovering the accurate precursor lesions and tumor carcinogenesis is essential to prevent these malignancies and to develop early diagnostic methods.

Introduction

Pelvic serous cancers (PSCs) are responsible for an important portion of mortality caused by malignancy in women, and only 2% of the cases are limited in the ovaries [1]. High grade serous cancers (HGSCs) constitute approximately 80% of PSC. PSC can originate from the ovaries, the peritoneum or the fallopian tubes. The origin and pathogenesis of epithelial ovarian cancers are poorly understood. Many morphologic, histopathologic and molecular studies have been conducted recently to understand the carcinogenesis of PSC and its origin as well as to develop new screening methods and to diagnose it in an early stage. Previous studies have proposed that ovarian carcinomas originate from outside of the ovaries and serous tumors arise from the implantation of epithelium (benign or malignant) of the fallopian tube [1–7]. A dualistic model has been proposed. According to this model, epithelial ovarian cancer is not a single disease but is composed of two groups of tumors: Type 1 and type 2. These two groups have distinctive histopathological, clinical and molecular features. Low grade serous carcinoma is an ideal model for type 1 epithelial ovarian cancer. Low grade endometrioid, clear cell, mucinous, and transitional (Brenner) carcinomas are in this group. This group is usually presented at stage 1 and progresses slowly and silently. It may possess a precursor, such as an atypical proliferative tumor (a

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borderline tumor), and is characterized by specific mutations including *KRAS*, *BRAF*, *ERBB2*, *CTNNB1*, *PTEN*, *PIK3CA*, *ARID1A*, and *PPP2R1A*, which target specific cell signaling pathways. HGSC is an ideal model for type 2 epithelial ovarian cancer. High grade endometrioid, undifferentiated carcinoma and malignant mixed mesodermal tumors are in this group. This group is aggressive and presents at advanced stages. It is characterized by p53 mutations. It has molecular alterations that perturb expression of BRCA either by mutation of the gene, or by promoter methylation. A hallmark of these tumors is that they are genetically highly unstable. It is widely accepted that endometriosis, which is supposed to be prompted by retrograde menstruation, is the precursor of endometrioid and clear cell carcinomas, besides, mucinous and transitional (Brenner) tumors arise from transitional-type epithelial nests at the tubal–mesothelial junction as a result of metaplasia. As a conclusion of these studies, serous tubal intraepithelial carcinomas (STICs) at the distal end of fallopian tubes have been considered as precursor lesions of most of the ovarian, tubal and peritoneal HGSCs [1–7].

In this study, we investigated the association of STIC with benign and premalign gynecologic diseases, non-serous gynecologic malignant diseases, and serous pelvic carcinomas to question the hypothesis that all high grade pelvic serous cancers (tubal, ovarian, and peritoneal serous carcinoma) arise from STIC precursors in the fallopian tubes. Pathologic features that support the idea suggesting that STIC is the precursor disease in addition to possible primary sites of pelvic serous tumors were studied in ovarian, tubal and peritoneal serous cancers with STIC.

Materials and methods

This trial was conducted prospectively among 495 patients who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for various reasons in the Zeynep Kamil Women and Children Health Research and Training Hospital between November 2011 and December 2013.

During the macroscopic evaluation, the following parameters were recorded: location, distribution and dimension of the tumor; bilaterality; existence of dominant ovarian mass; involvement of the fimbrial end of the fallopian tube; and omental involvement.

A dominant ovarian mass was defined as ovarian parenchymal involvement in the case of unilateral ovarian tumors or doubling of the mass comparing the contralateral one in size in the case of bilateral ovarian involvement. If any tumor was detected in the fimbrial end of the fallopian tube, it was regarded as 'positive fimbrial end involvement'.

In all cases, the tubes were completely subjected to the Sectioning and Extensively Examining the Fimbriated End Protocol (SEE-FIM) [8]. This protocol included amputation of each fimbria at the infundibulum, longitudinal sectioning of the fimbria and extensive cross-sectioning of the remaining tube at 2 mm intervals.

PSCs were classified as 'primary ovarian', 'fallopian tube', and 'primary peritoneal' according to the Gynecologic Oncology Group criteria [9,10]. A primary ovarian tumor was classified according to the following criteria: 1) involvement of the ovary in the largest tumor; 2) tumor ≥ 5 mm in size present in the ovarian parenchyma and stroma; and 3) tumor ≥ 5 mm in size present on the ovarian surface that is not imbedded in desmoplastic plaques (which is a characteristic of secondary involvement).

Primary tubal carcinoma was characterized by a tumor originating from the endosalpinx or when the tumor in the fallopian tube was larger than that in the ovary.

Diagnosis criteria for primary peritoneal carcinoma were as follows: 1) larger non-ovarian area involvement than ovarian area involvement; 2) no enlargement of bilateral ovaries by the tumor; and 3) no microscopically detectable ovarian tumor or <5 mm parenchymal involvement.

Hematoxylin and eosin (HE)-stained slides obtained from fallopian tubes were examined by two pathologists. Immunostainings for p53 and Ki-67 were performed in the areas that were indecisive about having STIC with HE staining and needed to be verified with immunohistochemical findings to diagnose STIC more precisely. Immunohistochemistry was performed on formalin fixed paraffin embedded tissue sections using manual polymer detection system with citrate buffer heat induced epitope retrieval. The following pre-diluted ready to use primary antibodies were used: p53 (clone DO-7 + BP53-12; Thermo) and Ki-67 (clone SP-6; Thermo). p53 expression was defined as 'abnormal expression' if it was diffusely expressed, which means >75% of the cells had moderate/strong expression, or it was not expressed at all [11–13]. Ki-67 was defined as positive when the Ki-67 labeling index was >10% [1,14,15].

STIC was diagnosed as non-invasive tubal epithelium displaying marked nuclear atypia characterized by loss of polarity, increased nuclear/cytoplasmic ratios, increased nuclear size, hyperchromasia, irregular nuclear membranes and chromatin distribution. In addition, absence of cilia and mitotic figures also characterized STICs [10,16].

STIC was confirmed according to the combination of atypia on HE-stained slides and abnormal p53 and Ki-67 expression. In p53-negative cases, STIC diagnosis was based on the Ki-67 index (if the main tumor was also p53-negative).

If STIC was not found in the first HE slides of the tubes of pelvic serous carcinoma cases, tubal tissues were leveled yielding 4 additional slides from each block.

Results

This study was comprised of 110 gynecologic malignancy cases in addition to 385 premalignant and benign lesions for a total of 495 abdominal hysterectomy and bilateral salpingo-oophorectomy cases (Table 1). Of the ovarian carcinomas, 25 were high grade serous carcinomas, and 3 were low grade serous carcinomas. Six of the seven tubal carcinomas and three peritoneal carcinomas were serous. High grade areas were detected in one of the low grade serous ovarian carcinomas. One of the serous ovarian carcinomas was accompanied by

Table 1
The origin, histopathologic diagnosis and number of cases.

Origin	Histopathology	Number of cases (n = 495)
Ovary	High grade serous carcinoma	25
	Low grade serous carcinoma	3
	Malignant mixed mullerian tumor	3
	Endometrioid adenocarcinoma	3
	Granulosa cell tumor	4
	Mucinous tumor	2
	Krukenberg tumor	3
	Mixed tumor (endometrioid + clear cell)	2
	Micropapillary serous carcinoma	2
	Borderline tumor (serous and mucinous)	15
	Benign serous cyst adenoma	18
	Benign mucinous cyst adenoma	4
Tuba	Serous carcinoma	6
	Endometrioid carcinoma	1
Peritoneum	Serous carcinoma	3
Endometrium	Endometrioid adenocarcinoma	29
	Serous carcinoma	3
	Clear cell carcinoma, undifferentiated, lymphoma	3
	Hyperplasia, simple	4
	Hyperplasia, complex	10
	Leiomyosarcoma, stromal sarcoma	4
Cervix	Squamous cell carcinoma	13
	Adenocarcinoma	2
	Glassy cell carcinoma	1
	Cervical intraepithelial lesions	12
Others[a]		320

[a] Endometrial polyp, leiomyoma, mature cystic teratoma, endometriosis, inflammation, and normal histopathologic findings.